Abstracts / 22nd Annual Congress
Vienna, Austria 1–5 September 2012
Annual Congress

VIENNA

September 1 – 5, 2012

2012

ABSTRACTS
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Identification of aspirin-induced asthma (AIA) subphenotypes using a clustering approach

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Background: AIA is a distinct asthma phenotype which symptoms are exacerbated by aspirin and other NSAIDs. It is generally recognized as a severe disease to treat asthma accompanied by chronic rhinosinusitis, nasal polyps, blood eosinophilia, elevated levels of urinary LTE4 (uLTE4). It seems, however, that AIA phenotype is not homogeneous.

Aim: To identify distinct subphenotypes in a cohort of AIA patients by applying a clustering technique.

Methods: Clinical data from 201 AIA patients (134 women, mean age 49.4 yrs) were collected using unified questionnaire. Asthma severity and control were assessed using NAEPPI EPR3 guideline. Spirometry, skin tests, blood eosinophilia, uLTE4 were evaluated.

Results: Four clusters of AIA were identified. Cluster 1: severe uncontrolled atopic asthma with non-reversible or reversible airway dysfunction, high rates of health care visits (HCU) for asthma. Cluster 2: moderate uncontrolled/partially controlled non-atopic asthma with non-reversible or reversible airway dysfunction, high rates of HCU. Cluster 3: mild partially controlled atopic asthma with normal airway function, lower rates of HCU. Cluster 4: intermittent well controlled atopic asthma with normal airway function, lower rates of HCU. Upper airway symptoms were very common in all clusters. The groups did not differ with respect to blood eosinophilia and uLTE4.

Conclusions: From a clinical point of view AIA patients are not a homogeneous population. Only part of them have severe uncontrolled asthma. Despite of the presence of upper airway symptoms, some subjects have milder, better controlled disease. Asthma not blood eosinophilia and uLTE4 may discriminate patients assigned to different clusters.

Safety of long-acting β2-agonist (LABA) withdrawal in patients in two clinical asthma trials

Ronald A. Simon 1,2, David S. Pearlman 3, Yun Chon 4, Joseph H. Lin 5, Shao-Lee Lin 6

Background: LABAs are used with inhaled corticosteroids (ICS) for asthma treatment. Due to safety concerns, the US FDA has recommended stopping LABA therapy when asthma control is achieved. Little data exists on the effect of LABA withdrawal in patients on LABA/ICS therapy.

Methods: Patients receiving LABA/ICS therapy at enrollment in Amgen AMG 317 and AMG 835 clinical trials underwent LABA withdrawal at screening. Patients who received either ineffective treatment with study drug or placebo were analyzed. Clinical endpoints were change from screening in prebronchodilator forced expiratory volume in 1 second (FEV1), percentage of predicted prebronchodilator FEV1, Asthma Control Questionnaire (ACQ) score, daily rescue medication use, daily symptom eDiary, exacerbation incidence, and adverse events.

Results: A total of 366 patients were previously treated with ICS+LABA (underwent withdrawal), and 177 patients were treated with ICS only. Changes in prebronchodilator FEV1%, percentage of predicted prebronchodilator FEV1%, ACQ score, daily rescue medication use, symptoms, and exacerbation incidence were not significantly different between patients with previous LABA use and those with-out. Time to exacerbation did not differ between groups (log rank test P=0.412; Cox regression analysis P=0.9755, adjusted for screening characteristics). Adverse events were similar between groups. Similar patterns were observed in placebo patients.

Conclusions: Asthma symptoms, lung function, and exacerbations were not significantly affected by LABA withdrawal in these clinical trial patients.

Managing asthma in the outpatient clinic – Athletes with exercise-induced asthma

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Background: In athletes with exercise-induced asthma, confirmation of the disease with an objective test is required as part of the Therapeutic Use Exemption (TUE) application. An objective test often requires multiple testing with bronchial provocations and lung function measurements. Currently no guidelines exist on a diagnostic strategy in this group of subjects.

Aim: To evaluate the use of diagnostic tests in newly referred athletes with possible exercise-induced asthma in a specialized outpatient clinic.

Methods: Medical records on all patients with a suspected diagnosis of asthma referred to the outpatient clinic at Bispebjerg Hospital, Copenhagen, Denmark in 2010 where reviewed. Data on reversibility to beta2-agonist and airway hyperresponsiveness (AHR) to inhaled mannitol, methacholine and eucapnic hyper- ventilation was collected. Subjects with exercise-induced symptoms that reported to spend at least 10 hours a week on their sports were defined as athletes and were included in the analysis.

Results: Of 221 subjects referred with possible asthma to the outpatient clinic, 51 (23%) were athletes with possible exercise-induced asthma. A total of 39% (72%) was concluded to have asthma, based on a specialist's assessment. Among these subjects the final diagnosis was confirmed by an objective test in 31/39 (80%). The number of tests required to confirm the presence of disease was one in 9 (29%) of the subjects, two in 15 (48%) subjects, three in 6 (19%) and four in 1 (3%) subject.

Conclusion: In more than eight out of ten athletes with exercise induced asthma, more than one test for AHR or reversibility was necessary as part of the diagnostic process.

A comparison of the frequency of cough with laughter in asthmatic and non asthmatic patients

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Cough is a frequent symptom in asthmatic patients. Cough may be induced by typical asthma triggers such as allergens, exertion or change in atmospheric temperature. This study investigates the symptom of cough with laughter as an asthmatic symptom.

Patients attending a general adult respiratory clinic were routinely asked if they experienced cough with laughter. Seventy four consecutive patients with a single respiratory diagnosis were included. The patients were divided into two groups: patients with asthma and those with another respiratory diagnosis.

The asthma group had forty three patients with a mean age of 57.7 years. Twenty seven were female and sixteen male.

The non asthma group had thirty three patients with a mean age of 63.9 years, sixteen were male and fifteen female. In this second group their diagnoses were chronic obstructive pulmonary disease in eleven, pulmonary fibrosis in eight, sarcoidosis in five, bronchiectasis in two, hyperventilation in two and one each of carcinoma of bronchus, tuberculosis and sleep apnoea.

In the asthma group forty two of the forty three patients had the symptom of cough with laughter.

In the non asthma group one of the thirty one patients had the symptom of cough with laughter.

The symptom of cough with laughter is highly significantly associated with a diagnosis of asthma compared to other respiratory diagnoses (p<0.0001) and has a 97.6% sensitivity and a 96.8% specificity as an asthma symptom in this study.

A retrospective analysis of methotrexate therapy as a steroid sparing agent within a UK severe asthma clinic

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Background: Treatment with Methotrexate (MTX) immunosuppressive therapy in severe asthma is used in an effort to reduce corticosteroid dependency and associated side effects. This study aimed to evaluate the effectiveness of MTX within this patient population as an efficient aid to reduce corticosteroids.

Methods: A retrospective data collection was performed within the severe asthma service. Patients whom were established on or had started MTX within the last twelve months were included. Variables explored included mean daily corticosteroid dose, exacerbation frequency, acute admission episodes and blood eosinophil count twelve months prior to and twelve months post commencement of Methotrexate therapy.

Results: n=30, 9 patients stopped MTX due to side effects. Within the ongoing stable group, corticosteroid dose was significantly lower post MTX compared to previous treatment (mean dose 10.4mg daily post MTX compared with 16.8mg pre
MTX \( (p < 0.001) \). The exacerbation frequency following MTX commencement was significantly lower (2.7) than in the year prior to treatment (6.1) \( (p < 0.002) \). Reduced hospitalization following MTX therapy was also demonstrated (0.4 episodes post treatment compared to 1.5 episodes pre treatment \( (p < 0.0006) \). There was a trend for a reduction in eosinophil level post treatment compared with prior to treatment, but this did not reach statistical significance.

**Conclusion:** MTX (where tolerated within this severe asthma population) was found to significantly reduce the demand for corticosteroids. A reduction in exacerbation rate and hospitalization are also demonstrated when sufficiently monitored and supervised within a specialist setting.

**165 Small airways involvement is associated with bronchial hyperresponsiveness in asthma**

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**Background:** Bronchial hyperresponsiveness (BHR) is a hallmark of asthma. Although, the role of small airways involvement in asthma has been well established, little is known about the association between BHR and small airways obstruction. We hypothesize that small airways disease contributes to BHR.

**Methods:** A total of 119 patients with a doctor’s diagnosis of asthma were included. All subjects underwent spirometry and a BHR testing \( (PD_{20} \text{ histamine}) \). Small airways involvement was defined as an \( \text{MEF}_{50} \leq \text{LLN} \) and \( \text{MEF}_{30} \leq \text{LLN} \) respectively. Patients with small airways involvement showed a more severe BHR than patients without \( (PD_{20} \text{ histamine} 0.2 \text{ vs.} 1.1 \text{ mg}) \). In addition, \( \text{FEV}_1, \text{FEV}_3/\text{FVC} \) and reversibility were lower in patients with small airways involvement. Both a lower \( \text{MEF}_{30} \) and \( \text{FEV}_1 \) were independent predictors of more severe BHR in multivariate linear regression models.

**Results:** We found 36 patients with and 83 patients without small airways involvement \( (\text{MEF}_{50} \leq \text{LLN} \text{ and } \text{MEF}_{30} \leq \text{LLN} \text{ respectively}) \). Patients with small airways involvement showed a more severe BHR than patients without \( (PD_{20} \text{ histamine} 0.2 \text{ vs.} 1.1 \text{ mg}) \). In addition, \( \text{FEV}_1, \text{FEV}_3/\text{FVC} \) and reversibility were lower in patients with small airways involvement. Both a lower \( \text{MEF}_{30} \) and \( \text{FEV}_1 \) were independent predictors of more severe BHR in multivariate linear regression models.

| Table 1. Differences between asthmatics with and without small airways involvement (MEF50 ≤ LLN and MEF30 ≤ LLN respectively) |
|-----------------|-----------------|-----------------|
| **Age (years)** | 45 ± 35–52 | 47 ± 34–57 | 0.42 |
| **Gender (m,%)** | 29 ± 34.9 | 14 ± 38.9 | 0.68 |
| **Smoking (m,%)** | 43 ± 52.4 | 22 ± 61.1 | 0.58 |
| **ex-smoker** | 29 ± 34.9 | 12 ± 33.3 | |
| **occasional smoker** | 3 ± 3.7 | 0 | |
| **habitual smoker** | 7 ± 8.4 | 2 ± 5.6 | |
| **Packyears** | 7 ± 0.8–5.6 | 4.0 ± 7.0–7.0 | 0.10 |
| **Bectamethasone equivalent dose (μg/day)** | 600 ± 400–800 | 800 ± 400–800 | 0.14 |
| **BMT (kg/m²)** | 26 ± 24–29 | 26 ± 24–30 | 0.66 |
| **PD20 histamine (mg)** | 1.1 ± 0.9–0.9 | 0.2 ± 1.9–0.9 | <0.001 |
| **FEV₁/VC (%)** | 6.3 ± 2.9–4.3 | 2.6 ± 2.3–4.1 | <0.001 |
| **Reversibility (%)** | 4.0 ± 2.2–6.8 | 8.7 ± 5.9–11.1 | <0.001 |
| **FEV₁/FVC (%)** | 82.4 ± 79.5–85.5 | 68.5 ± 61.2–73.0 | <0.001 |
| **MEF₃₀ (L/s)** | 3.9 ± 2.4–6.6 | 2.1 ± 1.6–2.5 | <0.001 |
| **MEF₅₀/predicted** | 86.5 ± 88.6–102.5 | 46.9 ± 39.2–51.5 | <0.001 |

**Conclusion:** Small airways involvement is associated with more severe BHR in asthma. Since \( \text{FEV}_1 \) is used as a read-out in current BHR tests, we hypothesize that small airways disease contributes to BHR.

**167 Local coagulation activation following bronchial instillation of house dust mite allergens (HDM) and HDM/Lipopolysaccharide (LPS) in mild asthmatics**

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**Rationale:** Exposure to house dust, containing HDM and LPS, is associated with exacerbations of allergic asthma. In patients with asthma, the hemostatic balance in the lungs is often unstable. We hypothesized that adding LPS to bronchial provocation with HDM increases activation of coagulation and complement pathways in asthmatics while on maintenance treatment with inhalation corticosteroids (ICS).

**Aim:** To assess the activation of coagulation in bronchoalveolar lavage fluid (BALF) induced by provocation with HDM +/- LPS.

**Methods:** We included 32 mild asthmatic patients with HDM allergy. After 2 weeks run-in with fluticasone 100μg bid, subjects underwent bronchoscopy for segmental instillation of saline in one lung followed by instillation of HDM +/- LPS in the contralateral lung. Six hours later, BAL was performed. Statistical comparisons were made by univariate analysis.

**Results:** Additional instillation of LPS to HDM resulted in a significant increase in levels of thrombin-antithrombin complexes \( (\text{TATc}) \) \( (p=0.015) \) and complement 4b \( (p=0.007) \) in BALF.

**Conclusion:** Additional instillation of LPS to a provocation with HDM in mild asthma increases pulmonary activation of coagulation and activation of the comple-
49. Sarcoidosis

168 Methotrexate vs azathioprine in chronic sarcoidosis
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Background: Although steroids remain the mainstay of therapy in sarcoidosis,
chronic use is associated with toxicity. Evidence is missing on which second
line therapy is most appropriate.

Aim: To compare the effect of methotrexate (MTX) and azathioprine (AZA) in second
line treatment of chronic sarcoidosis patients regarding steroid use, lung function
and side effects.

Methods: This is a retrospective cohort study, reviewing all patients who started
MTX or AZA in two Dutch/Belgian tertiary referral centres. Demographic data,
steroid use, lung function tests and side effects were noted from initiation until
2 years after or discontinuation. Treatment effect was calculated with a linear
mixed model with FEV1, VC, DLCO and prednisone dose changes over time as
endpoints. Differences in side effects were calculated with χ²-tests.

Results: 200 patients were included. 145 received MTX and 55 received AZA.
Prednisone daily dose decreased with 6.32 mg/year (p<0.0001) while on therapy,
with no difference between MTX and AZA. FEV1 showed a mean increase of
52 ml/year (p=0.0066) and VC of 95 ml/year (p=0.0001), with no difference be-
tween drugs for both. DLCO (% predicted) increased with a mean of 1.23%/year
(p=0.018). Mean DLCO was 5.12% lower in the AZA group (p=0.05), but this
difference was constant over time. There were significantly more patients with
infections on MTX (6.5% vs. 16.0%; p=0.01). No significant differences
were found regarding other side effects.

Conclusions: This is the first study comparing the effect of MTX and AZA in sarcoidosis
patients. Although more infections occurred in the AZA group,
this study shows both drugs were equally effective in terms of lung function
improvement and had a significant steroid sparing effect.

169 Concentration of sFas in bronchoalveolar lavage fluid of smoking patients
with sarcoidosis
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Sarcoidosis (SA) is a multifactor organ granulomatous disease of unknown etiology. SA is
more prevalent among non-smokers. The postulated protective role of smoking on
inflammation in SA remains enigmatic. Fas/FasL system is assumed to participate in
the regulation of immune response and granuloma formation in SA. Soluble Fas
(sFas) is known to inhibit Fas-induced apoptosis. In previous study we reported an
elevated number of Fas positive cells in the bronchoalveolar lavage fluid (BALF)
of smoking sarcoidosis patients.

The aim of this study was to find out whether sFas concentration in BALF differs
between ever smoking (S) and never smoking (NS) patients with sarcoidosis.
We investigated 57 patients with confirmed SA: 36 NS and 21 S. Total and
differential cell count in the BALF samples were performed according to standard
methods. The sFas concentration was measured by ELISA.

There were significant differences in BALF composition between NS and NS.
The total cell count and the percentage of macrophages were significantly higher
among S than among NS (11.3 vs. 6.5 x 10⁵, 62 vs. 50%, respectively), while the
percentage of lymphocytes was significantly lower among S than among NS (29
vs. 41%). The sFas concentration was lower in the BALF of S compared with NS
(median values 68.3 vs 95.5 pg/ml, p=0.01). Furthermore, the sFas concentration
among active smokers was significantly lower than among NS (65.6 vs 95.5 pg/ml,
p=0.01).

We found out that sFas concentration is reduced in the BALF of smoking sarco-
idosis patient. Lower sFas concentration may result in higher apoptosis rate of
inflammatory cells, thereby promoting granulomatous inflammation resolution.

170 Association study of ANXA1I-R230C with sarcoidosis
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Crete, Heraklion, Greece

Introduction: Recently, a genome wide association study demonstrates that the
polymorphism ANXA1I-R230C (rs1049550) is strongly associated with sarco-
idosis, a chronic granulomatous disease (GD) of unknown etiology.

Aim: Considering that also other diseases are accompanied by granulomas for-
mation, as observed in 10% of patients with common variable immunodeficiency
(CVID), the purpose of this study was to confirm the association of ANXA1I-R230C
with sarcoidosis and to examine its possible association with GD in CVID.

Methods: DNA was extracted from peripheral blood of 71 patients with sarco-
idosis (MF/24/47, mean age: 52.5 years, range-20-75), 101 normal individuals
(MF/35/66, mean age: 54.1 years, range-19-76), and 19 CVID patients (MF/7/12,
mean age: 28.1 years, range-2-60), two of which had granulomatous disease (one
with familial CVID history including a sister without GD). A PCR-RFLP protocol
was designed to detect ANXA1I-R230C and statistical analysis was performed using
the SPSS software (ver.-10.0).

Results: The difference in the allele frequency of ANXA1I-R230C between pa-
ients with sarcoidosis and healthy individuals was not marginally reached to be
significant (p=0.073). The allele frequency of ANXA1I-R230C in CVID patients
was 50.0% and no significant difference between patients with and without GD
was observed. However, in the family with CVID, the member with GD carried
only the R alleles, associated with granulomas formation, while her sister was
heterozygous.

Conclusions: The association of ANXA1I-R230C with sarcoidosis was not con-
firmed, while the emerged contribution of this polymorphism in the granulomas
formation in CVID needs to be further clarified.

171 HLA-DRB1 allele distributions in Danish sarcoidosis patients. Increased
prevalence of HLA-DRB1*15
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Background: The MHC class II region appears to play an important role in the
development and clinical picture of sarcoidosis, probably due to the influence on
the immune response against yet unknown antigen(s). A previous HLA-class II
study in Danes has shown that HLA-DR3 antigens is associated with a favorable
prognosis and HLA-DR6 with susceptibility to sarcoidosis (Hdum et al., Exp Clin
Immunogenet 1999;8:227-31).

Subjects and methods: HLA-DRB1 allele classification was performed by PCR
in ethnic Danish patients with biopsy-verified sarcoidosis (n=94). Danish blood
donors (n=10146) served as controls.

Results: The prevalence of DRB1*01 was lower and the prevalence of DRB1*15
was higher in sarcoidosis patients compared to controls.

<table>
<thead>
<tr>
<th>DRB1* allele</th>
<th>Sarcoidosis (n=94)</th>
<th>Controls (n=10146)</th>
<th>Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequency (%)</td>
<td>frequency (%)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>7</td>
<td>7.4</td>
<td>2048</td>
</tr>
<tr>
<td>03</td>
<td>23</td>
<td>24.5</td>
<td>2563</td>
</tr>
<tr>
<td>04</td>
<td>29</td>
<td>30.9</td>
<td>3279</td>
</tr>
<tr>
<td>07</td>
<td>20</td>
<td>21.3</td>
<td>2111</td>
</tr>
<tr>
<td>08</td>
<td>7</td>
<td>7.4</td>
<td>705</td>
</tr>
<tr>
<td>09</td>
<td>1</td>
<td>1.1</td>
<td>215</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1.1</td>
<td>155</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
<td>14.9</td>
<td>1375</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>8.5</td>
<td>475</td>
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<td>13</td>
<td>19</td>
<td>20.2</td>
<td>2522</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>3.2</td>
<td>441</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>44.7</td>
<td>2845</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>1.1</td>
<td>148</td>
</tr>
</tbody>
</table>

Conclusions: There exist no specific biochemical markers of sarcoidosis. Diagno-
sis relies on histological examination of tissue biopsy specimens in combination
with the exclusion of infection with mycobacteria and other causes of the gran-
ulomatous response. Due to the paucity of prognostic markers, we suggest that
analysis of HLA-DRB1 (and BTNL2 genotype (Milman et al., Clin Respir J
2011;5:105-11) be incorporated in the evaluation of sarcoidosis patients.

SUNDAY, SEPTEMBER 2ND 2012
Whole-body magnetic resonance imaging in sarcoidosis to assess extrapulmonary organ involvement

Methods: 24 consecutive patients at the Clinic of Respiratory Medicine, University Hospital Basel, Switzerland, with histologically-confirmed sarcoidosis were prospectively included. All patients underwent whole-body MRI. Results: In total 52/4 (38%) patients showed findings of probable or possible sarcoidal origin. 52/4 (21%) showed skeletal lesions, 3/4 (13%) had muscular findings and 1/4 (4%) had enhancement of the cauda equina. EPOST score was significantly higher in those 9 patients with abnormal whole-body MRI-findings (17.3) than in those with normal images (10.6). FVC percentage predicted (FVC%, TLC, FRC) were significantly lower in those patients with abnormal skeletal enhancement compared to those without skeletal abnormalities.

Conclusions: Whole-body MRI depicted manifestations of extrapulmonary sarcoidosis in 38% of cases in an unselected patient sample. Abnormal whole-body MRI findings correlated with high EPOST scores, and might thus be a valid tool to assess extrapulmonary disease activity. Abnormal skeletal findings correlated with decreased lung volumes, and might therefore be a marker of total disease activity.

HLA-DPB1 and chronic sarcoidosis

Methods: HLA-DPB1 was determined in 98 patients with chronic sarcoidosis. 17 different DPB1 alleles were observed. The DPB1*04:02 allele was less frequent among the patients (10.2% vs 20.3%; p=0.003, OR=0.45) than controls. A haplotype with DPB1*04:01, one C4A gene and one C4B gene was increased among sarcoidosis patients (30.6% vs. 22.5%; p=0.036, OR=1.5). By studying polymorphic amino acid residues of DPB1, we did not detect an association of Glu226, but a DPB1*04:02 specific amino acid variant was detected at the position 178 (Met) suggesting a protective role for chronic sarcoidosis (p=0.004, OR=4.42).

Furthermore, preliminary SNP analyses of HLA class II and III region showed a significant protection to sarcoidosis was observed, confirming previous data in populations from different geographic regions, but only in those patients without EN.

Results: The frequency of ANXA11 rs1049550 (R230C) allele was significantly lower in sarcoidosis patients (33.1% vs. 46.2%, p<0.01, OR=0.58, 95%CI=0.38-0.86). An OR=0.44 and OR=0.4 for sarcoidosis was obtained respectively, in the carriers of one (genotype ANXA11 CT) and two (genotype ANXA11 TT) copies. There is no valid tool to ANXA11 rs1049550*T allele normalised to the CC wild type genotype (p<0.01). When patients with erythema nodosum (EN) were removed, this association persists only in the group without EN. There was no significant difference among radiological Scadding stages.

Conclusions: In this population an association between ANXA11 rs1049550*T SNP and protection to sarcoidosis was observed, confirming previous data in populations from different geographic regions, but only in those patients without EN.

50. Chest wall, diaphragm and pleura

Pectus excavatum, small lungs or small chest cavity?

Conclusion: After 16 weeks of treatment, bosentan therapy was associated with a significant improvement in pulmonary artery mean (PAM) and pulmonary vascular resistance (PVR) for those treated with 16 weeks (wks) of bosentan (BOS) versus no change in those treated with placebo (PLA).

Introduction: We reported significant improvement in pulmonary artery mean (PAM) and pulmonary vascular resistance (PVR) for those treated with 16 weeks (wks) of bosentan (BOS) versus no change in those treated with placebo (PLA) for sarcoidosis associated pulmonary arterial hypertension (SAPAH).

Purpose of the study: To determine whether patients with advanced parenchymal disease were less likely to respond to BOS.

Methods: Patients with SAPAH confirmed by right heart catheterization (RHC) were randomised 2:1 to receive either BOS or PLA. After 16 wks of therapy, patients underwent repeat RHC. Patients had forced vital capacity (FVC) and Scadding chest x-ray (CXR) stage.

Results: Of the 25 patients treated with BOS, 2 stopped study drug before wk 8. At 16 wks, 21 had repeated RHC. Patients were subgrouped into those with FVC% 70% predicted (FVC% ≥70% predicted (FVC% ≥70%) and those with CXR stage 4 versus stage 4 (CXR=4). The table demonstrates the changes in PAM and PVR. There was significant improvement in PAM and PVR for those with FVC 70% but was not for those with FVC ≥70%. No changes were seen for the PLA group.

PAM and PVR

<table>
<thead>
<tr>
<th>Number</th>
<th>Wk 0</th>
<th>Wk 16</th>
<th>Wk 0 PVR</th>
<th>Wk 16 PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC%&lt;70</td>
<td>7</td>
<td>35±7.4</td>
<td>36±6.7</td>
<td>6.7±2.81</td>
</tr>
<tr>
<td>FVC%≥70</td>
<td>14</td>
<td>36±6.6</td>
<td>32±4.01 *</td>
<td>5.5±3.01</td>
</tr>
<tr>
<td>CXR Stage 1-3</td>
<td>9</td>
<td>37±6.0</td>
<td>35±6.5</td>
<td>6.8±4.10</td>
</tr>
<tr>
<td>CXR Stage 4</td>
<td>12</td>
<td>35±7.6</td>
<td>36±10.1 *</td>
<td>5.1±1.34</td>
</tr>
</tbody>
</table>

Means±SD, *P<0.05.

Conclusion: After 16 wks of treatment, bosentan therapy was associated with a significant improvement in PAM and PVR. These changes remained significant for patients with an FVC<70% predicted. SAPAH patients with advanced parenchymal lung disease may respond to vasodilatory therapy.
Results: Table 1. Spirometric functions before and after surgical correction

<table>
<thead>
<tr>
<th>Function</th>
<th>Before (%)</th>
<th>After (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>91.8 ± 4.9%</td>
<td>94.6 ± 6.3%</td>
</tr>
<tr>
<td>RV</td>
<td>153.3 ± 12.9%</td>
<td>156.7 ± 8.6%</td>
</tr>
<tr>
<td>VC</td>
<td>72.9 ± 4.6%</td>
<td>74.5 ± 5.1%</td>
</tr>
<tr>
<td>FRC</td>
<td>119.7 ± 10.2%</td>
<td>122.9 ± 9.1%</td>
</tr>
</tbody>
</table>

Discussion: The preoperative TLC and VC were almost normal, but FRC and RV were significantly increased in the 27 patients. Central hemodynamic parameters were also within normal limits. Hence, the chest deformity is a secondary effect caused by this ‘Little Lung Syndrome’.

After surgery, all lung volumes and hemodynamic functions decreased.

Conclusion: It is probable that we need to change the surgical technique to not only correct the chest wall defect but also to reduce the intra-thoracic volume, so as not to stretch the lungs.

177 Evaluation of the effects of surgical correction of left mediastinal displacement in children with pectus excavatum on pulmonary perfusion, using minimal radiation exposure

Methods: We prospectively evaluated 34 consecutive patients with PE pre- and post-Nuss procedure using chest radiography (CXR), echocardiography (UCG), and PP scintigraphy. CXR was used to visualize the vertebral index (VI) and left displacement index (LDI, ratio between the distance from the left border of the mediastinum to the left border of the thorax and the transverse thoracic dimension on posteroanterior CXR). PP scintigraphy was visually interpreted and left-to-right shunting ratio (RL) was calculated. Pre-ejection period, acceleration time (AcT), and ejection time (ET) of the right pulmonary artery (RPA) and left pulmonary artery (LPA) were measured by pulse Doppler UCG.

Results: VI and LDI improved postoperatively (P < 0.001). Preoperatively, left PP was impaired. Postoperatively, Ls/Rs increased (P = 0.001) and AcT/ET changed (LPA: P < 0.001; RPA: P = 0.008). Evaluation of the usefulness of CXR showed that LDI correlated with Ls/Rs (R = 0.411, P < 0.001) and LPA-AcT/ET (R = 0.50, P < 0.001), and that VI did not correlate with Ls/Rs and correlated poorly with LPA-AcT/ET (R = 0.28, P = 0.05).

Conclusions: The imbalance of PP improves after the Nuss procedure. The degree of leftward displacement of the mediastinum correlates with decreased left PP. Follow-up can be achieved with minimal radiation exposure.

179 Stabilization of sternum using absorbable copolymer plate in the open surgery for pectus deformities

Methods: We reviewed the records of 31 patients who had undergone open surgery for pectus deformities using absorbable copolymer plates between November 2008 and January 2012. All patients were evaluated retrospectively according to the demographics, type and form of deformity, operation duration, perioperative and postoperative complications, and recurrence.

Results: Twelve patients were male and the median age was 19.5 (range: 14-31). Seven patients had pectus carinatum, 7 had pectus excavatum, and 4 had mixed deformity. The median operation duration was 120 minutes (40-210). One patient had severe complications in the postoperative period. No recurrence was seen. Absorbable copolymer plates can be used for the stabilization of sternum in open surgery for pectus deformities with low morbidity rates, as it is a safe, durable, and easy-to-use material.

180 Surgery for sternal tumors: Extent of resection, reconstruction and survival

Methods: We conducted a retrospective study of 74 patients from January 1999 to December 2008. The histological diagnosis was salivary gland malignances. The chest wall reconstruction depends on the size and site of the malignances. The chest wall reconstruction depends on the size and site of the malignances. The chest wall reconstruction depends on the size and site of the malignances. The chest wall reconstruction depends on the size and site of the malignances.

Results: The median operation duration was 120 minutes (40-210). One patient had severe complications in the postoperative period. No recurrence was seen. Absorbable copolymer plates can be used for the stabilization of sternum in open surgery for pectus deformities with low morbidity rates, as it is a safe, durable, and easy-to-use material.

181 Our experience in the surgery of the chest wall tumors

Introduction: The tumor pathology of the chest wall is extremely interesting and wide, and still it rises a great amount of problems related to the diagnosis and surgical treatment. That is why the purpose of this article is to share our department’s experience confronting this type of pathology.

58
Material and method: We analysed a series of 154 patients that underwent surgery in our department in ap 10 years period (2001 – 2011), with ages between 21 and 74 years old. 43 of the patients had benign pathology, the rest of 111 had primary, secondary or contiguous malignancies of the chest wall. The surgical procedures applied were chest wall resection followed by reconstruction with several types of synthetic materials such as Thoratex mesh, “Spider Web” suture or the use of methylmetacrylate and chest wall resection without stabulation. In 74.6% of the patients. The mean hospital stay was 8 days.

Results: In all the cases the perioperative mortality and morbidity was zero. The immediate postoperative outcome off the patients was good in 150 cases, 3 cases developed wound seroma that was managed with conservative treatment and one patient underwent a second surgery with muscular flap after stabulation with methylmetacrylate. Conclusions: The tumoral pathology of the chest wall still raises a series of problems of surgical treatment, some cases are indeed a challenge for the surgeon, but the continuous development of the surgical techniques and of the materials for reconstruction along with the development of experienced surgical teams lead to obtaining optimal results without complications that require further surgical attention.

182
Eventration surgery of the diaphragm via trans-thoracic approach
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Eventration of the diaphragm is a rare anomaly due to congenital or acquired etiology. Congenital eventration of the diaphragm is probably a true congenital defect acquired during the fetal period. Eventration of the diaphragm also occurs in adults is thought to be caused by an acquired or complete or in complete paralysis of the diaphragmatic leaf. Operative repair is indicated for older patient who has symptoms. A transthoracic approach and diaphragmatic plication is preferred. We performed 32 diaphragmatic plication at our institution between 2005-2011. Six of the cases on the right, 26 on the left. All operation performed under laterally decubitus position and one lung ventilation. The classical approach was a posterolateral thoracotomy through 7th intercostal space. The thinned diaphragmatic leaf was repaired with plication. We had no postoperative mortality or any other major complication. The eventration of the diaphragm need to surgically repair to take away symptoms and respiratory relieve.  

183
Neural networks analysis of spontaneous pneumothorax development
Luca Bertolaccini1, Lucia Boschetto2, Claudio Cassardo2, Andrea Viti2, Alberto Zerra2. Thoracic Surgery, S. Croce e Carle Hospital, Cuneo, Italy; 1General Physics “Amedeo Avogadro”, University of Turin, Italy

Spontaneous pneumothoraces (SP) tend to cluster. Correlations between SP and atmospheric variations were reported by previous studies. In our work SP correlation with meteor variables and air pollutants in Cuneo County was analyzed. 2004-2010, 451 SP patients were prospectively evaluated. For each day of an-alyzed period, meteo parameters and pollutants were recorded. Statistics on SP occurrence significantly increases in warm windy days with high atmospheric pressure and high NO2 concentration. These data don’t affect SP treatment; nevertheless, they add information on SP tendency to cluster.

51. Diagnostics in OSA: from polygraphy to genetics and cancer

184
The method for diagnosis matters in sleep apnea. A systematic analysis of polygraphy and polysomnography data in the European Sleep Apnea Database (ESADA)
Pierre Escourrou1, Fadia Jilwan1, 1Centre de Médecine du Sommeil, Hôpital Béclère ; AP-HP, Clamart, France; 2ESADA office, Center for Sleep and Vigilance Disorders, Sahlgrenska Academy, Gothenburg, Sweden

In the ESADA study, each of the 23 participating centers used its own routine clinical and diagnostic procedures for OSA detection. Altogether, data from 8228 patients with suspected OSA (M or F, 18–80 yrs) were analysed in order to compare results obtained by polygraphy (PG) (n = 5032) or polysomnography (PSG) (n=3196). The AASM 2007 criteria have been used for visual scoring of apnoea/hypopnoea and in addition in a PSG study, an event with ≤50% flow reduction, associated with arousal was also classified as hypopnoea (Eur Respir J 2011; 38: 633–642).

AHI was higher by PG (29.9±26.2 hr-1) than by PSG (22.3±23 hr-1) (p<0.001). 66% of the patients had an AHI>15 by PG whereas only 50% of patients were above this limit by PG (p<0.001). Although analyzed time (7±4±0.9 hr) by PG was higher than total sleep time (6.4±1.3 hr) by PSG (p<0.001), oxygen desaturation index (ODI) (≥4%) was only marginally different: 21±24 hr-1 by PG and 19±22 hr-1 by PG. Furthermore the difference between the AHI and ODI scores was higher by PG (8.6±1.7) than by PG (1.1±1.0) (p<0.001). The average number of events per recording was similar by PG (186±183) and by PSG (184±189) (NS) which rules out a significant time dilation effect to explain the higher AHI by PG compared with PG.

In summary, the AHI is underestimated by PG leading to a lower rate of patients suffering from significant OSA than by PG. This discrepancy is likely to relate to the scoring of hypopnea by arousal rather than the result of the time dilation effect. Supported by enabling grants from RESMEDI and PHILIPS RESPRONICS.
Conclusion: Real-time attended HPSG through telematic data transmission is feasible and could be an interesting perspective to decrease the failure rate of home sleep studies even if some technical aspects need to be improved.

186 Contribution of APO E alleles and ACE I/D polymorphism in the development of hypoxia in sleep apnoea/hypopnoea syndrome

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Sleep apnea/hypopnea syndrome (SAHS) is a common condition affecting approximately 0.3–4% of the middle-aged population and is defined on the basis of symptoms of daytime sleepiness and objective measures of disordered breathing during sleep. Several studies have identified SAHS as a risk factor for hypertension, but a direct etiologic link between these disorders has not been established definitively. Aim: To evaluate the influence of polymorphisms on the APO E gene and the I/D polymorphism on ACE in the presence of hypoxia (HT) in Sleep Apnea – Hypopnoea Syndrome patients.

Methods: APOE and ACE I/D genotypes were obtained from 99 controls and 114 patients with a diagnosis of sleep apnea/hypopnea syndrome after polysomnography in the Sleep unit of the Rio Hortega Hospital.

Results: There were not any difference in the APOE alleles frequency between patients and controls, but SAHS patients carrying the APO E ε4 allele showed an increased frequency of HT 3.145 higher than ε3 homozygous and ε2 carriers (CI 1.29-7.79). These findings keep significant even after correction for sex. The ACE I/D genotypes were in Hardy-Weinberg equilibrium (< 0.05) and they seem don’t have any influence on the development of HT in these patients (DD OR 0.478 (CI 0.21-1.08)

Conclusions: Our results demonstrate that the presence of the ε4 allele increases the probability to develop HT in Sleep Apnea patients. We suggested that this allele could be useful as a biological marker for identification of a subgroup of SAHS patients who are more likely to have HT.

187 Independent impact of obstructive sleep apnea severity on glycated haemoglobin in adults without diabetes

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Hypothesis: There may be an independent association between obstructive sleep apnea (OSA) severity and glycated hemoglobin (HbA1c) in adults without known diabetes.

Methods: HbA1c was measured in 1,728 patients with no history of diabetes undergoing nocturnal recording for suspected OSA.

Results: A dose-response relationship was observed between apnoea-hypopnoea index (AHI) and percentage of patients with HbA1c >6.0% that increased from 13.8% for AHI<5 to 42.6% for AHI>50. After adjustment for age, gender, smoking habits, body mass index (BMI), waist circumference (WC), cardiovascular morbidity, daytime sleepiness, depression, insomnia and sleep duration, odds ratios (95% confidence intervals) for HbA1c >6.0% increased from 1.43 (0.88 to 2.33), 1.74 (1.08 to 2.81), 1.94 (1.23 to 3.09) and 2.89 (1.79 to 4.67) for AHI values <5, 5 to <15, 15 to <30 and >30 respectively. Increasing hypoxemia during sleep was also independently associated with the odds of HbA1c >6.0%.

Conclusions: Among adults without known diabetes, increasing OSA severity is independently associated with impaired glucose metabolism that may expose to higher risks of diabetes and cardiovascular disease.

Odds ratio (95% confidence intervals) for HbA1c >6% according to AHI (AHI<5(reference) after adjustment for age, gender, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia and total sleep time.

188 Prediction modeling and temporal validation of sleep disordered breathing from large community samples

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Aim: Common sleep apnea prediction tools (e.g. the STOP-BANG score) were derived using laboratory-based polysomnography in academic centers. In contrast, we assessed and temporally validated the sleep apnea risk factors in patients undergoing ambulatory screening and testing in community practice.

Methods: Two consecutive sets of 2000 ambulatory sleep monitor recordings referred for interpretation by community physicians and CPAP vendors were used for modeling and validation. With each study the patient’s age, gender, mass, height, neck circumference, use of dental appliances, reported excessive snoring and Epworth sleepiness score were reported. An estimated respiratory disturbance index (RDI) was derived from each study’s signals. Modeling of the predicted RDI was done using linear regression and induced error pruning tree methods on the first sample with temporal validation testing on the second sample (WEKA, v. 3.7.5).

Results: Linear regression modeling showed all risk factors significantly associated with RDI, however, the model’s correlation coefficient was poor in both the training (0.3953) and validation (0.4604) samples. Tree modeling showed sequential cutoffs for neck circumference < 44 cm, Epworth score < 18.5 and mass < 107 kg best modeled the estimated RDI. The tree model’s training (0.3755) and validation (0.3015) correlation coefficients were, like the regression model values, also poor.

Conclusions: Common sleep apnea risk factors have poor statistical validity for predicting sleep disordered breathing in patients undergoing ambulatory screening and testing.

189 Association between sleep apnoea and cancer incidence. Longitudinal study of a large multicenter Spanish cohort

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Background: The role of Sleep Apnoea (SA) in the development of cancer in humans has not yet been assessed.

Objective: To investigate whether SA is associated with increased cancer incidence.

Methods: We performed a multicenter, clinical cohort study, analyzing 8,961 patients referred to 8 Spanish Sleep Clinics for suspected SA. Subjects with an apnoea-hypopnoea index (AHI) ≥ 10 comprised the control group. SA was diagnosed when the AHI was ≥10. We used the log-rank test to compare cancer incidence between groups, and the Cox proportional hazards model to calculate both unadjusted and adjusted HR and 95%CI for incident cancer.

Results: 8,542 (93.3%) patients were finally analyzed. The median follow-up of the cohort was 5.1 years (interquartile range 4.0 to 7.1). SA was associated with increased incidence of cancer in unadjusted analyses (HR 1.27, 95%CI 1.04-1.56). The cancer incidence density rate was also significantly higher in patients with SA compared to the control group (14.99 vs. 11.71 per 1,000 person-years; incidence density rate 1.28 [95%CI 1.04-1.57]). Further adjustments for body mass index, smoking or alcohol intake did not modify these results. Cancer incidence was not associated with either mild-moderate SA (HR 1.02; 95%CI 0.81 to 1.28), or severe SA (HR 0.85; 95%CI 0.68 to 1.00) in the adjusted models.

Conclusions: Sleep Apnoea was associated with increased cancer incidence, but this association disappeared when the results were adjusted for confounders.
Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea

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Background: Obstructive sleep apnea (OSA) is associated with an increased risk of cancer mortality in humans (Nieto et al., ATS Congress, 2012). Experimental data in mice have recently shown that a pattern of intermittent hypoxia mimicking OSA: 20 s 5% O2 followed by 40 s room air, for 6 h/day. The other 15 animals were breathing room air (controls). After 30 days the mice were sacrificed, their lungs were excised and hematoxilin-eosin preparations were analyzed by a pathologist to quantify the number of metastases.

Methods: The number of lung metastases in each mouse was significantly greater in the animals subjected to intermittent hypoxia (5.5±3.2) (mean ± SE) than in control mice (1.0±0.6) (p=0.028).

Conclusion: The data from this animal study strongly suggest that intermittent hypoxia enhances metastasis to the lung from a subcutaneous melanoma.

Aim: To test the hypothesis that intermittent hypoxia enhances metastasis to the lung from a subcutaneous melanoma.

Methods: 28 male C57BL/6J mice were investigated. To induce a melanoma tumor in each mouse, one million of B16F10 cells were subcutaneously injected in the left flank region of the animal. Thirteen of these animals were then subjected to breathe intermittently hypoxic air with a pattern mimicking OSA: 20 s 5% O2 followed by 40 s room air, for 6 h/day. The other 15 animals were breathing room air (controls). After 30 days the mice were sacrificed, their lungs were excised and hematoxilin-eosin preparations were analyzed by a pathologist to quantify the number of metastases.

Results: The number of lung metastases in each mouse was significantly greater in the animals subjected to intermittent hypoxia (5.5±3.2) (mean ± SE) than in control mice (1.0±0.6) (p=0.028).

Conclusion: The data from this animal study strongly suggest that cancer metastasis could be enhanced in patients with OSA.

Mortality and morbidity after sleep disorders in Europe

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The long-term prognosis of obstructive sleep apnea (OSA) and obesity hyperventilation syndrome (OHS), as compared to age, gender and social controls, are incompletely described.

Using data from the Danish National Patient Registry (NPR) (1998-2010), 30278 individuals with a diagnosis of OSA (23208 men and 7070 women) and 1562 with a diagnosis OHS (1092 men and 470 women) were identified. For every patient, four ages-, sex- and social matched citizens were randomly selected from the Danish Civil Registration System, a total of 120506 OSA and 6241 HS controls.

The 10 year survival of treated and untreated OSA patients was 90.7% compared to 92.4% (controls) and of OHS patients 63.9% compared to 85.5% (controls) (both: p<0.0001).

Commonly significant (p<0.01) observed morbidities in OSA patients were related to respiratory (1.9 (1.82-2.0), ventilator duration, 1.65 (1.55-1.75), endocrine, metabolic, nutritional (1.35 (1.34-1.75), ENF1.39 (1.30-1.49), circulatory: 1.20 (1.16-1.29), musculoskeletale: 1.25 (1.20-1.30), digestive illnesses (1.09 (1.03-1.14), and injuries 1.12 (10.8-1.16). Mental disease and neoplasm showed a lower occurrence: 0.90 (0.81-0.99) and 0.85 (0.80-0.95), respectively.

OHS showed higher morbidities to respiratory: 4.03 (3.21-5.07), renal: 3.17 (2.43-4.15), endocrine, metabolic, nutritional (4.65 (3.67-5.90), ENF1.39 (1.30-1.49), circulatory: 1.84 (1.50-2.6), musculoskeletale: 1.25 (1.20-1.30) and digestive illnesses (1.09 (1.03-1.14), and injuries 1.12 (10.8-1.16). Neoplasm occurred less often: 0.70 (0.50-0.97).

OHS and especially OHS present significant mortality. The morbidity includes a wide range of medical disorders besides cardiovascular complications.

52. Exacerbations of asthma and COPD: assessment, impact and novel treatments

Once-daily QVA149 significantly improves lung function and symptoms compared to twice-daily fluticasone/salmeterol in COPD patients: The ILLUMINATE study

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Background: QVA149 is a novel dual bronchodilator combination of the LABA indacaterol and the LAMA NVA237 (glycopyrronium), in development for the treatment of COPD. QVA149 once daily (QD) vs salmeterol/fluticasone (SFC) twice daily (BID) was evaluated in moderate-to-severe COPD patients with no history of exacerbations in the previous year.

Methods: In a double-blind, double-dummy, parallel-group study, 523 patients (QVA=258, SFC=264) were randomized to receive QVA149 110/50 μg QD (via the Breezhaler device®) or SFC 500/50 μg BID (via the Accuhaler device®) for 26 weeks.

Results: Mean age was 63 years; mean post-bronchodilator FEV1: 60% predicted. Mean FEV1, AUC0-12h at Day 1 and Weeks 12 and 26 (primary endpoint) was significantly higher with QVA149 vs SFC (p<0.001 for all comparisons; table).

<table>
<thead>
<tr>
<th>Week</th>
<th>QVA149</th>
<th>SFC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>70*</td>
<td>70*</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>90*</td>
<td>150*</td>
<td>0.019</td>
</tr>
<tr>
<td>Week 26</td>
<td>100*</td>
<td>150*</td>
<td>0.019</td>
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</table>

* p<0.001.

Serial spirometry showed significantly higher and clinically meaningful improvements in FEV1 with QVA149 vs SFC at all timepoints from 5 min to 12 h at Day 1 and Weeks 12 and 26 (p<0.001). QVA149 significantly improved the Transition Dyspnea Index score vs SFC (treatment mean: 2.16 vs 1.41, respectively; p<0.003), reduced rescue medication use (~0.39 puff/day; p<0.019) and improved other lung function measures (table) over 26 weeks. The safety profile of QVA149 was similar to that of SFC.

Conclusion: QVA149 QD provided significant, sustained and clinically meaningful improvements in lung function vs SFC BID over 26 weeks, with significant symptomatic benefits.

193 Accuracy in assessment of acute asthma needs improved to avoid potential adverse outcomes

Selina Tump1, Lorraine Bridges, Grace Murphy, Peter Kewin. Respiratory Medicine, Southern General Hospital, Glasgow, United Kingdom

Introduction: Despite comprehensive BTS Asthma Guidelines (2011 revision), there are up to 1200 deaths annually in the UK, 90% due to identifiable and preventable disease, management and psychosocial factors. We retrospectively compared management of acute asthma admissions in a city centre hospital for 1 year (2010) with BTS guidelines to identify key areas for service improvement.

Results: Data was obtained for 72/106 admissions. The majority of admissions were female (70.8%), during winter months (63.9%), and outside normal working hours (63.9%; fig 1A). Initial peak expiratory flow rate (PEFR) and severity guide management decisions. While 79.2% had a best previous PEFR documented, pre-and post treatment PEFR were recorded in only 65.3% and 36.1% respectively. No severity was recorded in 68.1% and there was a tendency to underestimate it (fig 1B). In spite of this 91.7% of admissions were appropriate according to BTS criteria (fig 1C) and there were no subsequent deteriorations resulting in emergency treatment.

Table 1

<table>
<thead>
<tr>
<th>Week</th>
<th>QVA149</th>
<th>SFC</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>Day 1</td>
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<tr>
<td>Week 12</td>
<td>90*</td>
<td>150*</td>
<td>0.019</td>
</tr>
<tr>
<td>Week 26</td>
<td>100*</td>
<td>150*</td>
<td>0.019</td>
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Impact of a single chronic obstructive pulmonary disease (COPD) exacerbation on lung function decline: Analysis of UPLIFT

David Halpin, Mark Decramer, Bart Celli, Antonio Martin, Inge Leimer, Norbert Metzdorf, Donald Tashkin.

Aims and objectives: To examine the effect of a single COPD exacerbation on rate of decline in lung function, using data from a 4-year randomized, double-blind, placebo-controlled trial of tiotropium in moderate-to-severe COPD (UPLIFT).

Methods: Retrospective analysis of annual rate of decline in pre- and postbronchodilator (BD) forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Before and after first COPD exacerbation (increase in onset of respiratory symptom lasting ≥3 days and treated with antibiotics/ systemic corticosteroids). Eligible patients (pts) had ≥3 pulmonary function tests (PFTs) before exacerbation.

Results: 462 pts were eligible (mean age 64 y, 76% male, mean baseline FEV1 1.19 L and FVC/FVC 0.44). Mean annual rate of decline in pre- and post-BD FEV1 and pre-BD FVC significantly increased (Table).

Conclusion: A single exacerbation can lead to a significantly larger rate of decline in lung function in COPD pts 1-2 years post exacerbation.

195 Aclidinium bromide reduces COPD exacerbations as defined by healthcare resource utilisation and EXACT: Results from ATTAIN

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Introduction: COPD exacerbations can lead to considerable morbidity and mortality. ATTAIN investigated the effect of twice-daily (BD) aclidinium bromide, a long-acting muscarinic antagonist, on exacerbations in patients with moderate to severe COPD.

Methods: In this 24-week, randomised, double-blind trial, 819 patients (mean -SD FEV1, 56.8±12.8% predicted) received aclidinium (200 μg or 400 μg) BD or placebo. Prior exacerbation history was not an inclusion criterion. Exacerbations were assessed by healthcare resource utilisation (HCRU); increased symptoms on ≥2 consecutive days requiring a change in treatment and the EXacerbations of Chronic pulmonary disease Tool (EXACT); persistent increase in total score of ≥9 points for ≥12 points for ≥2 days).

Results: EXACT captured more exacerbations per patient per year than HCRU (EXACT: 1.0, 0.98 and 1.39 for aclidinium 200 μg, 400 μg and placebo, respectively; HCRU: 0.43, 0.40 and 0.66, respectively). Exacerbation rates were significantly lower for both aclidinium doses compared with placebo and ratio rate differences were: EXACT 200 μg 0.72 [p=0.017] and 400 μg 0.71 [p=0.012]; HCRU: 200 μg 0.72 [p=0.043] and 400 μg 0.67 [p=0.020]; corresponding to a rate reduction of about 28% with aclidinium using each method.

Conclusions: More than twice as many events were recorded using EXACT compared with HCRU. Aclidinium 200 μg and 400 μg BD reduced exacerbations compared with placebo as assessed by HCRU and EXACT. The proportional reduction in exacerbations demonstrated in the non-prespecified secondary outcome confirms the efficacy of aclidinium 200 μg, which was sufficient to reach statistical significance in both the primary and non-prespecified secondary outcomes.

196 Increased rate of mortality in COPD patients using tiotropium respimat vs tiotropium Handihaler

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Background: Tiotropium is a long-acting, once daily anticholinergic drug that is delivered via Handihaler (dry powder inhaler) or via Respimat (soft mist inhaler). Data from RCTs suggest that use of tiotropium Respimat is associated with an increased risk of mortality.

Objectives: To explore the risk of mortality in users of either tiotropium Handihaler or tiotropium Respimat.

Methods: Within the IPCI database, a Dutch GP database, we defined a source population of patients ≥ 40 years with at least 1 year of follow-up. The study ran from 2008 to 2011. Patients were followed from start of the study until the patient died or end of follow-up date. Date and cause of death were verified for all patients. From the source population, we defined a cohort of tiotropium users (Handihaler and/or Respimat) and created episodes of use. To assess the risk of dying, we considered a 30-day carry-over effect. The risk of mortality was calculated using a Cox proportional hazard regression analysis. Crude and adjusted HRs were calculated with corresponding 95% CI.

Results: From the source population, we defined a tiotropium cohort of 11,287 patients providing 24,540 episodes of use. 496 patients died while being exposed to either Handihaler or Respimat. Use of Respimat was associated with an increased risk of dying (HRadj 1.52, 95% CI 1.24-1.87) and this association remained upon adjustment (HRadj 1.33, 95% CI 1.07-1.65). The association was strongest for incident users and cardiovascular death, but due to low numbers not longer statistically significant (HRadj 1.87, 95% CI 0.74-4.73).

Conclusions: Use of tiotropium Respimat vs tiotropium Handihaler is associated with a 30% increase of mortality.
The anti-IL-17A-antibody secukinumab does not attenuate ozone induced acute airway neutrophilia in healthy volunteers

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Background: Interleukin-17 (IL-17) or IL-17A is linked to neutrophilic airway inflammation.

Aim and Objective: To evaluate the effect of a novel anti-IL-17A antibody secukinumab (AIN457) on ozone-induced airway neutrophilia in healthy volunteers.

Methods: 24 healthy volunteers with normal neutrophil levels in sputum and a proven inflammatory response to ozone 24 and 48 hours after the baseline ozone challenge (3 hours intermittent exercise with inhalation of 250 ppb ozone during the challenge) were randomized to secukinumab (10mg/kg bodyweight) or placebo or an open label prednisolone (50mg) arm in the ratio 2:1:1. Secukinumab or placebo was administered as an infusion whereas prednisolone was administered as an oral tablet. Sputum analyses were performed 24 and 48 hours following ozone challenges during the treatment phase at various time-points. Safety and pharmacokinetics were also assessed.

Results: Administration of secukinumab was safe and well tolerated. Compared to placebo, secukinumab did not attenuate ozone-induced sputum neutrophilia 24 and 48 hours after ozone challenge. Prednisolone treatment resulted in an increase of neutrophils in sputum and in peripheral blood. No immunogenicity with secukinumab was observed. Mean half life of secukinumab was 29.8 days.

Conclusions: Neutralizing IL-17A by secukinumab did not attenuate acute ozone-induced airway neutrophilia in healthy subjects. Study of the effects of anti-IL17A treatment on chronic neutrophilic airway diseases may be warranted in patients with disorders characterized by airway neutrophilia.

The Abstract was funded by Novartis Institutes for BioMedical Research, Switzerland.

198 Reducing exacerbations in omalizumab in a real-world setting

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Asthma exacerbations are a major cause of morbidity and mortality. Omalizumab (OMA) reduced exacerbations in clinical trials. The 2-year, global, observational eXpeRience registry was initiated to collect data from OMA-treated allergic (IgE-mediated) asthma patients (pts), and to assess whether results from clinical trials apply in real-life practice. The intent-to-treat population included 916 pts (734 and 643 evaluable pts at Month 12 and 24, respectively). In the 12 months prior to inclusion in the registry, only 11.8% of pts were exacerbation free; at months 12 and 24, 54.9% and 65.8% of pts, respectively, were exacerbation free over the prior year.

Compared with the 12-month pre-treatment period, clinically significant and severe clinically significant asthma exacerbations decreased over time following OMA initiation (Table).

<table>
<thead>
<tr>
<th></th>
<th>Baseline 12 months pre-treatment (N=916)</th>
<th>Month 12 (N=734)</th>
<th>Month 24 (N=643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations per patient-year</td>
<td>4.9±5.32</td>
<td>1.0±1.85</td>
<td>1.6±2.74</td>
</tr>
<tr>
<td>Exacerbations per patient-month</td>
<td>0.41</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Exacerbations per patient-month (clinically significant)</td>
<td>2.2±2.80</td>
<td>0.2±0.75</td>
<td>0.3±1.02</td>
</tr>
</tbody>
</table>

These real-world data and safety profile are consistent with results from clinical trials. OMA reduces clinically significant and severely clinically significant exacerbations in pts with uncontrolled persistent allergic asthma.

Rationale and Objectives: There is growing evidence linking asthma severity with fungal allergy. We assessed the effect of voriconazole or posaconazole therapy on asthma control and severity (GINA criteria) among patients with SAFS and ABPA.

Methods: We conducted a retrospective review of adult asthmatic patients with either ABPA or SAFS receiving voriconazole or posaconazole. Clinical, radiological and immunological evaluation was used to assess response. Voriconazole (500-600 mg/day) or posaconazole (800 mg/day) (adjusted by plasma level monitoring) was given for at least 6 months, if tolerated.

Results: There were 26 patients, ABPA (n=21, severe=17) or SAFS (n=5), 11 males, median age 59 yrs. Eighteen of 24 (75%) discontinued oral corticosteroids, 12 of them within 3 months of therapy. Asthma severity was downgraded from severe to moderate (n=8) and moderate to mild (n=1) in 9 of 24 (38%) patients. There was a marked reduction in OCS and SABA use, health care utilization due to asthma and improvement in overall health status. Furthermore, there was a statistically significant reduction in immunological markers appearing at 9 months (p=0.008) for total IgE and at 12 months for RAST IgE Aspergillus fumigatus (p=0.0056). Six of 23 (26%) patients on voriconazole had AEs requiring discontinuation before 6 months compared to none on posaconazole (p=0.15). Four relapsed (57%), one at 3 months and 3 at 12 months after discontinuation.

Conclusion: Both voriconazole and posaconazole are effective treatment options which can improve asthma control and severity, though larger prospective studies are required.

53. MDR- and XDR-TB: epidemiological and public health overview

200 Time trends in multidrug-resistant tuberculosis

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Background: To investigate time trends in multidrug-resistant tuberculosis (MDR-TB) in different geographical settings worldwide we used data collected by the World Health Organization over the period 1994-2010.

Methods: Time trends in MDR-TB rates from 45 countries or territories were calculated by multiplying the new TB case notification rates by the frequency of MDR-TB in new TB cases in the same year. The number of available country-year data points differed between countries. The annual percentage change in MDR-TB rates was plotted against the annual percentage change in TB notification rates, placing all countries or territories in one of six groupings according to whether MDR-TB rates and TB notification rates were increasing or decreasing.

Results: In countries like Japan, Japan, Poland, Singapore and the US, the incidence of MDR-TB has been falling quicker than the incidence of TB. Countries with a high proportion of MDR-TB among TB cases (Georgia, Russian Federation: Tomsk Oblast), with a majority of TB cases of foreign origin (Sweden, United Kingdom) and with high HIV prevalence (Botswana, South Africa: Mpuanalago Province, Swaziland) show net increments in both TB and MDR-TB incidence, with the latter increasing faster than the former.

Conclusions: While global trends in MDR-TB may not be inferred directly from
the national data currently available, MDR-TB incidence is increasing in countries with disparate epidemiological and geographical settings.

201 Determinants of multidrug-resistant tuberculosis (MDR-TB) in Belarus
Alena Skrahina1, Henza Huereux2, Aksana Saluntskaya2, Andrei Avchupoko1, Sven Hofnife1, Valiantas Rusovich1, Andrei Dadu2, Pierpaolo de Colomn3, Masoud Dara4, Wayne Van Gemer5, Matteo Zignol5
1Clinical Department, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; 2Laboratory Department, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; 3Laboratory Department, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; 4Department of Preparedness, Swedish Institute for Communicable Disease Control, Stockholm, Sweden; 5Communicable Diseases, WHO Country Office in Belarus, Minsk, Belarus; 6Tuberculosis and M/XDR-TB Programme, WHO Regional Office for Europe, Copenhagen, Denmark

Introduction: A nationwide survey to investigate risk factors for multidrug-resistant tuberculosis (MDR-TB) was conducted in Belarus in 2010-2011. A total of 1,344 TB patients were enrolled.

Results: MDR-TB was found in 32.3% (95% CI: 29.7-35.0) and 75.6% (95% CI: 72.1-78.9) of new and previously treated patients, respectively. History of previous treatment for TB was the strongest independent risk factor for MDR-TB (Odds Ratios [OR] 6.1, 95%CI: 4.8-7.71) followed by HIV infection (OR 2.2, 95%CI: 1.4-3.5). Other independent risk factors were young age (<35 years) (OR 1.4, 95%CI: 1.0-1.8), history of imprisonment (OR 1.5, 95%CI: 1.1-2.0), disability in such a way as to be unable to work (OR 1.9, 95%CI: 1.2-3.0), alcohol abuse (OR 1.3, 95%CI: 1.0-1.8), and smoking (OR 1.5, 95%CI: 1.1-2.0).

Discussion: MDR-TB is a widespread problem in Belarus, with very high levels documented nationwide. The convergence of the MDR-TB and HIV epidemics and association between MDR-TB and numerous risk factors calls for stronger collaboration between TB and HIV control programmes and a more targeted approach to high-risk groups. Adherence to TB treatment could be improved by integrating treatment for alcohol use disorders into TB services and enhancing patient incentives and enablers.

202 Survival and risk factors of mortality among defaulters from treatment of pulmonary tuberculosis
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Defaulters from treatment of pulmonary tuberculosis (PTB) convey a significant transmission risk that is particularly dangerous during increasing prevalence of MDR-TB and TB/HIV co-infection. We estimated 1- and 5-year survival, assessed infectiousness and identified risk factors of mortality of PTB patients after treatment default. We observed all patients with PTB registered in the Estonian Tuberculosis Registry as defaulters during 2004-2006 (n=160) in a cohort study until 12.12.2011 and used multivariate Cox regression analysis to identify risk factors of mortality. Median follow-up time was 5.94 (IQR: 3.21-6.68) years after default. One-year and 5-year survivals were 90.5% and 86%, respectively. Among the 50 patients (31.3%) who died, median survival time was 1.86 (IQR: 0.88-3.04) years; 24 deaths (48.0%) occurred due to TB and 26 (52.0%) due to other reasons. At 1 and 5 years after default, 22.8% and 12.2% of surviving patients, respectively, were smear/culture positive. Smear-positivity (HR 2.86, 95% CI 1.05-7.80), previous TB (HR 2.99 95% CI 1.27-7.04) and offtreatment resistance (HR 5.77, 95% CI 1.74-19.18) increased risk of TB-related mortality. Disabled (HR 7.97, 95% CI 1.01-62.63), retired (HR 17.10, 95% CI 1.71-171.41), homeless (HR 2.36, 95% CI 1.61-4.78) and imprisoned people (HR 34.01, 95% CI 2.92-398.11) were at increased risk of all-cause mortality, whereas targeted case detection by medical personnel lowered this risk (HR 0.19, 95% CI 0.56-0.61).

Among defaulters, TB-related mortality is not associated with demographic factors, which influence all-cause mortality instead. Infectiousness of defaulters remains high, though decreases with time. Funded by ESF grant No. 8188.

203 Is multidrug-resistant TB more common in children? An analysis of surveillance data
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Background: Despite the limited availability of data and the possible bias from selective diagnostic testing, results indicate that MDR-TB in children is no less frequent than in adults in many settings. Of particular concern is the link between children and MDR-TB in southern African countries with high HIV prevalence.

Results: In all 5 countries a significant positive association between MDR-TB and HIV was documented (range OR: 1.5-2.6, p value <0.05 for all). Overall, combining data from all countries (6,455 TB cases tested for HIV and MDR-TB) the odds of having MDR-TB among HIV-positive patients were 110% higher than among HIV-negative patients (pooled OR: 2.1, 95%CI: 1.2-3.3), OR consistent across countries (P=19.2%) and the difference was statistically significant.

Conclusions: The association between HIV and MDR-TB epidemics found in these countries is alarming. Patients with dual HIV/MDR-TB infection require complex treatment with anti-retrovirals and toxic, expensive anti-TB drugs. The likelihood of successful outcome is low and transmission of MDR-TB to others is high. Urgent measures should be implemented to strengthen HIV prevention and treatment, contain the spreading of MDR-TB, and improve collaboration between HIV and TB control activities, particularly for individuals at high risk of dual infection such as people who inject drugs and those in congregate settings. Further operational research to identify the determinants and conditions leading to MDR-TB in people living with HIV is needed.
Rational use of tuberculosis drugs to prevent the development of drug resistance

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The tuberculosis (TB) drug pipeline has finally thickened and several new agents are under clinical development. We assessed risks related to the introduction of new drugs and the development of drug-resistance with the aim to support stakeholders when introducing new drugs and regimens in TB Programs. Using standardised Cochrane and PRISMA Guidelines systematic reviews were done to identify inappropriate TB regimens; the knowledge of healthcare workers (HCW) on TB regimens; and the risk of developing multi-drug resistant TB (MDR-TB) when an inappropriate regimen is used. These studies provide evidence that TB drugs are prescribed in inadequate regimens and that inadequate regimens, or the use of fluoroquinolone (FQ) for community acquired pneumonia (CAP), present an increased risk of developing MDR-TB or XDR-TB after treatment for CAP was assessed.

Background: Systemic inflammation is a potential determinant for the excess cardiovascular mortality in COPD. Endothelial dysfunction, a marker of subclinical atherosclerosis correlates with circulating inflammatory markers in stable COPD. Acute exacerbations of COPD are characterized by a transient aggravation of systemic inflammation and might be accompanied by deteriorated endothelial function.

Aim: We aim to assess endothelial dysfunction and systemic inflammation during acute exacerbations of COPD and after clinical restitution.

Methods: We enrolled patients admitted to our hospital due to an acute exacerbation of COPD. Study related procedures comprised spirometry, measurement of systemic inflammatory markers (i.e. C-reactive protein [CRP] and leukocyte count) and endothelial dysfunction by means of the flow-mediated dilatation technique.

Results: We recruited 28 patients (female: n=20) during acute exacerbation. Baseline characteristics were as follows: age: 64.8±5.9 years, BMI: 24.6±3.9 kg/m²; FEV1: 36.5±12.1, %pred. During the acute exacerbations patients showed a median CRP of 7.0 (2.0-26.0) mg/l, leukocytes of 9.7±4.3 G/l and a FMD of 6.8±3.6% indicating severe endothelial dysfunction. After confirmed clinical stability we observed a decrease of systemic inflammation (CRP: 4.0 (2.0-7.0) mg/l; leukocytes: 8.2±2.9 G/l) and a simultaneous improvement in FMD (10.6±3.4%).

Conclusions: Our results indicate endothelial dysfunction in COPD patients. Furthermore, acute exacerbations deteriorate endothelial function in COPD, probably via aggravation of systemic inflammation.
Bone radio density (BRD) was lower in COPD patients than smokers or non-smoker controls (163.4±48.6 vs 185.1±89.8 vs 213.8±50.2 HU, p<0.001). In the COPD group, BRD correlated with age (r=0.256, p<0.001), FEV1% predicted (r=0.367, p<0.001), FEV1/FVC (r=0.31, p=0.002), BMI (r=0.231, p<0.001), mMRC (r=0.089, p=0.006), BODE (r=0.116, p<0.001), exacerbation rate (r=0.088, p=0.006), dyspnea (r=0.126, p<0.001). Agatston score (r=0.252, p<0.001) and MESA score (r=0.197, p<0.001). However, BRD in COPD patients did not correlate with pack years smoked (p=0.398) or decline in FEV1 (p=0.546). Comorbid heart failure in COPD patients was associated with lower BRD (0.1±1.5 vs 165.1±48.5 HU, p=0.025).

We show in a COPD cohort that low bone radio density is associated with adverse clinical features and with high CACS.

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Coronary artery calcification in COPD is associated with adverse functional assessment and mortality

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COPD is associated with coronary artery disease (CAD). Coronary artery calcium score (CACS) can identify and stratify risk in CAD. We evaluated CACS and its relationship with clinical outcomes using non-gated chest CT in a well-characterised cohort of COPD patients (ECLIPSE study).

CACS (Agatston score) was assessed in 946 patients (COPD n=476, FEV1% predicted 48.7±14.1, age 63.4±2.4 yrs; Smokers controls: n=199, FEV1% predicted 110.0±11.0 yrs; Non-smokers controls: n=71, FEV1% predicted 114.4±13.8, age 54.7±7.0 yrs). CACS was higher in COPD patients than smokers or non-smoker controls (415.6±89 vs 141.7±39.6 yrs vs 66.6±22.8 yrs, p<0.001). When corrected for pack years, the calcium score percentile based on age, sex and smoking was greater in the COPD group (56.4±16 vs 40.5±22 vs 30.5±15, p<0.001). CACS in the COPD group correlated with age (r=0.40, p<0.001), pack years (r=0.20, p<0.001), function (6 minute walking distance (r=0.13, p<0.001) and mMRC dyspnoea score (r=0.196, p<0.001) and some biomarkers (Interleukin 13 vs 0.18, p<0.001; Clara Cell secretory protein16 R=0.18, p<0.001; Surfactant Protein-D vs 0.11, p=0.006) but not with emphysema (% low attenuation areas), FEV1% predicted, exacerbation frequency or decline in FEV1. CACS and calcium percentile corrected for pack years were higher in those who died during 3 years follow up (65.3±SD23 vs 39.6±60, p<0.003 and 68.4±46 vs 57.2±15, p=0.027) and a significant association between high CACS and mortality was confirmed by a Cox Proportional Hazard model. Thus in a cohort of COPD patients higher CACS was associated with poor function and increased mortality.

Supported by GlaxoSmithKline (SCO104960, NCT0292552).

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Clinical impact of anaemia in patients with chronic obstructive pulmonary disease: Results from ECLIPSE study

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Anaemia is common in chronic diseases, associated with poor outcomes. In COPD, data on the effects of anaemia are scarce and inconclusive. We assessed the prevalence, incidence, clinical impact of anaemia in the ECLIPSE study,a large well characterised COPD cohort.

Methods: We included patients with haemoglobin (Hb) value at baseline and at least one measurement during 3-years follow-up. Analyses were performed. The study population was divided into three groups, smokers, never smokers and non-smokers smokers, and current or former smokers.

Results: In 2997 COPD patients (63.7% men, 65% current or former smokers, and 168 current or former smokers, 162 never smokers, 162 former smokers, 162 never smokers). Individuals with diabetes were excluded from this study. The CML and sRAGE levels in COPD patients were measured by using a sandwich enzyme-linked immunosorbent assay (ELISA) in 146 subjects, aged ≥ 65 years, divided into five groups: 58 with CHF, 23 with COPD, 29 with CHF and COPD and 36 controls (18 current or former smokers, and 18 never smokers). In the control group, the CML and sRAGE levels were higher in CHF patients than in controls [CML: 1.9 (1.5-2.4) vs 1.6 (1.4-2.0) ng/mL; sRAGE: 0.51 (0.3-0.8) vs 0.41 (0.3-0.5) ng/mL; p<0.01]. By contrast, both CML and sRAGE were not different between the group with COPD and that with CHF/COPD were compared with controls (p<0.05). CML and sRAGE positively correlated with N-terminal proBNP (N-Pro BNP) in the three patient groups: CHF (r=0.43, p<0.001), COPD (r=0.77, p<0.001) and in CHF/COPD (r=0.60, p<0.01).

In conclusion, subjects with CHF have high plasma levels of CML and sRAGE. The binding of the receptor for advanced glycation end products (RAGE) with its ligands begins a cellular activation and an inflammatory signal amplification in different diseases. We determined the plasma levels of Neopterin-cobalamin/iron (CML) and soluble RAGE (sRAGE) in chronic heart failure (CHF) patients, in cases with chronic obstructive pulmonary disease (COPD) and in healthy controls. We also investigated the associations between these biomarkers and the clinical and functional characteristics of the study populations. The CML and sRAGE plasma levels were measured by using a sandwich enzyme-linked immunosorbent assay (ELISA) in 146 subjects, aged ≥ 65 years, divided into five groups: 58 with CHF, 23 with COPD, 29 with CHF and COPD and 36 controls (18 current or former smokers, and 18 never smokers). The CML and sRAGE plasma levels were measured by using a sandwich enzyme-linked immunosorbent assay (ELISA) in 146 subjects, aged ≥ 65 years, divided into five groups: 58 with CHF, 23 with COPD, 29 with CHF and COPD and 36 controls (18 current or former smokers, and 18 never smokers). Individuals with diabetes were excluded from this study. The CML and sRAGE levels were higher in CHF patients than in controls [CML: 1.9 (1.5-2.4) vs 1.6 (1.4-2.0) ng/mL; sRAGE: 0.51 (0.3-0.8) vs 0.41 (0.3-0.5) ng/mL; p<0.01]. By contrast, both CML and sRAGE were not different between the group with COPD and that with CHF/COPD were compared with controls (p<0.05). CML and sRAGE positively correlated with N-terminal proBNP (N-Pro BNP) in the three patient groups: CHF (r=0.43, p<0.001), COPD (r=0.77, p<0.001) and in CHF/COPD (r=0.60, p<0.01).

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P214
Investigation of neuromuscular transmission in patients with chronic obstructive pulmonary disease: A preliminary report
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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is accepted as a pulmonary disease that affects all systems of the body. There is growing awareness about systemic inflammation and cardiovascular, neurologic, psychiatric, and endocrine comorbidities associated with COPD. Various studies of patients with COPD affecting both the central and peripheral nervous system, either sequentially or simultaneously, have been reported by electrophysiologic studies. Single-tiber electromyography (SFEMG) is an electrophysiological technique of great value in the assessment of neuromuscular disorders. The aim of study was to delineate any dysfunction of NMT by SFEMG in COPD patients.

Methods: Sixteen COPD patients without evident clinical signs of muscle involvement and 16 healthy controls underwent SFEMG. Ten to 20 different potential pairs were recorded and individual jitter values calculated. The results obtained from patients were compared with those from the controls.

Results: Of 201 individual jitter values of the patients, 15 (7.4%) were abnormally high, whereas only 1/65 (0.6%) jitter values from normal subjects were abnormal. Abnormal NMT was found in 6/16 (37.5%) patients, but in none of the control subjects.

Conclusion: Our study demonstrates that subclinical NMT abnormality is present in COPD patients. To our knowledge, this is the first study to explore NMT abnormality in patients with COPD, and we believe that further comprehensive studies are needed to clarify whether patients with NMT abnormality have different clinical/laboratory characteristics and prognosis than patients with normal NMT.

P215
The impact of bacterial colonisation on airway inflammation in stable COPD
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Culture-independent approaches are increasingly used for diagnostic microbiology. Quantitative PCR (qPCR) enables accurate assessment of bacterial load in sputum. We hypothesised that the degree of airway inflammation relates to bacterial load in colonised stable COPD patients and may increase over time. Sputa prospectively collected from stable patients in the London COPD Cohort were analysed using qPCR, to detect H. influenzae, M. catarrhalis and P. aeruginosa. The samples were cultured and qPCR was done for the above three pathogens. The results were normalised and expressed as maximum bacterial load (MBL) per sample.

Mean age was 71.1 years (SD 8.0), FEV1 1.3L (0.5), FEV1 predicted 51.0% (17.5).

There was no change in bacterial load or airway inflammation over time (table 1). Bacterial load and airway inflammation are stable over time in successive samples. Increasing bacterial load, identified by qPCR, is associated with airway inflammation in stable COPD, suggesting the importance of airway infection in COPD pathogenesis.

Table 1. Changes in bacterial load and airway inflammation over time

<table>
<thead>
<tr>
<th></th>
<th>Stable visit 1</th>
<th>Stable visit 2</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Total bacterial load (Log10, copies/ml)</td>
<td>7.4 ± 3.5</td>
<td>7.5 ± 3.3</td>
<td>0.76</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>4043(5659)</td>
<td>3979 (4421)</td>
<td>0.26</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>2873 (3461)</td>
<td>2919 (3566)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

P216
The evaluation of sensory gating with P50 paradigm in chronic obstructive pulmonary disease
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Objective: Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistant airflow limitation in the airway. It is major cause of morbidity and mortality throughout the world. It is well known that COPD is associated with significant systemic abnormalities. Numerous neurologic involvement like cerebrovascular diseases, motor neuron diseases and cognitive impairment has been reported in COPD. Cognitive dysfunction is usually associated with hypoxia or hypercarbia in these patients. We aimed to investigate the relationship between arterial blood gas analysis and sensory gating test parameters with P50 sensory gating in COPD patients.

Methods: 25 male (mean age 65.16±9.95 years) patients with COPD and 17 healthy male controls (61.52±6.33 years) were included into the study. The diagnosis of COPD was defined according to GOLD guidelines. N100 measurements were taken, the suppression percentage of P50 and N100 was calculated.

Results: COPD patients showed significantly less P50 and N100 suppression when compared to healthy controls. P50 suppression percentage mean was 43.82±30.23 in COPD patients, and 65.21±15.77 in controls (p=0.012). N100 suppression percentage was 35.56±8.28% in COPD patients and 55.63±31.66 in controls (p=0.042).

Conclusion: We found reduced P50 and N100 suppression in COPD patients. This impairment is more clear in hypoxic COPD patients. Hypoxia leads to a decrease in cerebral perfusion and an impairment of some cognitive abilities. P50 sensory gating may be considered as a marker for cognitive decline in COPD patients. To our knowledge, this is the first P50 sensory gating study in COPD.

P217
Oxidative stress, inflammation and endothelial function in patients with combined flow of chronic obstructive pulmonary disease and arterial hypertension
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Objective: To study oxidative stress, inflammation and endothelial function in patients with combined flow of chronic obstructive pulmonary disease (COPD) and arterial hypertension (AH).

Design and methods: 106 patients with COPD and combined flow of COPD and AH were examined. The first group was formed by patients with combined flow of COPD and AH (n=61), the second by patients with COPD (n=45). All patients underwent clinical examination, measurement of C-reactive protein (CRP), ultrasound estimation of endothelium-independent vasodilation (EINVD). As oxidative and proinflammatory stress markers – the levels of spontaneous and iron induced aldehydehydrolephinehydrazine’s (SAPH and ISAPH) and carboxyhydrolephinehydrazine’s (SCPH and ICPH) were measured.

Results: Patients with COPD and AH had higher levels of CRP (7,1 mg/l; CI 95% 5,21 -9,22) while comparing with COPD group - CRP (5,1 mg/l; CI 95% 2,79-7,56; p=0,03). The patients with combined flow had impaired EINVD (7,5%; CI 95% 4,19-10,99) than COPD only (15.7%; CI 95% 11,79-19,63; p=0,001). The levels of SAPH (0,062 units/g; CI 95% 0,044-0,079) and SCPH (0,041 u/g; CI 95% 0,027-0,055) in COPD and AH group were also greater than COPD only - SAPH (0,042 u/g; CI 95% 0,022-0,051; p=0,009) and SCPH (0,032 u/g; CI 95% 0,019-0,042; p=0,025). The patients with combined flow had higher levels of ISAPH (0,212 u/g; CI 95% 0,187-0,242) and ICPH (0,124 u/g; CI 95% 0,014-0,148) comparing with COPD patients - ISAPH (0,143 u/g; CI 95% 0,118-0,168; p=0,001) and ICPH (0,07 u/g; CI 95% 0,075-0,112; p=0,001). The impairments found in EINVD may lie in the increase of oxidative stress and systemic inflammation.
P219
The absolute risk of osteoporotic fractures according to the program of FRAX patients with chronic obstructive pulmonary disease
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Bone loss may be asymptomatic, and the first sign of osteoporosis are bone fractures. Assessment of absolute risk of osteoporotic fractures by using FRAX method in patients with COPD using the FRAX computer program is of great practical interest.

Objective: To examine the absolute risk of osteoporotic fractures by using FRAX method in patients with COPD.

Methods and materials: We examined 108 patients with COPD. The study group comprised men with long smoking history. Mean age 60.2±5.5 years. The study of bone mineral density (BMD) of lumbar spine and proximal femur was performed by X-ray absorptiometry at the densitometer “Lunar DPX-NT”. Evaluation of ten osteoporotic fracture risk was calculated using the computer program FRAX. To calculate the Risk methodology used FRAX T-score femoral neck index (RN) of the digital volume pulse in response to salbutamol (RISALB) and serum endotelin-1 (ET-1) were used to assess ED.

Results: The assessment of absolute risk (AR) of all hip fracture patients were divided into 3 groups (AR <1, AR 1-3 and AR> 3). The maximum number of patients with high risk of hip fracture observed among patients with COPD stage 4 - 84.6% (p <0.05). In evaluating the 10-year probability of any major osteoporotic fracture patients were divided into 3 groups (AR <10, AR 10-20 and AR> 20). AR 10-20 major fractures in the stages of COPD was observed in 15.68%, of patients with stage 4 COPD in 30.8%. These figures are significantly higher than the corresponding figures in patients with COPD stage 2 (p <0.05).

Conclusion: Assessment of absolute risk of fractures provides useful information to forecast the fracture in patients with COPD.

P220
Arterial stiffness and endothelial dysfunction in stable COPD patients
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Cardiovascular disease is common in COPD patients and is associated with poorer prognosis. Arterial stiffness (AS) is a validated measure of cardiovascular risk. Aim: to assess AS and endothelial dysfunction (ED) in COPD patients, to determine their association with other clinical and cardiologicalpulmonary functional parameters.

Methods: We enrolled 41 COPD patients (64.5±7.6 yrs, FEV1 37.7±14.1% and 34 normal control subjects (CS). Lung function, blood gases, six-minute walking distance (6MWD), nocturnal pulseoximetry, serum C-reactive protein (CRP) were measured. Assessment of AS was performed by use of digital plethysmography (Pulse Trace PCA 2 Medical). Change in reflection index (RI) of the abdominal obesity measured as an increased WC is associated with COPD. The abdominal obesity measured as an increased WC is associated with COPD. The abdominal obesity measured as an increased WC is associated with COPD.

Results: In COPD patients stiffness index (SI) was higher than in CS: 11.3±3.3 vs 6.9±4.0 mmHg, p<0.05. There were significant correlations of SI with FEV1 (r=0.40), BMI (r=0.53), 6MWD (r=0.53), pulse during sleep (r=0.50), CRP (r=0.47). RISALB was lower in COPD patients than in CS (1,15±0-10% vs 11,50±6-19%, p<0,05) and decreased according to COPD stages: GOLD II 5,85±15-13%; GOLD III 1,65±7,1-10,35%; GOLD IV 0.0-2%; p<0.05. The ET-1 levels were elevated in COPD patients and correlated with RISALB (r=0.46, p=0.03). RISALB was significantly associated with mean nocturnal SpO2 (r=0.38), DLCO (r=0.45).

Conclusion: AS and ED are significantly impaired in COPD patients. Decreased FEV1, 6MWD and systemic inflammation were associated with AS and ED. Hypoxemia, elevated ET-1 level and decreased DLCO have an association with both AS and ED.

P221
Evaluation of carotid intima media thickness in COPD patients
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Background: Chronic obstructive pulmonary disease (COPD) and atherosclerosis may occur due to similar risk factors and have a significant cause of morbidity and mortality. In this study we assess the relationship between COPD and atherosclerosis; carotid intima media thickness (CIMT) of COPD patients and healthy individuals with normal BMI and metabolic parameters compared.

Methods: 2230 participants aged between 18 - 96 years diagnosed with COPD according to clinical features and pulmonary function tests study the test, 47 healthy controls while 1124 exclusion criteria were associated with COPD. The pulsed Doppler ultrasound was performed for the assessment of CIMT to all participants.

Results: Mean CIMT in COPD group and control group were 0.79±0.16 mm and 0.67±0.1 mm, respectively (p <0.001). In logistic regression analysis that made to determine the parameters affecting atherosclerotic, it was found that CIMT was related to age with direct proportion (p = 0.004) and to FEV1% with inversely proportion (p = 0.029).

Conclusion: Persistent low-grade systemic inflammation in COPD and atherosclerotic disease may possibly have been reported a factor in both pathologies. Early atherosclerosis and cardiovascular risks in adults with COPD increases independent of other risk factors. CIMT which shows direct proportion with age and inverse proportion with FEV1% is a non-invasive, easily applicable and cheap method that can be used in determining the risk of atherosclerosis.

P222
Myocardial injuries in patients with chronic obstructive pulmonary disease
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The purpose of this study is to determine a value of computer electrocardiography (CECTG) in myocardial injuries revealing in patients with obstructive pulmonary disease (COPD) and to determine hypoxemia role in its developing.

Methods: We examined 62 male patients with COPD (15 – moderate, 28 – severe, 19 – very severe stages). CECTG method has been in addition to common physical examination. This technique allows to evaluate condition of all heart’s portions using multielectrode belt consisted of 65 unipolar leads, which makes it possible to consecutively applied to the frontal and right side of the chest, abdomen and the backside of the chest. Therefore, amount of monopolar leads increases to 260 electrocardiographs. That allows estimating panoramic view of electrical field of the heart. 10 myocardial regions were detected with estimating terminal part of QRS complexes. Patients have been divided into 2 groups by PaO2 level: first group (n=29) with PaO2<80 mmHg, second group (n=33) had PaO2>79 mmHg.

Results: CECTG method revealed significant generalization of the myocardial injuries in right ventricle as well as in the left one in patients with COPD (79.6%). Myocardial injuries were detected mostly in right ventricle area and posterioro- atragmatic area of left ventricle. In compare with standard ECG CECTG revealed myocardial injuries in 1.6 times often. Myocardial injuries in right ventricle area in patients with COPD has been detected significant more often (p<0.01) than in patient without hypoxemia.

Conclusion: CECTG method revealed myocardial injuries in right and left ventricle in 79.8% patients with COPD. Hypoxemia takes a definite role in injuries forming.

P223
The metabolic syndrome (MetS) in patients with chronic obstructive pulmonary disease (COPD) and its association with airway obstruction
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Background: The metabolic syndrome (MetS) is common in patients with COPD and shows part of the so called chronic systemic inflammatory syndrome. Aim: to investigate the presence of MetS in patients with COPD and healthy subjects and to assess the association of its components with airway obstruction.

Methods: We performed a cross-sectional study with 244 participants (mean age 60.5±9.5 years) divided into 2 groups: 141 subjects with COPD and COPD and 103 healthy matched controls. We measured the characteristics of the syndrome as stated by the IDF definition. Anthropometry and biochemical tests were performed, as well as spirometry to define the stage and severity of the disease.

Results: 41.8% of the COPD patients presented 3 or more features of the MetS versus 39% in the control group. Using multiple linear regression analysis we defined that the main predictor of MetS was the increased waist circumference (WC) (p=0.263, p=0.022). Among the MetS subjects, COPD patients had significantly higher WC compared to the controls (111.0±17.8 vs 104.0±12.4 cm, p=0.032). In COPD subjects with the syndrome BMI, WC, SHP DHP, fasting blood glucose and triglycerides were significantly higher compared to those without MetS (p<0.01 for all), while HDL-cholesterol was significantly lower (p=0.017). In patients presenting MetS we also found a significant negative correlation between WC and FVC and FEV1% predicted (r=-0.291, p=0.011 for FVC and r=-0.327, p=0.004 for FEV1, respectively).

Conclusion: The present study suggests that the MetS is frequent among patients with COPD. The abdominal obesity measured as an increased WC is associated with the airway obstruction.

P224
Increased sympathetic nerve activity in COPD associated with elevated morbidity and mortality
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Chronic obstructive lung disease (COPD) is characterized by systemic effects. Studies using microneurographic recordings and heart rate variability proved an increase in sympathetic nerve activity in COPD, which possibly contributes to progression and severity of the disease. Aim of this study was to investigate in a follow-up survey if increased sympathetic nerve activity is associated with elevated morbidity and mortality in patients with COPD.

Methods: Evaluations of the sympathetic nerve activity via microneurographic recordings were performed in two studiesa in 1998/99 and 2005/06 at the Univer-
sity Medical Center Göttingen, including an overall of 20 patients with COPD (as published in AJRCCM 2001;164:597 and ERJ 2008;32:387). The study participants or their relatives were contacted via a telephone survey in the year 2010/11 and asked for the number of hospitalizations or date of decease of the participant. The results of the survey were correlated with the collected data of the past two studies.

**Results:** COPD patients who were hospitalized or deceased (n=12) compared to live patients without hospitalizations (n=8) show a significant increase in muscular sympathetic nerve activity (MSNA) in bursts/min (60.3 to 40.5, p=0.022), furthermore lower values in FEV1 (% pred) (39 to 54, p=0.035) and lower pO2 (69.12 to 78.04, p<0.025).

**Conclusion:** As well as other characteristics of COPD (decrease in FEV1, pO2) the increase in sympathetic nerve activity is likely to be associated with elevated morbidity and mortality in patients with COPD.

*Supported by Deutsche Forschungsgemeinschaft (DFG) An 2602/1-1 An 2602/1-1.

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**55. Asthma: risk factors and effect of anti-IgE**

**P225**

Assessment of long-term omalizumab treatment in severe allergic asthma

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**Objectives:** Several clinical studies have demonstrated omalizumab efficacy in patients with severe allergic asthma, but the treatment period has always been relatively short (4-12 months). There are a few data long term omalizumab therapy. We aimed to assess the long-term clinical and functional effectiveness of the omalizumab treatment in severe allergic asthmatic patients.

**Methods:** Medical registries were used to evaluate the 0, 4, 12 and 36 months effectiveness of omalizumab treatment. 26 females (female/male=21/5) with severe allergic asthma, uncontrolled despite GINA Step 4 therapy. Effectiveness outcomes included spirometry, level of asthma control which evaluated by asthma control test (ACT), systemic glucocorticosteroid (oCSS) use, emergency room (ER) visits and hospitalizations for severe exacerbations.

**Results:** The mean age was 47.6±13.9 and duration of allergic asthma 22.7±10.1 years. Total IgE serum levels was 322±89.7 IU/mL. Mean duration of omalizumab treatment was 40.8±8.2 months. FEV1 improved significantly at all time points versus baseline (p<0.05). The level of asthma control as evaluated by ACT was significantly improved after treatment (p<0.05). We determined significant reduce numbers of exacerbation (p<0.05), emergency visits (p<0.05), hospitalizations (p<0.05), sGCS (p<0.05) and SABA (p<0.05) use at 36 months.

**Conclusion:** This study showed that long-term therapy with omalizumab for up to 3 years was well tolerated with significant improvement of both symptoms and function. For this reason, suggesting that administration of omalizumab for longer than 12 months could be beneficial for responders patients.

**P226**

Omalizumab improves lung function in severe persistent allergic (IgE-mediated) asthma patients: Pooled data from 5 UK centres

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Omalizumab is an effective add-on therapy for patients with severe persistent allergic (IgE-mediated) asthma. However, in the UK there are limited data reporting on the real-life effectiveness of omalizumab therapy on patient outcomes, particularly with regard to effect on lung function. We retrospectively reviewed outcomes in severe allergic asthmatic patients receiving omalizumab at 5 South West UK centres (Exeter, Plymouth, Bath, Taunton, Torbay). Data were compared for 12 months pre-omalizumab vs 16 weeks and most recent assessment (last 12 months) post-omalizumab initiation. Patients (n=51); age 17–69 years; received omalizumab for an average of 788 days (range: 190–1569). 41/51 (80%) patients responded to treatment at 16 weeks and are included in this analysis. Post omalizumab initiation, mean FEV1 (L/min) improved from 1.9 pre-omalizumab to 2.3 (16 weeks) and 2.1 (most recent). Mean maintenance oral corticosteroid (OCS) dose pre- and post-omalizumab was 22.7 and 8.9 mg/day, respectively. Overall mean [SD] scores for AQLQ and ACT improved after 16-weeks’ treatment: +1.6 [0.86] and +3.0 [9.5], respectively. Reductions were seen post-omalizumab in hospital admissions/bed days, accident & emergency (A&E) and GP visits were seen post-omalizumab (Table). These results demonstrate omalizumab’s effectiveness in improving lung function and other clinical/patient-reported outcomes in severe persistent allergic asthma patients in a ‘real-life’ clinical setting.

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**P227**

Long-term effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: Real-life data from 3 UK centres

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For patients with uncontrolled severe persistent allergic (IgE-mediated) asthma, omalizumab is an effective add-on therapy. However, limited data are available reporting on long-term effectiveness of omalizumab in UK clinical settings. In a previous pooled analysis using data from 3 UK centres, healthcare utilisation substantially reduced and patient reported outcomes improved post-omalizumab in patients with severe allergic asthma (mean treatment duration: 982 days; range: 112–3839). Using the same patient cohort, data were compared for 2 years pre-omalizumab and for most recent assessment post-omalizumab initiation, to determine if improvements were sustained with longer-term treatment. Patients (n=50; age 18–74) received omalizumab for mean of 1318 days (range: 238–4217). 38/50 patients were responders at 16 weeks. Reductions in hospital admissions/bed days, accident & emergency (A&E) and GP visits were seen post-omalizumab (Table).

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**P228**

Real-life effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: Pooled data from 4 UK centres

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Omalizumab is an effective adjunctive therapy for patients (age ≥6 years; European Union), with uncontrolled severe persistent allergic asthma. To evaluate the effectiveness of omalizumab on real-life outcomes in UK clinical settings, we retrospectively reviewed records from severe allergic asthma patients who were receiving omalizumab (150-600 mg q4wk or q2wk) at 4 UK centres. Data were compared for 12 months (Plymouth) or 2 years (Chertsey; Bradford; Colchester) pre-omalizumab and for the most recent assessment following omalizumab initiation. Patients (n=80; age 14–74 years) received omalizumab for an average of 1190 days (range: 112–4217). 82% patients responded to treatment at 16 weeks. There was a decrease in hospital admissions/bed days, ICU admissions, and accident & emergency (A&E) and GP visits (Table) and in oral corticosteroid (OCS) use post omalizumab initiation; mean maintenance dose of OCS pre- and post-omalizumab was 14.6 and 4.7 mg/day, respectively. Mean [SD] improvements were also observed in Asthma Quality of Life Questionnaire (AQLQ) score (+1.6 [1.4]) and...
P229
Efficacy and safety of omalizumab in real-life practice in India
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A 2-week, post-marketing study to assess the efficacy and safety of omalizumab in an Indian population is ongoing; we present interim 16-week data. This is an open, uncontrolled, observational, post-marketing study in 72 patients (mean age 51.7±14.9 y) with moderate-to-severe persistent allergic asthma. Endpoints are asthma exacerbations, work/college days missed, hospitalizations, and medication use. Safety and tolerability were carefully assessed. Qualitative and quantitative variables are analyzed using Chi-Square tests and paired t-tests, respectively. All parameters are compared from baseline to week 16 of omalizumab treatment.

35.9% of patients experienced ≥1 exacerbation at baseline. This reduced significantly to 15.4% at week 16 (p=0.046). The proportion of patients missing college/work and requiring unscheduled hospitalizations also reduced significantly with mean values of 0.85 (0.3 vs. 2.5; 95%CI -1.4 to -0.2; p=0.015). ACT scores improved significantly by 5.3 (10.1 vs. 15.4; 95%CI 2.4 to 8.4; p=0.002); FEV1 improved by 0.51L (1.23 vs. 1.74; 95%CI 0.38 to 0.64; p<0.000), and mean ICS dose decreased by 199g (700.8 vs. 501.1 g; 95%CI -205.4 to -125; p<0.028). One gastrointestinal adverse event of moderate intensity (suspected drug related) was reported during the study and resolved with concomitant medication.

Omalizumab is an effective and safe therapeutic option in Indian patients with uncontrolled allergic asthma despite high-dose ICS plus LABA.

P230
Natural history of IgE sensitisation to food allergens in a cohort of adults
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The prevalence of sensitisation to food allergens is reported to be unchanged or to decrease in adults in longitudinal studies. No longitudinal studies examine omalizumab (14.1% to 12.5%, p<0.039; 23.7% to 26.6%, p<0.021, respectively). ACQ scores significantly improved with omalizumab; composite scores decreased by 4.2 (14.8 vs. 10.6, 95%CI -6.5 to -1.9; p<0.001) and mean scores by 0.8 (0.3 vs. 2.5; 95%CI -1.4 to -0.2; p<0.015). ACT scores improved significantly by 5.3 (10.1 vs. 15.4; 95%CI 2.4 to 8.4; p=0.002). FEV1 improved by 0.51L (1.23 vs. 1.74; 95%CI 0.38 to 0.64; p<0.000), and mean ICS dose decreased by 199g (700.8 vs. 501.1 g; 95%CI -205.4 to -125; p<0.028). One gastrointestinal adverse event of moderate intensity (suspected drug related) was reported during the study and resolved with concomitant medication.

Omalizumab is an effective and safe therapeutic option in Indian patients with uncontrolled allergic asthma despite high-dose ICS plus LABA.

P231
Analysis of IL-6 function in transmammary asthma protection induced by Acinetobacter Iwoffii
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Introduction: It has been shown in a mouse model that treatment of pregnant mice with the farm-derived bacterium Acinetobacter Iwoffii F78 protects the progeny of these mice against experimental induced asthma but until now it is not clear how the protective effect is transmitted from the mother to the fetus.

Aim and subjectives: To find out if the upregulation of IL-6 during the treatment of pregnant mice with Acinetobacter Iwoffii is involved in transmitting the asthma-protective effect from the mother to the offspring.

Methods: To analyze the role of IL-6 in transmammary asthma protection female IL-6 KO mice in a Balb/c background (IL-6 +/-) were treated with Acinetobacter Iwoffii F78 and mated to wildtype males (IL-6 +/-). The heterozygous offspring (IL-6 +/-) was then sensitized and challenged with OVA to analyse the asthmatic phenotype. To rule out that the loss of one copy of IL-6 affects the asthmatic phenotype without A. Iwoffii treatment the asthmatic phenotype of IL-6 KO and IL-6 heterozygous mice was additionally analysed in an acute asthma model.

Results: In the acute model IL-6 KO mice exhibit an exacerbated asthma phenotype with increased numbers of eosinophils in the BAL and augmented concentration of Th2 cytokines compared to the wildtype. The heterozygous mice show the same phenotype as wt mice. In the prenatal model the offspring of IL-6 KO female treated with A. Iwoffii display a strong protective phenotype.

Conclusions: IL-6 might be involved in transmammary asthma-protection induced by the farm-derived bacterium Acinetobacter Iwoffii.

P232
Allergyprotective effects of Staphylococcus scuiri in a house dust mite (HDM) model of allergic airway inflammation
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Background: Recently, epidemiological studies revealed a specific association between Staphylococcus scuiri exposure and reduced asthma prevalences.

Aim: To investigate the influence and role of S. scuiri, a Gram-positive bacterium, on allergen-induced sensitization and airway inflammation in a murine model with a mixed phenotype (with eosinophil and neutrophil inflammation) using a clinically relevant allergen (HDM model).

Methods: Mice were treated intranasally with S. scuiri three times a week for 7 weeks and repeated intranasal exposure to HDM extract. Histological examination of inflammatory cells as well as production of related cytokines and chemokines were measured.

Results: The application of S. scuiri strongly inhibited the generation of HDM extract-induced airway inflammation. Analyses of bronchoalveolar lavages showed a reduction of both, eosinophil and neutrophil numbers, in comparison to control animals. The reduction of eosinophils correlated with a reduction of IL-5, and of goblet cell hyperplasia. The chemokines Rantes, MIP-2, and KC, the key chemokines in the induction of eosinophils and neutrophils into allergic tissue, were markedly reduced.

Conclusions: Administration of S. scuiri to mice challenged with HDM extracts protects them from the development of airway inflammation and associated pulmonary pathology.

P233
Balance disturbances in asthmatic patients. An unrecognized link between asthma, breds and labyrinth
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Background: Correlations between asthma and anxiety and between anxiety and balance disorders have been repeatedly described. These observations suggest, that equilibrium abnormalities may also be present in asthmatic patients. This issue is clinically relevant because untreated postural deficits can potentially worsen the prognosis of asthma by triggering anxiety and, consequently, respiratory symptoms. This study aimed to evaluate the efficiency of postural control in asthma patients and its potential correlation with anxiety symptoms.

Methods: We compared 30 subjects with persistent, controlled asthma to 30 age- and sex-matched controls. Anxiety symptoms were evaluated using the Spielberg State-Trait Anxiety Inventory (STAI). Balance control was evaluated by dynamic posturography using measurements of the center of pressure (CoP) displacement in the latero-lateral and antero-posterior directions.

Results: The asthma group had significantly higher scores for the STAI-State (46.8±11.38 vs 38.2±13.16; t = 2.89; p<0.005) and the STAI-Trait (50.1±13.60 vs 37.9±12.67; t = 4.22; p<0.001). An analysis of covariance (using anxiety as the covariate) showed increased values for the area delimited by the CoP in asthmatic patients.

Conclusions: Balance abnormalities seem to occur frequently in asthmatic patients independently of the presence of anxiety symptoms. However, the presence of vestibular dysfunction caused by anxiety provocation may have a major impact on the prognosis of these patients. These findings suggest that disequilibrium-related complaints must be investigated in asthmatic patients, particularly in those presenting with higher levels of anxiety.
P234
Is serum cholesterol a risk factor for asthma?
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Background: Proinflammatory role of serum cholesterol in asthma has been recently explored with contradicting results. Clarity on the link between serum cholesterol and asthma may lead to newer options in planning management strategies. The objective of our study was to examine the relationship between serum cholesterol, asthma and its characteristics.

Method: Forty asthmatics and 40 normal subjects were examined cross-sectionally and their serum fasting cholesterol and serum highly sensitive C reactive protein (hsCRP) levels were measured along with other baseline investigations. All subjects were non smokers.

Results: Serum total cholesterol (mean ± SD) among asthmatics was 176.45±30.77 mg/dL as compared to 163.33±26.38 mg/dL among normal subjects (P < 0.05). This higher serum cholesterol level was found to be associated with asthma independent of age, gender, BMI, socioeconomic status and serum hsCRP levels. However the association was only modest (adjusted odds ratio 1.027 (95% CI 1.005 – 1.049) p < 0.05). There was no association between serum cholesterol and asthma characteristics like duration of illness, intake of inhaled steroids and frequency of emergency department visits.

Conclusion: Our study found a weak but statistically significant association between higher levels of serum cholesterol and asthma which is independent of age, gender, BMI, socioeconomic status and serum hsCRP. Future research is required in a larger population to substantiate above association and its clinical implications.

P235
Climate change: The impact of different pollen burden on hay fever prevalences
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The aim of the study: To compare hay fever prevalences and clinical duration in children and adolescents of the same region in the conditions of different pollen burden.

Material and methods: The study conducted in seasons of 2010 and 2011. The special allergological questionnaires were completed. Pollen burden count was assessed by the standard method. Correlation between intensity of clinical manifestations and meteorological factors like average temperature, atmospheric moisture capacity and precipitations were determined. Meteorological data were obtained in the Civil Aviation Meteorological Station of Astana airport.

Results: We compared two different pollen loads, two consequent pollen seasons of 2010 and 2011. Due to unusually warm April of 2011 with average temperature more than 17°C, a great shift in polleniation duration and intensity ascertainment. The total pollen load in August 2010 was from 14 to 37 pollen grains per one liter3, whereas in the same period in August 2011 it varied from 31 to 64 pollen grains per one liter3. Totally 467 patients with hay fever were examined. In comparison to 2010, the season of 2011 showed high incidence of first diagnosed hay fever cases (18.2% instead of 17.3%, P < 0.001) and increase of morbidity rate from 4.3% to 7.4%, (P<0.01) in young age children. Pollen asthma incidence increased from 26.8% to 42.4%, (P<0.001) and the incidence of dermatological symptoms increased from 24.0% to 29.8%, (P<0.05). The consultation rate increased with the atmospheric moisture capacity higher than 42% and with temperature above 31.0°C.

Conclusions: Climate change has a great influence on hay fever clinical peculiarities in children and adolescents.

P236
Association between body mass index and asthma, rhinitis and eczema in Chinese school children
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This study aimed to investigate the association between the prevalence of allergic diseases in children and body mass index (BMI). 10338 Chinese children (5095 boys and 5243 girls, aged 6-18 years) were assessed using an ISAAC questionnaire. BMI was calculated as weight over height squared. The World Health Organization (WHO) defined overweight children as those with BMI above the 85th percentile. Overweight and obese children were defined as BMI > 85th percentile and BMI > 95th percentile, respectively. Systolic and diastolic blood pressures were recorded using a mercury sphygmomanometer. The prevalence rates of asthma, rhinitis and eczema in these children and risk factors of asthma and allergies in Chinese children including high level of air pollution were examined. The prevalence rates were higher in boys compared to girls (wheezing ever 6.6 vs 4.9; exercise-induced wheeze 3.4 vs 3.2; asthma ever 1.5 vs 0.8; ever rhinitis 15.4 vs 12.2; current rhinitis 11.1 vs 8.3; hay fever ever 4.3 vs 3.8; chronic rash ever 2.7 vs 2.2; and eczema ever 12.4 vs 10.7). The prevalence rates were lower in Chinese children living in Hong Kong (wheezing ever 5.7 vs 13.0; asthma ever 1.1 vs 0.9; ever rhinitis 16.6 vs 10.1; current rhinoconjunctivitis 2.4 vs 2.7; and current flexural eczema 0.9 vs 4.3). These differences may be due to different early life experience and exposure including dietary and aerollergens exposure. The present study will help to add new knowledge related to the longitudinal effects of air pollution and allergies in Chinese children.

P237
Prevalence and severity of asthma, rhinitis and eczema in Chinese school children
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The prevalence of asthma has been increasing in the industrialised world over the past few decades. We studied 10824 Chinese school children (5305 boys and 5519 girls) from Shijiazhuang city in Hebei Province in China. We used ISAAC questionnaire (the International Study of Asthma and Allergies in Childhood). This major project is a baseline of a longitudinal study looking at changes in the prevalence rates of asthma, rhinitis and eczema in these children and risk factors of asthma and allergies in Chinese children including high level of air pollution. The prevalence rates were higher in boys compared to girls (wheezing ever 6.6 vs 4.9; exercise-induced wheeze 3.4 vs 3.2; asthma ever 1.5 vs 0.8; ever rhinitis 15.4 vs 12.2; current rhinitis 11.1 vs 8.3; hay fever ever 4.3 vs 3.8; chronic rash ever 2.7 vs 2.2; and eczema ever 12.4 vs 10.7). The prevalence rates were lower in Chinese children living in Hong Kong (wheezing ever 5.7 vs 13.0; asthma ever 1.1 vs 0.9; ever rhinitis 16.6 vs 10.1; current rhinoconjunctivitis 2.4 vs 2.7; and current flexural eczema 0.9 vs 4.3). These differences may be due to different early life experience and exposure including dietary and airpollergens exposure. The present study will help to add new knowledge related to the longitudinal effects of air pollution and allergies in Chinese children.

P238
Time changes in allergic rhinitis in Skopje, the Republic of Macedonia
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Aim: The aim of the study was to assess the 4-year time changes in allergic rhinitis (AR) due to the lifestyle in young adolescents in Skopje, R. Macedonia.

Methods: Two cross-sectional surveys using ISAAC Phase 3 questionnaires on AR and environmental risk factors were performed. The self-reported data from 3026 adolescents aged 13-14 yrs in the first and from 1088 adolescents in the second survey were analyzed. Pearson chi-square test was conducted in comparisons of prevalence figures between the two surveys.

Results: In 2001-2004 and 2005-2008 survey the established prevalence rates of AR were as follows, respectively: for AR symptoms “ever” 30.0 vs. 27.9%, for current AR symptoms 23.1 vs 19.9% (p=0.034), for current severe AR symptoms 2.8% vs. 2.3% and for ever-diagnosed hay fever 6.7 vs. 4.4% (p=0.007). Significantly decreased prevalence rates of frequent milk and egg intakes (68.3 vs. 62.7% and 23.6 vs. 20.3%), TV-watching time 3 hours daily (63.3 vs. 38.9%), gas cooking (12.0 vs. 9.1%) and wood/coal/soil heating (18.0 vs. 10.8%) at home, cat and dog ownership (24.1 vs. 13.5% and 27.7 vs. 22.0%) and increased ones of frequent vegetables intake (55.6 vs. 70.9%), seafood (3.4 vs. 6.2%), fast food (17.8 vs. 26.0%) and acetaaminophen (6.8 vs. 22.0%) intake as well overweight (15.2 vs. 18.1%) and older siblings (50.6 vs. 54.8%) in the two surveys were established.

Conclusion: The findings suggest a decrease in allergic rhinitis in young adolescents due to changes in their lifestyle during the 4-year study period. An effort to educate them to reduce their fast food and acetaminophen intake as well overweight should be made.

P239
Impact of adult rhinosinusitis on asthma severity
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Objectives: This study aimed to evaluate the prevalence of rhinosinusitis in patients with asthma, and to examine the interrelationship between both conditions, as well the correlation of rhinosinusitis symptoms to radiological findings.

Methods: A prospective study was carried out during the period 2009 - 2010 enrolled 280 asthmatic patients of different severity scores, all screened for any as-
suppressed remodeling

Anti-IgE antibodies inhibit the expression of amphiregulin in mast cells and allergic symptoms in children and the protective effect of pet ownership on fever (5.1% vs 4.1%, P=0.06, respectively). However, the prevalence of eczema with asthma, and its correlation with the severity of asthma for the in-
cluded patients, as well the rhinosinusitis symptoms was significantly linked to the radiological findings seen at the sinuses CT scan in this group.

Key Words: Rhinosinusitis, Asthma, severity score, CT scan.

P240 Association between pet ownership and asthma, rhinitis and eczema in Chinese schoolchildren
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Introduction: The association between pet ownership in childhood and asthma and allergies is very controversial. Our objective was to determine the effects of exposure to cat or dog allergens or both cat and dog allergens on asthma, rhinitis and eczema in a large number of schoolchildren in Shijiazhuang City in Hebei Province in China, which is part of a major longitudinal Chinese study on childhood asthma and allergies.

Body: We studied 10824 schoolchildren, boys and girls, aged 6-18 years. We used the ISAAC questionnaire and we added questions regarding pet ownership. The prevalence rates of asthma and rhinitis symptoms were higher in children exposed to cats and dogs compared with children not exposed to cats and dogs (whrever 6.1% vs 5.6%; current wheeze 2.4% vs 1.7%; exercise-induced wheezing 4.7% vs 2.9%; P<0.01; cough 12.5% vs 10.9%; P=0.05; ever rhinitis 18.9% vs 12.5%, P<0.001; current rhinitis 13.1% vs 8.8%; rhinoconjunctivitis 3.3% vs 2.1%; hay fever 5.1% vs 4.1%, P=0.06, respectively). However, the prevalence of eczema was higher in children not exposed to cats and dogs compared with those exposed to cats and dogs (11.7% vs 10.5%, P=0.07). Children exposed to dogs had higher prevalence rates of most allergic disorders compared with children exposed to cats. The present study confirms the association between pets ownership and asthma and allergic symptoms in children and the protective effect of pet ownership on eczema.

P241 Anti-IgE antibodies inhibit the expression of amphiregulin in mast cells and suppress remodeling
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Airway remodeling is a characteristic finding of severe, refractory asthma. Recent studies have demonstrated that anti-IgE antibodies have a high response rate in patients with severe asthma. However, the effects of anti-IgE antibodies on established airway remodeling remain to be established. In the present study, we compared the effects of an anti-IgE antibody with those of steroids in a mouse model of airway remodeling. A model of airway remodeling was prepared by continuously sensitizing B6LacJc mice with ovalbumin. After preparing the remodeling model, the mice were divided into 4 groups: a group treated with an anti-IgE antibody (A), a group treated with steroids (B), a group that received both treatments (C), and an untreated control group (D). A group, basement membrane thickening, a marker of remodeling, was significantly inhibited, similar to the effect in the B group. In the C group, synergistic effectiveness was obtained. Smooth muscle thickening was significantly inhibited in the A group, and the effect was stronger than that in the B group. Similarly, in the A group significantly suppressed mast cell proliferation and also inhibited the expression of amphiregulin, a steroid-resistance molecule. Smooth muscle thickening positively correlated with amphiregulin expression, and this correlation was weakened by treatment with A group. In the present study, the inhibitory effect of A group on basement membrane thickening was similar to that in the B group. However, smooth muscle thickening was more strongly inhibited by A group than by B group, suggesting that the mechanism of action involved the suppression of amphiregulin expression by mast cells.

P242 NT-proANP and lung diffusion in sarcoidosis
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Background: Since that several lines of evidences support a role in modulating pulmonary circulation for the natriuretic peptides, we aimed to investigate possible relationship between NT-proANP (NT-proANP) and NT-proBNP (NT-proBNP) natriuretic peptides and lung diffusion abnormalities, as assessed by lung diffusion for carbon monoxide (DLco), in patients with pulmonary sarcoidosis.

Methods: Resting NT-proBNP and NT-proANP were determined in thirty-two outpatients with pulmonary sarcoidosis, subdivided in two subgroups according to a cut-off DLco values equal to 75%, and eighteen well-matched healthy volunteers. Each subject underwent, besides pulmonary lung function test, Doppler echocardiographic examination with Tissue Doppler Imaging analysis and cardiopulmonary exercise test.

Results: NT-proANP levels were significantly higher in patients with DLco < 75% (2092±768 fmol/mL) with respect to those with DLco ≥ 75% (1575±488 fmol/mL) whereas no difference was found for NT-proBNP. A significant univariate relationship was found between NT-proANP and age (r=0.403, p=0.022), DLco (r=0.540, p=0.001), specific membrane diffusion capacity (r=0.480, p=0.006), peak oxygen uptake (r=-0.386, p=0.023), and ventilator efficiency (r=0.431, p=0.011). DLco was the only variable independently associated with NT-proANP levels at multivariable analysis (β=0.464; standard error:0.03; p=0.009).

Conclusions: Our findings support a key role of NT-proANP into mechanisms underlying modulation of lung function. The NT-proANP release specifically oriented to counterbalance the lung diffusion impairment is a stimulating hypothesis which warrants confirmation.

P243 Hydrogen peroxide in exhaled air: A source of error, a paradox and its resolution
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Background: The concentration of hydrogen peroxide (H2O2) in exhaled air has been reported to be elevated in asthma and COPD, but the data are inconsistent and difficult to reproduce. Notably, a relevant concentration of H2O2 can be found in ambient air. Therefore, we examined the association between H2O2 in ambient and exhaled air.

Methods: Exhaled breath condensate (EBC) of 12 COPD patients and 9 healthy subjects was collected with an inhalation filter (F; efficiency 81%) without (nF) Ambient air condensate (AAC) was collected in parallel and all samples were analysed for H2O2. Additionally, ambient H2O2 concentration was recorded by an analyser for atmospheric H2O2.

Results: H2O2 concentration in AAC (3.60±1.40 μmol, mean±SD) was higher (p<0.01) than in EBC (Table). It showed meteorological variations concordant with atmospheric measurements. In both groups studied, the inhalation filter caused a reduction of H2O2 values (p<0.01). Despite the comparatively low levels in exhaled air, analysis by means of a mathematical model revealed an endogenous H2O2 contribution which was more pronounced when using the inhalation filter.

<table>
<thead>
<tr>
<th>Median (interquartile range), μmol</th>
<th>COPD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaled F</td>
<td>0.42 (0.13)</td>
<td>0.45 (0.22)</td>
</tr>
<tr>
<td>Exhaled nF</td>
<td>0.78 (0.51)</td>
<td>0.75 (0.32)</td>
</tr>
<tr>
<td>Exhaled (microliter cond. equivalent)</td>
<td>0.46 (1.30)</td>
<td>0.49 (3.40)</td>
</tr>
</tbody>
</table>

Conclusion: The paradox of low H2O2 values in exhaled air assessed by EBC dissolves when taking into account the reconditioning of inhaled air containing H2O2. This may partially explain the heterogeneity of study results and their limited reproducibility. Still, there seems to be endogenous H2O2 production but its valid determination requires inhalation filters. This suggests a reanalysis of studies from the literature.
Introduction: Tetraplegic individuals show a paradoxical inward motion of the diaphragm during inspiration. Abdominal binding is supposed to decrease paradoxical breathing by decreasing abdominal compliance and increasing the zone of apposition of the diaphragm. We hypothesized that abdominal binding would reduce the paradox during quiet breathing (QB) as well as during different levels of hyperpnoea (HYP) and increase maximal voluntary ventilation (MVV).

Methods: Chest wall kinematics were assessed by optoelectronic plethysmography in three male complete tetraplegics (C4-C7) during QB and during HYP at 40 and 100% MVV with and without abdominal binding. Tidal volume (Vt) was partitioned into the relative contribution of the pulmonary rib cage (ΔVRCP), abdominal rib cage (ΔVPRCA), and abdomen (ΔVAB). Inspiratory paradox time (IPT) was calculated as the percentage of inspiratory time (TI) with a decrease in VAB and/or VPRCA.

Results: Abdominal binding reduced IPT at all ventilatory levels. The reduction was higher in RCP than in RCP. At rest, abdominal binding increased ΔVRPMC more effectively than ΔVMVP. MVV was larger with abdominal binding in all subjects (105.1±49.0 vs. 92.0±35.9 ml/min without abdominal binding).

Conclusion: The reduction in IPT and the increase in MVV in tetraplegic individuals suggest a functional benefit of abdominal binding which is mainly seen in the lower rib cage (RCA).

P245 Comparison of measures of ventilation heterogeneity derived from multiple breath inert gas washout
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Introduction: Multiple breath inert gas washout (MBW) is a technique for quantifying ventilation heterogeneity (VH). We compared four measures of VH with asthma, and robustness to variations in tidal volume (Vt), anatomical dead space (Vd) and functional residual capacity (FRC).

Methods: MBW was performed in triplicate on 13 healthy subjects and 22 patients with moderate to severe asthma, using a previously published method (Horsley et al. 2008; 63(2): 135-140). Lung clearance index (LCI); mixing ratio (MIR) and moment ratio (MoR) were calculated. A novel marker of VH, the rate constant ratio (RCR), was calculated by fitting the washout data to a two-phase decay model and calculating the ratio between the fast and slow rate constants. Repeatability and discriminatory ability were assessed using intraclass correlation coefficients (ICC) and receiver operating characteristic (ROC) curves, respectively. Robustness of the parameters was assessed by calculating the signal-to-noise ratio (SNR), using simulated MBW data to determine the noise caused by variations in FRC, Vt and Vd.

Results: LCI, MoR and MIR exhibited good repeatability, with ICC values of 0.899, 0.885 and 0.885 respectively, but RCR was less repeatable (ICC = 0.783). The parameters all had areas under the ROC curve between 0.7 and 0.75. The most robust parameter was the RCR (SNR = 5.1), followed by the MIR (SNR = 6.8), LCI (SNR = 3.4) and MoR (SNR = 1.2).

Conclusion: MIR appears to be the most favourable measure of VH. We recommend that it is reported alongside the LCI.

P246 The role of forced partial expiratory flows to test the bronchodilator response in COPD
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Lung distention (FRC) and air trapping (TVR) are associated with airflow obstruction in COPD patients. Distal obstruction can be assessed by the measurement of forced expiratory partial flows (PF) at low lung volume, 80%ml above residual volume, RV, (PF800). The acute effects of salbutamol were evaluated using the Peripheral Obstruction Index (POI), the ratio of RV to PF800. POI can be regarded as a time constant for emptying the lung periphery and has a unit of second.

Methods: Eighty-nine COPD subjects underwent measurement of FVC, FRC, RV, PF800 and FEV1 before and after inhalation of 40mcg of salbutamol (BD). PF800 was acquired in a body plethysmograph within 30 seconds of steady tidal breathing, the patient expired maximally to RV starting from a normal inspiratory tidal volume (Exp/Air Medisoft Be). Full maximal expiratory manoeuvres were performed after PF800.

Results: Prebronchodilator POI values ranged from 2.6-60. POI decreased in 69/89 patients including 19 patients with increases in PF800 but no decrease in RV. The mean decrease in POI was 21%. Of the 50 subjects with decreases in POI and RV, only 26 had increases in FEV1 (>0.2L) and only 35 increases in FVC (>0.2L). Among the 31 patients who increased their RV (mean ± SD: 0.3±0.33) after the challenge, only 2 increased their FEV1 whereas 12 increased POI. This suggests a release of pneumoconstriction (Duartebande 1948) associated with peripheral bronchodilation.

Conclusion: POI appears to be more sensitive than FEV1 for reflecting air trapping and peripheral obstruction. The manoeuvre is less tiring than the maximal forced expiration. The clinical significance of changes in POI remains to be studied.

P247 Non-invasive detection of diaphragmatic weakness in acid maltase deficiency (AMD)
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Patients with AMD, a glycogen storage disease resulting in loss of skeletal muscle function, become ventilator dependent when respiratory muscles, particularly the diaphragm, are significantly involved. To identify predictive factors of diaphragmatic weakness in AMD, we studied 10 untreated AMD patients and 8 healthy controls. Supine postural drop of vital capacity (ΔVC) was measured by spirometry, while rib cage (RC) and abdominal (AB) volume variations by opto-electronic plethysmography during quiet breathing and slow vital capacity in seated and supine posture. RC and AB contributions to tidal volume (VT), inspiratory capacity (IC) and expiratory reserve volume (ERV) were derived. Diaphragmatic weakness, defined as ΔVC<25% (Fromagot et al,2001), was present in 3 patients (DW). Posture had a significant effect on IC and AB volume changes during IC and ERV (left and central panel) in controls and patients without DW (noDW). Conversely, in DW patients IC and AB volume changes during IC did not vary with posture, while AB contribute paradoxically (negative values) to ERV in supine position. DW patients also showed negative (i.e., paradoxical inward movement) AB contribution to VT which correlated with ΔVC (right panel). AB volume variations in both DW and noDW patients were generally lower than controls.

In conclusion, abdominal displacement during VT and VC maneuver is a better indicator of diaphragmatic weakness in AMD.

P248 Effect of pulmonary rehabilitation on dynamic hyperinflation according to the BODE Index
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Background: The increase of dynamic hyperinflation (DH) is one of the most important causes of exercise intolerance in COPD patient.
Objective: The aim of this study was to evaluate the effects of pulmonary rehabilitation (PR) on dynamic hyperinflation, as evaluated by the BODE index.

Method: Prospective study in 17 COPD patients, including 30% more than 80 yrs. After PR (56% 20% of the final training session, measured at baseline and at the end of 2 months). Dynamic hyperinflation was measured using the Baseline and Post-PR values were compared using paired t-tests. A p-value of <0.05 was considered significant.

Results: Changes in the BODE index were significant for all patients. In the PR group, the BODE index decreased by 0.6 units at 2 months (p=0.03). In the control group, the BODE index increased by 0.2 units at 2 months (p=0.01). The difference between the groups was statistically significant (p=0.01).

Conclusion: The results of this study suggest that a 6-month rehabilitation program can significantly improve dynamic hyperinflation in COPD patients. Further studies are needed to determine the long-term effects of PR on dynamic hyperinflation in COPD patients.
Comparison of different measurement methods of gas diffusion in the lung

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Background: Lung fibrosis results in decreases of oxygen diffusion and oxygen arterial partial pressure (PAO2) especially during exercise. Obstructive airway diseases are often associated with a mismatch of ventilation and perfusion. We investigated the validity of the CO diffusion capacity (DCO) in comparison with PAO2 and alveolo-arterial oxygen gradient (AaDO2) in different lung diseases.

Methods: 250 subjects (52 ± 12.5 yrs) were examined, out of 206 there were: 13 with VC < LLN (normal FEV1, VC, DCO normal or reduced); 19 with normal VC but DLCO < LLN; 86 with mild or moderate bronchial obstruction (FEV1/VC < LLN, VC-LLN), and 88 healthy controls. Pearson correlation coefficient of DCO vs PAO2 and AaDO2 were analyzed in each group.

Results: DCO were 0.23 of the phase shift between the rig cage and abdominal compartments during the observed a distinct behavior between EG and CG, in series 1 to 3 respectively.

Conclusions: Only in patients with reduced VC and/or impaired DC CO all three parameters are likely to objectively improve gas exchange in the lungs. AaDO2 relates to the ventilation, this may be the cause of the good correlation with DCO. In the group with bronchial obstruction DC CO seems to be influenced by other pathophysiological aspects, resulting in only moderate correlation between the different parameters.

Asynchronous breathing movements during slow controlled deep inspiration in chronic stroke patients

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Aim: To assess the asynchrony index of respiratory movements during the slow controlled deep inspiration in chronic stroke patient’s and healthy subjects.

Methods: Ten chronic stroke patients (experimental group - EG) (53 ± 9.2 years) and ten age-matched healthy subjects (control group, CG) (53.6 ± 9.4 years) were studied by Optoelectronic Plethysmography in 3 moments, quite breathing (QB), slow controlled deep inspiration in chronic stroke patient’s and healthy subjects.

Results: Both groups were similar during the QB and QB. During Deepel series we observed a distinct behavior between EG and CG, in series 1 to 3 respectively. Time of the phase shift between the rig cage and abdominal compartments during the Deepel series were 0.23 ± 0.10 vs. 0.15 ± 0.11a, 0.22 ± 0.10 vs. 0.11 ± 0.15a, 0.21 ± 0.10 vs. 0.12 ± 0.10, p = 0.037.

Conclusion: Slow controlled deep inspiration induces more asynchronous breathing movements in chronic stroke patients than healthy subjects.

Experimental air hunger induces lactate-evoked potentials

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Rationale: The supplementary motor area (SMA) has functional connections with the diaphragm. Facilitatory conditioning of the SMA using repetitive transcranial magnetic stimulation induces diaphragm motor-evoked potentials in healthy humans.

Methods: Eight naive healthy subjects (age 25 ± 3 years, mean ± SD, 3 men) were studied. DiMEPs (surface electromyogram) were elicited by single-pulse TMS over the primary motor area of the SMA (M1dia). DiMEPs were recorded at baseline and after rests at 25, 10 and 5 minutes after I-TMS (post1, post2, and post3, respectively).

Results: I-TMS over the SMA reduced the amplitude of DiMEPs, from 272 ± 18 μV at baseline, to 229 ± 126 μV, 209 ± 144 μV and 212 ± 123 μV at post1, post2 and post3, respectively (F1,11 < 0.005 vs. baseline). These changes were observed in the absence of any reduction in the amplitude of the pre-stimulus EMG (F2,22 > 0.05).

Conclusions: Inhibitory theta-burst stimulation of the SMA decreases the excitability of the corticospinal pathway to the phrenic motoneurons. This suggests the existence of a tonic excitatory connection between the SMA and M1dia. The possibility of targeting this connection to interfere with respiratory sensations remains to be determined.

Dyspnea in patients with idiopathic pulmonary fibrosis: The mechanisms of exertional dyspnea

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Background and objective: Very often, some idiopathic pulmonary fibrosis (IPF) patients with the severe exertional hypoxemia may realize only mild dyspnea, the mechanisms underlying the exertional dyspnea in such patients have not yet been elucidated. We investigated the exercise responses to hypoxia in relation to dyspnea profile as well as cardiorespiratory and acidotic parameters in 13 patients with stable IPF.

Methods: This was a single-blind trial, in which subjects breathed 30% O2 or compressed air (CA) in random order during two incremental treadmill exercise tests.

Results: PaO2 and Paco2 were higher during exercise (p < 0.01, p < 0.001, respectively, by repeated-measures ANOVA). At the peak exercise, 30% O2 reduced plasma lactate level (p < 0.05), and dyspnea score and the mean change from resting condition in pH were similar while breathing 30% O2 and CA. The dyspnea ratio (%) of Oxygen uptake (peak minus resting oxygen uptake) curve reached a break point that occurred at a similar exercise point while breathing 30% O2 and CA.

Conclusions: Despite inhaling 30% O2 and CA, IPF patients did not develop ventilatory compensation in exertional acidosis, stopped exercise when the similar changes from resting condition in pH were seen. Furthermore, hypoxic conditions did not alter the pattern of exertional dyspnea in IPF patients during a standardized exercise program.

Study of pulmonary function in type 2 diabetes mellitus and its changes with change in duration and glycemic control

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Rationale: Diabetes mellitus (DM) is a metabolic disease causing changes in...
multiple systems, and pulmonary system is not an exception to this rule. As the prevalence of T2DM is increasing, the potential implication of diabetic status affecting pulmonary system demand attention.

Objectives: To assess the pulmonary function in Type2 DM patients and its dysfunction may preclude the execution of important social tasks such as speech. Here we investigate whether the double command involved in respiration (cortical and medullary) has an impact on the inhibitory mechanisms. Specifically, we studied the inhibition properties (baseline, rate, threshold) of voluntary respiratory movements in relation with the phase of the breathing cycle in which the command is given.

Results: Subjects were instructed to produce inspiratory movement in response to a visual stop signal was presented, being shorter during inspiration (21 ms; mean ± SD) than expiration (29 ms). The estimated respiratory SSRT was 299 ± 200 ms. This might either indicate that respiratory RTs depended on the context in which the stop signal was presented, being shorter during inspiration (541 ± 289 ms) as its dysfunction may preclude the execution of important social tasks such as speech.

Conclusion: There is significant changes of pulmonary functions with changes in duration and hemodynamic control, which may be due to non enzymatic glycosylation of tissue proteins and chronic diabetic microangiopathy. So, in routine screening by doing PFT, we can reduce mortality and morbidity of the patients (type2DM) due to subclinical or overt pulmonary dysfunctions.

P239
Inhibition of voluntary respiratory movements depends on the phase of the respiratory cycle
Elisene Allard1,2,3, Thymothée Poitou3,4, Hadrien Caron2,3, Thomas Sambouw1,2, Pierre Pointet3,4,1 ER10-UPMC, Laboratoire de PhysiologieRespiratoire, Université Pierre et Marie Curie, Paris, France; 2UMR 7225, CNRS, Paris, France; 3UMRS 975, INSERM, Paris, France

Movement inhibition is important, notably for the voluntary control of respiration, as its dysfunction may preclude the execution of important social tasks such as speech. Here we investigate whether the double command involved in respiration (cortical and medullary) has an impact on the inhibitory mechanisms. Specifically, we studied the inhibition properties (baseline, rate, threshold) of voluntary respiratory movements in relation with the phase of the breathing cycle in which the command is given.

Subjects were instructed to produce inspiratory movement in response to a visual stop signal was presented, being shorter during inspiration (541 ± 289 ms) as its dysfunction may preclude the execution of important social tasks such as speech.

For −50% of the trials, a stop signal was presented (a second visual target) in response to which subjects had to inhibit the inspiratory movement. Respiratory movement was measured through abdominal expansion using a magnetometer. Respiratory reaction time (RT) and stop-signal accuracy were used to calculate stop-signal reaction time (SSRT), an estimate of the time required to inhibit the respiratory movement.

The results indicate that respiratory RTs depended on the context in which the stop signal was presented, being shorter during inspiration (541 ± 21 ms; mean ± SD) than expiration (568 ± 20 ms). The estimated respiratory SSRT was 299 ± 48 ms. 

Conclusion: There is significant changes of pulmonary functions with changes in duration and hemodynamic control, which may be due to non enzymatic glycosylation of tissue proteins and chronic diabetic microangiopathy. So, in routine screening by doing PFT, we can reduce mortality and morbidity of the patients (type2DM) due to subclinical or overt pulmonary dysfunctions.

57. Functional imaging in pulmonary oncology and COPD. Radiation dose in chest CT: survey and real life

P260
Agreement between tumor measurement on computer tomography and resected specimen size in lung cancer
Jeong Ik1, Catarina Calde2, Susana Esteves1, Nuno Nuno Abacauce3, Fernando Cunha2, Isabel Duarte2,1, Maria Teresa Almodovar5.

Introduction and aim: To compare the radiologic preoperative size of the primary tumor in LC with their pathologic size following excision. Materials and methods: 88 LC patients who undergone surgery in our institution from 2008 - 2011, CT-staged T1 or T2 were included. Images were reviewed by two independent observers. Tumor maximal diameter on axial-plane was obtained using PACS caliper segmentation algorithm and adjusted based on a radiologist’s input; largest single diameter from Pathology gross report was utilized. Agreement was evaluated between CT and Pathology using Bland-Altman methods for measurements and using Cohen-Kappa for T-staging classification. Results: 46 adenocarcinoma, 31 squamous cell carcinoma. The mean CT measurement was 30.27mm, pathology was 30.63mm. The mean difference between CT and Pathology measurements was -0.35 mm (95% Confidence Interval -2.15; 1.45, p-value < 0.001). The lower and upper 95% limits of agreement were -17.3mm and 16.62mm. Clinical T-staging based on CT was T1a=21, T1b=34, T2a=20, T2b=13 and on pathology was T1a=30, T1b=22, T2a=27, T2b=9. Stage agreement was seen in T1a=17/30 (57%), T1b=16/22 (73%), T2a=14/27 (52%) and T2b=8/9 (88%) with a moderate agreement in 14.6 patients complete TNM staging was documented with c or p N-stage. The SUVmax ranged 53±6.64 HU. The SUVmax ranged 53±6.64 (52%) and 18±10 (29%) in non-small cell and small cell lung cancers respectively. The SUVmax (r = -0.13) as well as histology and grading were determined. Univariate analysis was performed between all tumor parameter.

Conclusion: There was no significant correlation between the different metabolic and morphologic tumor parameter from PET/CT and clinical data of patients with NSCLC. Up to now we could not identify a combination of imaging data from PET/CT with a predictive capability for tumor staging.

P262
Performance of segmentation software on large longitudinal database of pulmonary nodules in the Danish Lung Cancer Screening Trial (DLCST) Ziaheem Saghir1,2, Colin Jacobs2,3, Bram van Ginneken4, Marleen de Bruijne4,5, Jan Vanhocke6,7, Jasper Holst Pedersen8,9,10, Department of Respiratory Medicine, Gentofte University Hospital, Hellerup, Denmark; 2Fraunhofer MEVIS, Bremen, Germany; 3Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 4Department of Computer Science, University of Copenhagen, Denmark; 5Department of Medical Informatics and Radiology, Erasmus MC - University Medical Center, Rotterdam, Netherlands

Introduction and aim: Growth measurements of pulmonary nodules are subject to great interest due to the risk of malignancy. We examined the reproducibility of lung nodule volumetric software that offers two different volumetric algorithms. Materials and methods: In the Danish Lung Cancer Screening trial, 2,052 patients were linked chronologically (same nodule in different scans) and independently reviewed by two readers using volumetric software. The software offers readers two different analysing algorithms, “solid nodule algorithm” and “part/solid/nonsolid algorithm”. We compared the inter-observer variability regarding use of algorithm and rate of success. Results: 1,442 nodules were measured 5,988 times. The readers reviewed the segmentations visually and were able to correctly segment and measure 94% and 97% of the nodules, respectively. In 90% of these cases, the readers chose the same algorithm.

Conclusion: Using this volumetric software on a large database with longitudinal data shows a high success rate and large agreement in choosing algorithm.
Contrast-enhanced ultrasound examination of pulmonary lesions

Despite the current availability of diagnostic procedures, the diagnosis of solitary pulmonary nodules still remains challenging. The aim of this clinical study is to evaluate the lung magnetic resonance imaging (MRI) with focused conventional sequences and diffusion weighted imaging.

**Methods:** We assessed 55 subjects with pulmonary lesions under blinded conditions using a MRI scanner. The exam was carried out with diffusion-weighted sequences (B500 and B1000 DWIBS) and ADC map with a qualitative and quantitative analysis.

**Results:** Out of 5 mm nodules (n=23) studied with DWIBS, 16 did not show abnormalities and were unchanged in 1 year follow-up and 3 were not identified compared with CT. DWIBS was positive in 2 cases, false-positive in 1 case and false-negative in 1 case. In 32 lesions >10 mm, histologically confirmed, DWIBS helped the biopsy planning, the definition of neoplastic tissue within atelectatic lung parenchyma, the differentiation of parietal pleura from pleural effusion and the characterization of mediastinal lymph nodes.

**Conclusion:** The study on large size lesions and nodules showed a considerable statistical significance (p<0.001; diagnostic accuracy 86.5%). The technique, despite the limitations of a preliminary study, may increase nodules detection and, with CT or PET, provide additional useful information.

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**P264**

Contrast-enhanced ultrasound examination of pulmonary lesions

**Aim:** The aim of this study is to assess the clinical value of contrast-enhanced ultrasound (CEUS) for the diagnosis of peripheral pulmonary lesions (PPL).

**Materials and methods:** We examine 30 patients using a 2nd generation transpulmonary contrast Sonovue and US system Philips XE-11 equipped with low acoustic power mode software.

**Results:** By 15 patients (8 with pneumonia and 7 with atelectasis), the baseline US examination presents PPL with preserved bronchial and vascular structure. CEUS establishes a short time to enhancement (TE) < 6 sec (x ± SD = 4.1±1.1 sec) and hyperchogenic tissue enhancement during the parenchymal phase, due to preserved pulmonary artery (PA) blood supply. By 6 patients (PTE n=2; abscess in the infiltrated lung tissue n=2; pneumolesschrosis n=1; metastasis n=1), CEUS does not show contrast enhancement. Peripheral lung cancer (n=8pms) as well as some types of pulmonary metastasis are characterized by delayed TE >7sec. (x ± SD = 15.1±5.7 sec) and sparse tissue enhancement, suggesting bronchial arterial (BA) supply.

**Conclusion:** CEUS is a safe and effective method for differentiating PA from BA blood lesions supply. It could be a useful method for diagnosis of pneumonitis/atelectasis and is particularly valuable to differentiate them from PTE. CEUS improves the US control of transbronchial needle biopsies especially in lesions among atelectasis or inflammatory infiltrate. It is reasonable to carry out further research to clarify the role of CEUS among the diagnostic procedures in patients with PPL.

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**P265**

Radiological features of solitary pulmonary nodule (SPN) and application of two lung cancer prediction models

The diagnostic accuracy of solitary pulmonary nodules (SPN) still remains challenging, and the evaluation of benign and malignant SPNs is crucial for the correct management of patients. The study of the radiological features and the application of two lung cancer prediction models help to improve the accuracy of the diagnosis of SPNs.

**Objective:** To summarize the imaging features of solitary pulmonary nodules, and compare the two types of lung cancer prediction models for solitary pulmonary nodules.

**Methods:** A retrospective study of Ruijin Hospital between 2002 and 2009 with newly discovered SPNs which is less than 30mm. The patients all received pathological diagnosis. Summarize the clinical and imaging characteristics, then validate and compare the diagnostic accuracy of two lung cancer prediction models for estimating the probability of malignancy in patients with SPNs.

**Results:** 90 patients were enrolled, of which 32 cases are benign. 58 cases are malignant. Our study showed that we can identify the SPNs between benign and malignant by the SPN edge features of lobulation (P<0.05). The area under ROC curve of VA model was 0.712 (95% CI 0.606 to 0.821); Area under ROC curve of Mayo Clinic model was 0.753 (95% CI 0.652 to 0.843), and it is superior to VA model.

**Conclusions:** It is meaningful for the identification of benign and malignant SPNs by the lobulation sign in CT scan. We can integrate the clinical features and the lung cancer predicting models to direct our clinical work.
Hypertension, pack years history and COPD diagnosis were predictors of EFMV.

Variables with statistically significant differences were included in the multivariate analysis to determine those that independently predict EFMV. Male gender, hypertension, pack years history and COPD diagnosis were predictors of EFMV.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, yrs (±SD)</th>
<th>Male (%)</th>
<th>Pack years (≥25-57)</th>
<th>BMI, Kg/m² (≥25-34)</th>
<th>Total Cholesterol, mg/dl (≥210-280)</th>
<th>HCr, mg/dl (≥160-260)</th>
<th>Gluc, mg/dl (≥80-200)</th>
<th>CRP, mg/dl (≥2.5-3.5)</th>
<th>Hypertension, %</th>
<th>FEV₁, %</th>
<th>DLCO, %</th>
<th>FVC%, %</th>
<th>FEV₁/FVC, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>53</td>
<td>41 (11.7)</td>
<td>43 (81.1)</td>
<td>34.06 (23-46)</td>
<td>27.5 (4.6)</td>
<td>207.6 (43.8)</td>
<td>55.5 (15.1)</td>
<td>0.61 (14.1)</td>
<td>0.2 (0.65-0.46)</td>
<td>20 (7.7)</td>
<td>9 (11.3)</td>
<td>97.28 (13.5)</td>
<td>103.58 (14.2)</td>
<td>77.36 (9.4)</td>
<td>103.14 (13-3.22)</td>
</tr>
<tr>
<td>COPD</td>
<td>67</td>
<td>54 (19)</td>
<td>64 (90)</td>
<td>41 (71.2)</td>
<td>47.41 (25-60)</td>
<td>207.4 (45.8)</td>
<td>54.7 (17.0)</td>
<td>103 (25.2)</td>
<td>0.31 (0.94-0.96)</td>
<td>33 (48.5)</td>
<td>0.62</td>
<td>9 (12.6)</td>
<td>78.2 (19.8)</td>
<td>59.94 (10.5)</td>
<td>134 (167-190)</td>
</tr>
</tbody>
</table>

Conclusions: COPD is an independent risk factor for an increased EFMV. Further studies should assess the impact of this finding as a non-invasive marker of cardiovascular events in this high risk population.

P268
High resolution CT scan (HRCT) thorax differences between biomass-smoke exposure induced COPD (BM COPD) and tobacco-smoking COPD (TS COPD)

Bill Brashier 1, Shilpa Kajale 2, Sajid Tambe2, Rahul Kodgule 1, Jyoti Londhe 1, Deepak Gopakumar 1

BM COPD accounts for a substantially large proportion of COPD especially in developing countries. However, little is known whether this COPD is different from TS COPD radiologically.

Aims: To study and compare the radiological changes in the lung parenchyma between BM COPD and TS COPD.

Method: 20 stable BM COPD (M:F 1:19) and 34 stable TS COPD (M:F 34:0) underwent HRCT thorax. Helical HRCT sections were taken from apex to domes of diaphragm at 1cm thickness and 10mm intervals during deep inspiration maneuvers. Emphysema was quantified using “Quantification of Emphysema” software and depicted as area less then -950HU, while bronchial wall thickness was defined as presence of ≥1.5mm thickness. Independent sample t-test was used to compare the two groups of COPD.

Results: BM COPD [age: 65yr (8.5)] subjects showed significantly lesser mean lung volumes (cc) compared to TS COPD [age: 63 yrs (5)] [2916±2589 vs 4347±4580; p < 0.0001] TS COPD subjects had more mean % emphysema compared to BM COPD [13%±1.1% vs 6.4±6.3%; p = 0.022]. 80% of subjects with BM COPD showed presence of pure form of emphysema pattern (either centrilobular (40%) or panlobular (40%)), whereas there was no distinct pattern seen with TS COPD. There is predominance of either centriacinar or panacinar in BM COPD. Biomass smoke-induced COPD subjects showed lower lung volumes and lesser mean % emphysema than TS COPD on HRCT imaging.

P269
Phantom-based evaluation of computed tomography parameters: Understanding the differences in automated emphysema scoring

Johan Coolen 1, Frederik De Keyzer 1, Walter De Wever 2, Elis Wauters 3, Wim Janssens 1, Marc Decramer 1, Johny Verschakelen 1

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Purpose: Automated lung emphysema (E) measurements vary strongly between examinations. We examined the effect of CT scanners, acquisition parameters, kernels and windowing on the software-based E scoring (S) in a phantom.

Material and methods: A human preserved torso in eposix was used as phantom and was scanned on 5 different scanners using various settings of the following parameters: KV, mAs, care dose, slice/increment, window and kernel. For each of these data sets, the E was evaluated. The ES was performed using both 2D and 3D software. A multiple linear regression analysis (LRA) was used to evaluate the importance of each examined parameter.

Results: Measured E values ranged between 17.0% and 70.5% for 3D software evaluation. A similar range could be seen at 2D evaluation, ranging between 13.9% and 66.8%. The used kernels had the strongest impact on the measured ES, and a strong effect could also be seen for slice/increment, mAs, window and KV. However, the scanner-dependent parameters and the usage of the caredosis option proved to have only a minor impact on the measurement of E. The LRA found a very strong correlation between the measured values, and the estimated values based on the optimal regression formule, with R² values of 0.828 and 0.772 for the right and left lungs on 3D evaluation, and 0.872 and 0.851, resp. on 2D evaluation.

Conclusion: A fixed phantom allows assessing the influence of different scanners, acquisition parameters and evaluation techniques on the software-based ES. The current dataset indicates that scan parameters and the used kernels have the strongest effect, and that the induced differences can be estimated using multiple LRA.

P270
Interobserver variability in visual evaluation of thoracic CT scans and comparison with automatic computer measurements of CT lung density

Johan Coolen 1, Fredeke De Keyzer 1, Laura H. Thomsen 1, Saher B. Shaker 1, Asger Dijkers 1, Jesper H. Pederson 1, Department of Respiratory Medicine, Gentofte University Hospital, Hellerup, Denmark; 2Department of Computer Science (DIKU), University of Copenhagen, Copenhagen, Denmark; 3Department of Thoracic Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Introduction: Emphysema is defined by pathology, but is most precisely evaluated in vivo by computed tomography (CT).

Aims were to determine the reproducibility of visual evaluation of emphysema, i.e. the observer variability, and furthermore to compare the visual evaluations to automatic CT lung density measurements, i.e. densitometry.

Methods: In a pilot study 60 CT scans were selected from a sample of 3980 CT scans from The Danish Lung Cancer Screening Trial (DLCST). The amount of emphysema in these scans was scored independently by two observers, who were blinded regarding clinical information.

The lung was segmented automatically by in-house developed computer software, and the percentage of pixels below -950 HU was used as a surrogate marker for emphysema.

Conclusion: We found a high degree of interobserver consistency in emphysema grading. However, the agreement with the CT lung density measurement was poor, indicating that the two types of evaluation represent different aspects of emphysema. Most likely, they should be seen as complementary rather than competitive evaluations. Future comparison with physiological tests might elucidate the reason for differences and demonstrate the usefulness of these evaluations.

P271
A new method for evaluation of severity in COPD using dynamic chest x-ray examination

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1Radiology, Fukujuji Hospital, JATA, Tokyo, Japan; 2Chest Surgery Division, Fukujuji Hospital, JATA, Tokyo, Japan

Purpose: Spirometry which requires maximum effort tasks COPD patients. In this study, we proposed a new method for evaluation of severity in COPD using dynamic chest X-ray examination without effort breathing.

Subjects: Dynamic chest X-ray from 29 normal volunteers, 30 mild COPD patients (GOLD Stage I or II) and 31 severe COPD patients (GOLD Stage III or IV) were obtained. The upright position in about 10 seconds of tidal breathing at rest. The dynamic image data captured at 7.5 frames per second was synchronized with the pulsed X-ray. The institutional review board approval and written informed consent were obtained in all patients.
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 standard deviation of flow rate ratio.

Results: The average of the ratio in normal volunteers, in mild COPD patients and in severe COPD patients were 0.21±0.03, 0.22±0.04 and 0.26±0.04 (mean±SD), respectively. Significant difference was confirmed between the normal volunteers and the severe COPD patients (p=0.0047), and between the mild COPD patients and the severe COPD patients (p=0.0092), respectively.

Conclusion: The variation of the inspiratory/expiratory flow rate ratios in COPD patients were larger than those of healthy volunteers. The new method for ventilation function has possibility to evaluate severity of COPD.

P272  
Ultrasoundographic assessment of the diaphragm in patients with chronic obstructive pulmonary disease (COPD): Relationships with pulmonary function and the influence of body composition

Andrea Smargiassi, Riccardo Inchingolo, Linda Tagliaboschi, Alessandro Di Marco Berardinou, Giuseppe Maria Corbo, Salvatore Valente. Pulmonary Medicine, Universita Cattolica Del Sacro Cuore, Roma, Italy

Background: Skeletal muscle weakness and loss of fat-free-mass (FFM) is one of the main systemic effects of COPD. Also diaphragm is involved leading to disadvantageous conditions and poor contractile capacities. We measured the thickness (TD) of diaphragm by ultrasonography to evaluate the relationships between echographic measurements, parameters of respiratory function and body composition data.

Material and methods: 24 patients (17 males) underwent: a) pulmonary function tests; b) echographic assessment of TD in the zone of apression at various lung volumes (TDRV, TDFRC, TD TLC); c) biochemical body impedance analysis. BMI was calculated.

Results: Mean FEV1 as percentage of the predicted value was 49.6% (min 22%, max 86%). Mean BMI was 27±5.3 kg/m² (min 17.2 max 38.8). TDRV, TDFRC and TD TLC measured 3.28, 3.58, 5.92 mm respectively. Reproducibility of measures was good (R=0.93, 0.93, 0.77 for TDRV, TDFRC, TD TLC respectively). All the TD were found correlated to FFM being the relationship greater for TDFRC (R²=0.51, p=0.0002). As regards lung volume IC, was found related to TDRV (R²=0.21, p=0.025). TDFRC (R²=0.16, p=0.05). TD TLC (R²=0.36 p=0.002). No significant association was found between TD and TLC, FRC, RV. Using a multiple regression model TD TLC was found related to RV/TLC, FEVI/FVC and FFM (R²= 0.55 p=0.004). Lastly, the difference between TDFRC and TDRV was closely related to FVC (R²=0.33, p=0.036).

Conclusion: Ultrasoundographic assessment of the diaphragm could be a useful tool to study the progression of the disease in COPD patients in terms of static hyperinflation and loss of FFM.

P273  
Longitudinal imaging characterisation of a model of chronic allergic lung inflammation in mice

Kumar Changani1, Catherine Pereira2, Simon Young2, Robert Shaw1, Tony Nials1, Simon Campbell1, Kamshira Pindada1, Steve Jordom1, Michael Haase1, Mike Pedrick2, Richard Knowles1, 1RRI & LAS, GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom; 2Respiratory & Inflammation, Astazeneca, Macclesfield, Cheshire, United Kingdom

The aim of the study was to investigate the role that imaging could have for longitudinally assessing allergic lung inflammation. This is usually assessed using terminal procedures eg bronchoalveolar lavage (BAL) & tissue histology. We describe how MRI & CT methods provide sensitive early readouts of inflammation in the chronic HDM mouse model. LTI changes correlate directly with classical inflammatory readouts allowing more accurate assessments of the lung are required to assess this. Micro-CT permits direct examination of the small airways and microvasculature. However, most studies to date have used eosin or other contrast agents precluding the use of historical samples.

Aim: To use micro-CT to identify and measure the small airways in paraffin embedded tissue without contrast agents.

Methods: Tissue from the distal airways was fixed and embedded in paraffin wax. It was scanned with a Nikon/Perkin HMX XCT scanner at the μ-VES X-ray imaging centre, University of Southampton to obtain CT data with a scan time of four hours. An acquired voxel resolution of 7.9μm allowed examination of airway lumens along its length and a 3D volume reconstruction of a branching small airways network created using VG Studio Max (v2.1) and Arisio 7 image processing software.

Results: Lung tissue was clearly distinguishable from the airspaces in scans permitting a clear 3D reconstruction of all airways and blood vessels in the sample. Airway cross section measurement was possible down to the respiratory bronchioli at ~<0.5mm. This will permit the estimation of potential volumetric air flows from the alveoli to the small airways.

Conclusion: We have shown that it is possible to use micro-CT to analyse and reconstruct small airways structure in human tissue down to the respiratory bronchioli with a resolution of 7.9μm. Using formalin fixed and paraffin embedded tissue without any contrasting agents can provide robust 3D structural data from archival material.

P274  
Using micro-CT to map the small airways

Katherine Scoll1, Dnutry Griner2, Sam Kayes2, Peter Lackie2, Jane Warner1. 1Faculty of Medicine, University of Southampton, United Kingdom; 2Engineering Materials Group, Faculty of Engineering and the Environment, University of Southampton, United Kingdom

Introduction: The loss or narrowing of small airways (~<2mm) leads to an increase in peripheral resistance and is a major site of airway disease in COPD. Quantitative studies of the structural changes in the small airways in COPD patients is required to assess this. Micro-CT permits direct examination of the small airways and microvasculature. However, most studies to date have used eosin or other contrasting agents precluding the use of historical samples.

Aim: To use micro-CT to identify and measure the small airways in paraffin embedded tissue without contrast agents.

Methods: Tissue from the distal airways was fixed and embedded in paraffin wax. It was scanned with a Nikon/Perkin HMX XCT scanner at the μ-VES X-ray imaging centre, University of Southampton to obtain CT data with a scan time of four hours. An acquired voxel resolution of 7.9μm allowed examination of airway lumens along its length and a 3D volume reconstruction of a branching small airways network created using VG Studio Max (v2.1) and Arisio 7 image processing software.

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Conclusion: We have shown that it is possible to use micro-CT to analyse and reconstruct small airways structure in human tissue down to the respiratory bronchioli with a resolution of 7.9μm. Using formalin fixed and paraffin embedded tissue without any contrasting agents can provide robust 3D structural data from archival material.

P275  
CT protocols in interstitial lung diseases – A survey among members of the European Society of Thoracic Imaging (ESTI)

Helmut Prosch1, Cornelia Schaefer-Prokop1, Edith Eisenhuber2, Daniele Kiendl1, Christian Herold3. 1Department of Radiology, Medical University of Vienna, Austria; 2Department of Radiology, Hospital Gartenthaller, Heiland, Vienna, Austria; 3Department of Radiology, Academic Medical Center, Amsterdam, Netherlands

Objective: To survey the current HR-CT protocols used by members of the European Society of Thoracic Imaging (ESTI) to evaluate patients with interstitial lung diseases.

Materials and methods: A questionnaire was e-mailed to 173 ESTI members. The survey focused on questions regarding the practice of CT protocols in patients with suspected interstitial lung diseases. In particular, the members were asked whether they used discontinuous HR-CT or volume CT protocols, performed additional expiratory scans, or obtained scans in the prone position. In addition, the questions focused on dose considerations and on which reconstructions were performed routinely.

Results: The overall response rate was 37%. Seventy-seven percent of the respondents indicated that they evaluated their patients with routine protocols; 85% used either volume CT alone or in combination with discontinuous HR-CT, only a minority of 15% performed discontinuous HR-CT only. Fifty-three percent reported that they applied a low-dose volume CT protocol. Expiratory scans or scans in the prone position were performed by a majority of the respondent on demand only (58% and 59%, respectively). The number of reconstructions ranged from two reconstructions to up to eight standard reconstructions. Fifteen respondents reconstructed two series, 18 respondents routinely reconstructed three or four series, and 16 respondents reconstructed five series or more.

Conclusion: ESTI members seem to prefer volume CT to investigate patients with suspected interstitial lung diseases. The reported and surprisingly high prevalence of low-dose CT protocols may be due radiation dose considerations and requires further investigation.

P276  
Cumulative exposure to ionising radiation in adults with non-CF bronchiectasis

Liam Taha, Dinez Nazareth, Syed Kazmi, Martin Walsham. Department of Respiratory Medicine, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

Background: As treatments improve and patients with non-CF bronchiectasis are surviving longer, the cumulative exposure to potentially carcinogenic ionising radiation is important. We looked at the amount of ionising radiation given to adults with this condition (n=66) attending our Respiratory clinic over a 12-month period.

Method: All ionising radiation studies were reviewed for their impact on management. Radiation was calculated using standard reference doses and expressed as mSv.

Results: See Table. The average radiation dose was 11.43 mSv. Overall, only 15%
of chest X-rays and 62% of Chest CT’s resulted in a change in management. Those with more severe disease had a greater cumulative dose of radiation. 

**Conclusion:** Patients with bronchiectasis receive significant medical radiation each year, but most impacts on their management. Those colonised with *Pseudomonas* are associated with greater levels, in keeping with the more significant disease burden in these individuals. Care should be taken when ordering investigations associated with ionising radiation, to reduce the long term effects of potentially harmful investigations.

**P277**

**Cumulative exposure to ionising radiation in adults with interstitial lung disease (ILD)**

Lamis Taha, Dilip Nazareth, Syed Kjrmi, Martin Wilshaw. Department of Respiratory Medicine, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

**Background:** The cumulative exposure to potentially carcinogenic ionising radiation is important in patients with ILD as they are exposed to multiple radiological investigations. The risk is compounded as the amount of ionising radiation given to adults with ILD (n=41) attending our Respiratory clinic over a 12-month period.

**Method:** All ionising radiation studies were reviewed for their impact on management. Radiation was calculated using standard reference doses and expressed as mSv.

**Results:** See Table. The average radiation dose was 12.33 mSv with 56% of investigations impacting care. Those with UIP pattern of fibrosis had a greater cumulative dose of radiation.

<table>
<thead>
<tr>
<th>Radiation doses and % impacting care</th>
<th>Mean Radiation Dose (mSv)</th>
<th>% impacting care</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=41)</td>
<td>12.33</td>
<td>56</td>
</tr>
<tr>
<td>UIP (n=24)</td>
<td>12.98</td>
<td>62</td>
</tr>
<tr>
<td>NSIP (n=8)</td>
<td>11.29</td>
<td>71</td>
</tr>
<tr>
<td>Other Fibrosis (n=9)</td>
<td>11.9</td>
<td>68</td>
</tr>
</tbody>
</table>

**Conclusion:** Patients with ILD receive significant medical radiation each year, but most impacts on their management. Those with NSIP had a greater number of investigations impacting care as compared to those with UIP, in keeping with the wider spectrum of disease and more treatment options being available in this sub-group of patients. Care should be taken when ordering investigations associated with ionising radiation, to reduce the long term effects of potentially harmful investigations.

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**58. Ultrasound in pulmonary medicine: from inside and outside**

**P278**

**Diagnostic performance/learning curve and tolerance of endobronchial ultrasound (EBUS)**

Estefanía Luque, Pablo Sanchez. Ultrasound (EBUS)

**Objectives:** To analyze the diagnostic performance of transbronchial needle aspiration guided by endobronchial ultrasound (EBUS-TBNA) in diagnosing hilar/mediastinal lymphadenopathies and/or lung masses in our department and the possible effects of the learning curve. To evaluate the tolerance of the procedure by both the patient and the bronchoscopist.

**Materials and methods:** Retrospective study of all patients referred to our department (January 2010-October 2011) to perform EBUS-TBNA. At the end of the technique, both the patients and bronchoscopist answered a tolerance questionnaire (scale of 0 to 10).

**Results:** 129 patients. 325 aspirations were performed. The most common indication was suspicion of malignancy (48.8%). The most frequent final diagnosis was normal lymph nodes (46.5%), followed by neoplasm (35.6%). The sensitivity (S) and specificity (N) were 83.3%. The most frequent final diagnosis was normal lymph nodes (46.5%), followed by neoplasm (35.6%). The sensitivity (S) and specificity (N) were 83.3% and 94.1%, respectively. With regard to complications, 90.7% did not register any complication.

**Conclusions:** EBUS-TBNA is a diagnostic tool with a high profitability in the study of hilar/mediastinal lymphadenopathies which was higher in neoplastic lymphadenopathy. In our case, there were not statistically significant differences regarding the diagnostic performance of the technique during the learning curve. EBUS-TBNA is a safe and well-tolerated method by both the patient and the endoscopist.

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**P279**

**Modified technique for endobronchial ultrasound-guided transbronchial needle sampling of the mediastinum**

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**Background:** The endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a method of endoscopic diagnosis for study of mediastinal involvement. Fine needle capillarity sampling has been applied in other organs and has shown high performance in terms of efficacy and sample adequacy to EBUS-TBNA yields. Furthermore, it is arguably simpler than the classical technique.

**Methods:** We included all patients undergoing EBUS exploration between January 1 to August 31 of 2011 in the Pulmonology Department at Clínica Universidad de Navarra in Pamplona, Spain. The samples were collected by capillarity (FNC). No suction was applied with the Vaclock syringe and the inner stylet was never completely removed, as dictated by the classical technique.

**Results:** Forty-four patients (75% male) were included in the study. EBUS exploration of the mediastinum identified lymphadenopathy or mediastinal masses in 38 patients (86.4%). More than one lymph node was sampled in 23 patients (52.3%). The analysis of samples reported that all punctures in lymph nodes with the capillarity technique provided adequate and representative material for interpretation, with a diagnostic yield of 86.8%. The diagnostic sensitivity achieved with EBUS-FNC for adequate samples was 88%, and 84.1% considering all samples. Complications were reported in only two patients (4.5%).

**Conclusions:** Our study suggests that the modified technique (EBUS-FNC) is safe and comparable in terms of efficacy and sample adequacy to EBUS-TBNA yields. Furthermore, it is arguably simpler than the classical technique.

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**P280**

**Lymph node core retrieval comparison between 22 and 21 gauge EBUS-TBNA needle**

Prashant Chhipa1, H.S. Sandeep1, Parag Chaudhari1, Sejal Gandhi1, Ramesh Tikare2, Joesy Leuppi2, Arvind Kanji1. Pulmonology, Institute of Pulmonology, Medical Research & Development; Lung Care & Sleep Centre, Vashi, Navi Mumbai, Maharashtra, India; 2Pulmonology, Institute of Pulmonology, Medical Research & Development, Mumbai, Maharashtra, India; 3Anaesthesiology, Fortis-Hiranandani Hospital, Vashi, Navi Mumbai, Maharashtra, India

**Introduction:** Yield of EBUS-TBNA depends upon the quality of aspirate/ core obtained.

**Aim:** Analysis of diagnostic yield of lymph node aspirate using 22 and 21 gauge EBUS-TBNA needle.

**Methods:** A retrospective analysis was performed on 72 consecutive patients who underwent EBUS-TBNA. Of 72 patients first 44 patients underwent EBUS-TBNA using 22 gauge needle and subsequent 28 patients underwent EBUS-TBNA using 21 gauge needle. EBUS-TBNA was performed by single experienced interventional pulmonologist under sedation. By coincidence, since availability of 21 gauge needle suction is not being routinely applied for initial passes. Needle is moved back and forth without suction. Suction with provided syringe is applied only in cases with inadequate sample.

**Conclusions:** EBUS-TBNA using 21 gauge needle is comparable in terms of efficacy and sample adequacy to EBUS-TBNA using 22 gauge needle.

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**SUNDAY, SEPTEMBER 2ND 2012**

**Table 1. Diagnostic yield**

<table>
<thead>
<tr>
<th></th>
<th>EBUS-TBNA using 21 gauge needle</th>
<th>EBUS-TBNA using 22 gauge needle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>28</td>
<td>44</td>
</tr>
<tr>
<td>Histology core samples available</td>
<td>26 (92.8%)</td>
<td>23 (52.2%)</td>
</tr>
<tr>
<td>Histological opinion possible</td>
<td>19 (67.8%)</td>
<td>10 (22.7%)</td>
</tr>
<tr>
<td>Final diagnosis possible</td>
<td>21 (75%)</td>
<td>35 (79.5%)</td>
</tr>
<tr>
<td>Diagnosis on histology only</td>
<td>8 (28.5%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Diagnosis on cytology only</td>
<td>1 (3.3%)</td>
<td>26 (59%)</td>
</tr>
</tbody>
</table>
P281

Achieving core biopsies for histology using gauge 21 needle during endobronchial ultrasound guided transbronchial needle aspiration

Dimitria Petkou1, Edward Nash2, Simon Trotter3, 1Respiratory Medicine, Heart of England NHS Foundation Trust, Sutton Coldfield, West Midlands, United Kingdom; 2Respiratory Medicine, Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Birmingham, West Midlands, United Kingdom; 3Histopathology Department, Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Birmingham, West Midlands, United Kingdom

Introduction: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is a safe method for sampling mediastinal lymph nodes. A dedicated 22 or 21 gauge (G) needle is used to perform EBUS-TBNA. The 22G needle provides material for cytology. The 21G needle is stiffer and allows larger samples.

Objectives: To evaluate whether the material obtained using 21G needle will be suitable for histological assessment and to determine the safety of the procedure.

Methods: 106 consecutive patients were included. The samples obtained by 21G needle after were received as friable cores of tissue. Their size was suited for histological processing and examination as biopsies. Microbiology was performed in selected cases.

Results: Core biopsies were obtained in 105 patients (99%). Malignancy was confirmed in 51 patients (48%). The histology of 20 (19%) patients showed granulomatous inflammation. Normal lymph node or reactive changes were reported in 22 (21%) cases. The samples of the remaining 11 (10%) patients were not representative. 3 patients with suspicious of malignancy imaging and negative histology underwent mediastinoscopy which confirmed reactive lymph tissue. EBUS-TBNA material was sufficient for EGRF testing. In 3 patients tuberculosis was confirmed by microbiology culture. The procedure was completed in all patients but one. 15 (14%) patients had significant cough, 2 (2%) patients complained of chest discomfort and 5 (5%) developed transient hypoxia, which did not require termination of the procedure.

Conclusion: Using 21 G needle for EBUS-TBNA is safe. It provides core biopsies for histological evaluation of mediastinal lymphadenopathy.

P282

Using forceps biopsy during endobronchial ultrasound is feasible in routine practise*

Bruno Escarguel1, Georges Thomas1, Cécile Tchoudjian1, Alexandre Chollat2, Namy2, Cyril Fou3, Jean Baptiste Paoli3, Alain Poisson1.

1, Georges Thomas1, Cécile Tchoudjian1, Alexandre Chollat2, Namy2, Cyril Fou3, Jean Baptiste Paoli3, Alain Poisson1.

Material and methods: In the thoracic endoscopic unit of the hopital St Joseph (Marseille, France) during June 2011-decembrer 2011, we used a pediatric for-
ces biopsy after each puncture by EBUS TBNA. 13 patients were analysed, 16 mediastinal sites (7, 4R, 10R, 11R, 12R, 4L, 11L) were biopsied (3 histological specimens) after using a 21 or 22G needle. All the procedures were doing under local anaesthesia. Especialy during a staging in lung cancer, big tissue become more necessary.

Forceps biopsy have been used in biopsy of subcarinal masses with interesting results for lymphomas or sarcoidosis, without major complications. What happend in routine practise and using forceps for other mediastinal sites ?

Introduction: EBUS is becoming a gold standard in exploring mediastinum ab-normality. Especially during a staging in lung cancer, big tissue become more necessary.

Forceps biopsy have been used in biopsy of subcarinal masses with interesting results for lymphomas or sarcoidosis, without major complications. What happend in routine practise and using forceps for other mediastinal sites ?

Material and methods: In the thoracic endoscopic unit of the hopital St Joseph (Marseille, France) during June 2011-decembrer 2011, we used a pediatric for-
ces biopsy after each puncture by EBUS TBNA. 13 patients were analysed, 16 mediastinal sites (7, 4R, 10R, 11R, 12R, 4L, 11L) were biopsied (3 histological specimens) after using a 21 or 22G needle. All the procedures were doing under local anaesthesia using a laryngeal mask.

Results: The average diameter of lymph nodes was 15.3 mm. In only two samples, the results were not significant. Concerning cancerous results (50%), the forceps biopsy did not increase diagnostic yield versus TBNA (Slides or cytology). Biomarker analyses were possible for metastasis patients. In one case, sarcoidosis diagnosis was made only with forceps biopsy. There were no immediate complications.

Conclusion: Using forceps biopsy during EBUS is feasible and safe. We can per-
form this procedure for the different sites of the mediastinum. The result doesn’t show an increasing diagnostic value in lung cancer but could be interesting for lymphoma or non malignant disorders as sarcoidosis.

P283

Endobronchial ultrasonography: Initial experience at a reference center in South America

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Introduction: Minimally invasive diagnostic procedures as endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), have been incorpo-
rated to the diagnostic algorithm of mediastinal pathologies or lesions adjacent to the central airways. There are multiples publications on its diagnostic performance in Europe, North America and Asia, but not in South America.

Objectives: To report the initial experience in EBUS-TBNA in a reference center of South America.

Patients and methods: Retrospective analysis of consecutive patients in whom EBUS-TBNA was performed for mediastinal and/or hilar lesions or lesions adja-
cent to central airways, demonstrated by chest CT-scan. Demographic information, lesions number, localization, and results together with definitive diagnosis, and com-
plications of the procedure, were registered. Sensitivity, specificity, predictive values and accuracy were calculated.

Results: 129 lesions were punctured in 85 patients (47 males), mean age of 62.8 years (25-86). Stations 4R, 7, 10R and 4L were the most frequently sampled. 82% were lesions of 20mm or less. Lung cancer and metastatic disease were the most common diagnosis (62%). Sensitivity 91% (CI 95%: 84-96), specificity 100% (CI 95%: 82-100), positive predictive value 100% (CI 95%: 94-100), negative predictive value 72% (CI 95%: 53-86), accuracy 93%. No complications were reported.

Conclusion: Our series has demonstrated the usefulness of EBUS-TBNA for the diagnosis of mediastinal lymph nodes or lesions adjacent to the central airways, in a Latin American reference center. Our diagnostic accuracy has been in agreement with previously published results in centers of Europe, Asia, and Northamerica.

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Complications and diagnostic outcome of endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) of mediastinal lymph nodes

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Background: EBUS guided TBNA enables tissue sampling of mediastinal lymph nodes with sensitivity and specificity comparable to mediastinoscopy in nodal staging of lung cancer. It is generally safe but not without complications.

Objectives: We studied the complications and diagnostic outcome of EBUS-TBNA performed under local anaesthesia and sedation using intravenous mi-
dizolam and pethidine in the endoscopy suites.

Methods: We retrospectively studied consecutive EBUS examinations performed over 28 months since July 2008. Pathology and clinical follow-up data till end of 2010 were reviewed.

Results: Totally 110 EBUS-TBNA were performed in the study period. Complications occurred in 21 (19%) patients. Difficulty in conscious sedation accounted for the majority (97% 12 patients, 11%) including oversedation requiring antidotes (2), failed sedation (2) and one struggling patient leading to probe damage. Other complications included moderate bleeding of 15cc blood loss (2), bronchospasm (2), fever (1), pneumonia (1), paroxysmal atrial fibrillation (1). No long term adverse effect was found after EBUS-TBNA.

Among 80 patients referred for nodal staging of lung cancer, 131 lymph nodes were sampled, resulting in 53 true positives, 20 true negatives, 7 nondiagnostic TBNA. The sensitivity of EBUS-TBNA for diagnosing metastatic lymph node disease was 88.3% and the specificity was 100%. The diagnostic yield of EBUS-TBNA was 63% in 30 patients with inflammatory diseases including tuberculosis.

Conclusion: EBUS-TBNA is a safe procedure with reasonable diagnostic value and its complications were mostly associated with conscious sedation.

P285

Impact of multiple operators on diagnostic yield of EBUS-TBNA

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Background: EBUS-TBNA is usually performed by a limited number of operators at each institution in order to achieve optimal yield by accumulating individual ex-
pertise. We aimed to assess the diagnostic performance and safety of EBUS-TBNA when this procedure is learned by every trainee.

Methods: All consecutive patients undergoing EBUS-TBNA were prospectively included since the introduction of EBUS in our institution in January 2008 until December 2011. Each procedure was done by 2 or 3 operators including 1 senior supervisor. Rapid on-site cytologic evaluation (ROSE) was performed since June 2011. Predicting factors for the diagnostic accuracy of EBUS-TBNA were analyzed per patient and per sampled lymph node.
Results: 15 operators performed EBUS-TBNA in 160 patients. Definitive diagnosis was available for 156 patients (mean age 59.4±14.6 years; 38.5% F). Lymph nodes were malignant in 53.2%. Overall diagnostic accuracy was 82.7% (95% CI: 76.4-88.2) and 90.3% (95% CI: 81.3-97.1) for NSCLC and SCLC (n=72). Overall diagnostic accuracy tended to increase over years: 70.6%, 81.8%, 82.9%, and 85.9% in 2008, 2009, 2010 and 2011 respectively (p<0.51). Subgroup analysis showed no significant influence of ROSE, number of sampled nodes per case, localization and size of lymph node and SUN >10. Complications were restricted to 3 minor endobronchial bleeding.

Conclusion: A) Genova University Hospitals, EBUS-TBNA performance increased over years following well-known learning curves. Yet, in our setting, EBUS-learning curve seemed rather center-than operator-related. Providing on site direct supervision by a senior-experienced operator, EBUS is indeed constantly performed by junior operators without affecting the performance of the method.

P286 Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) under conscious sedation: Patient satisfaction in a UK tertiary center

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Background: There is a variation in the modality of sedation/anaesthesia used during EBUS-TBNA. Despite this, there are no studies assessing patient satisfaction.

We therefore conducted a prospective study to characterize patient satisfaction with EBUS-TBNA performed under conscious sedation.

Methods: 101 consecutive patients (mean age 64) undergoing EBUS using topical lignocaine and iv midazolam were evaluated using a structured questionnaire 2 hrs post procedure.

Results: The mean dose of lignocaine throat spray was 178 mg and 99% received transtracheal lignocaine. The mean dose of iv midazolam was 3.3 mg and all patients were adequately sedated. 161 lymph nodes (stations 2, 4, 7, 10 & 11) were biopsied with a mean procedure duration of 17 cm (range 0.6-4 cm, less than 1 cm nodes 22). Mean duration of procedure was 20 mins and the mean number of needle passes per node was 2.3. EBUS was diagnostic in 96% and there were no complications.

Frequency of reported symptoms (%): 86% were tolerant of the procedure and the overall patient satisfaction was 97% (good - excellent). 78% would definitely return and 19% would probably return.

Conclusion: EBUS-TBNA under conscious sedation is safe and well tolerated. Conscious sedation is physician delivered and less resource intensive, and therefore could be adopted as the method of choice as EBUS services continue to expand.

P287 Assessing the learning curve for EUS(b)-FNA in comparison with classical ‘blind’ TBNA

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Background: Transbronchial needle aspiration (TBNA) is a challenge due to very flat learning curve. Now, EUS and EBUS significantly improved the results of TBNA. Nevertheless, number of ‘learning’ procedures to become an expert in this type of biopsy is controversial.

Aim: To determine the efficacy of EBUS-TBNA results in the evaluation of mediastinal lymph nodes in patients with extrathoracic malignancy.

Material and Methods: Retrospective analysis was performed in 40 patients with proven (n=38) or suspected metastasis of unknown origin (n=2) who underwent EBUS-TBNA between July 2007 and August 2011.

Results: All 40 patients successfully underwent EBUS-TBNA and no complications were observed. In 16 (40%) patients, EBUS-TBNA demonstrated metastasis of extrathoracic malignancy. Two (5%) patients diagnosed as a new lung cancer with EBUS-TBNA. The diagnostic sensitivity, accuracy, and negative predicted value (NPV) of EBUS-TBNA per patient were 90.0%, 95.0%, and 90.9%, respectively.

Conclusion: EBUS-TBNA is a sensitive and specific method for the histopathological diagnosis of mediastinal and hilar lymph nodes in patients with extrathoracic malignancy.

P288 The usefulness of endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of sarcoidosis

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We evaluated the usefulness of endobronchial ultrasound guided-transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of sarcoidosis in comparison with transbronchial lung biopsy (TBLB), endobronchial biopsy (EBB), and bronchoalveolar lavage (BAL). The consecutive patients who were suspicious for sarcoidosis (stage I and II) on chest radiography and chest computed tomography scan were included in the study. All study patients underwent EBUS-TBNA, TBLB, EBB and BAL at the same session. Between July 2009 and June 2011, 33 patients underwent EBUS-TBNA, TBLB, EBB, and BAL. EBUS-TBNA was performed for 71 lymph node stations. Among these 33 patients, 29 patients were diagnosed as histology proven sarcoidosis and two patients were compatible with clinical diagnosis of sarcoidosis during follow-up. The other two patients were diagnosed as metastatic carcinoma and reactive lymphadenopathy. Among 39 patients with histology proven sarcoidosis in combination with EBUS-TBNA, TBLB, and EBB, only EBUS-TBNA and TBLB revealed non-caseating granuloma in 18 patients and 1 patient, respectively. Overall diagnostic sensitivities of EBUS-TBNA, TBLB, EBB, and BAL (CD4/CD8 >3.5) were 90%, 35%, 6%, and 71%, respectively (p<0.001). Combined diagnostic sensitivity of EBUS-TBNA, TBLB, and EBB were 94%. In conclusions, EBUS-TBNA is most sensitive method for the diagnosis of stage I and II sarcoidosis compared with conventional bronchoscopic procedures. EBUS-TBNA could be considered first for the histopathologic diagnosis of stage I and II sarcoidosis.

P289 Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of extrathoracic lymphadenopathy in patients with extrathoracic malignancy: A study in a tuberculosis-endemic country

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Background: Mediastinal lymphadenopathy in patients with malignancy is a common clinical problem in tuberculosis-endemic countries. The recently developed endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) procedure enables direct and real-time aspiration of mediastinal and hilar lymph nodes and is a less invasive alternative to mediastinoscopy.

Aim: To determine the efficacy of EBUS-TBNA results in the evaluation of mediastinal lymph nodes in patients with extrathoracic malignancy.

Methods: Retrospective analysis was performed in 40 patients with proven (n=38) or suspected metastasis of unknown origin (n=2) who underwent EBUS-TBNA between July 2007 and August 2011.

Results: All 40 patients successfully underwent EBUS-TBNA and no complications were observed. In 16 (40%) patients, EBUS-TBNA demonstrated metastasis of extrathoracic malignancy. Two (5%) patients diagnosed as a new lung cancer with EBUS-TBNA. The diagnostic sensitivity, accuracy, and negative predicted value (NPV) of EBUS-TBNA per patient were 90.0%, 95.0%, and 90.9%, respectively.

Conclusion: EBUS-TBNA is a sensitive and specific method for the histopathological diagnosis of mediastinal and hilar lymphadenopathy in patients with extrapulmonary malignancy.

P290 The role of endobronchial ultrasound guided biopsy in diagnosis of mediastinal/hilar lymphadenopathy in patients with extrathoracic malignancy

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Accurate diagnosis of enlarged hilar/mediastinal lymph nodes is mandatory for adequate management of patients with known primary malignancy. We aimed to determine the sensitivity, specificity, accuracy of EBUS-TBNA for clarification of the nature of enlarged hilar/mediastinal lymph nodes in patients with known extrathoracic malignancy. Patients with extrathoracic malignancy who had undergone EBUS-TBNA for assessment of enlarged hilar/mediastinal lymph nodes in December 2008-September 2011 were reviewed. 48 patients who underwent EBUS-TBNA...
were included. Mean age of 12 male, 36 female patients was 57.38±11.60. Malignancy was detected in 18 (37.5%), tuberculosis in 6 (12.5%), sarcoidosis in 4 (8.3%), lung abscess in 2 (4.2%), reactive adenitis in 18 (37.5%). EBUS-TBNA was also found to offer an effective accurate and minimally invasive strategy for evaluating non-malignant lesions of pathological hilar and mediastinal lymph nodes such as tuberculosis and sarcoidosis. The sensitivity and specificity of EBUS-TBNA for malignancy in patients with reference pathology was 83% and 100%, respectively. Negative predictive value for malignancy was 90%. Procedure-related complications were minor being bleeding in 2(4.2%) and reversible desaturation in 1. When benign hilar lymph nodes are considered sensitivity, specificity and negative predictive value were 88%, 100% and 88%, respectively. We conclude that EBUS is a safe, minimally invasive, inexpensive and accurate procedure for diagnosing mediastinal/hilar lymphadenopathy in patients with extrathoracic malignancy. Nevertheless, due to the possibility of underdiagnosis, an invasive technique is indicated when results are negative.

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The diagnostic yield of ultrasound-assisted pleural biopsy in pleural effusions following non-diagnostic thoracentesis

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Background: Unailed (“blind”) pleural biopsy is prone to sampling error and may not represent the true pleural pathology. US-assisted closed pleural biopsy in the setting of undiagnosed effusions, and investigated how pleural morphology could guide the selection and execution of closed pleural biopsy.

Methods: Patients with an exudative effusion who had had a non-diagnostic thoracentesis were prospectively stratified on imaging as having (A) an associated mass lesion (>10mm) abutting the chest wall; (B) diffuse pleural thickening (>10mm) and/or nodularity or (C) insignificant/no pleural thickening. US-assisted repeat thoracentesis and transthoracic fine-needle aspiration (TTFNA) were performed on patients stratified to (A), and if non-diagnostic on on-site analysis, followed by a Tru-Cut biopsy. US-assisted thoracentesis and Abrams needle biopsies were performed on all others aiming at the region(s) of interest (B) or low supra-diaphragmatic pleura (C).

Results: Final diagnoses in 41 consecutive patients (30 males, 47±18 years) included pleural TB (n=21), malignancy (n=16) and other causes (n=29). Accurate diagnoses were obtained in 34 (82.9%) patients. US-assisted biopsy; thoracotomy (n=6, 14.6%) or bronchoscopy (n=11) were required in the rest. The yield of US-assisted biopsy was higher for TB (93.3%, 90.48%) than malignancy (12/16, 75.0%, p=0.037). One patient experienced mild haemoptysis following TTENPA. Conclusion: A diagnostic algorithm based on pleural morphology and US-assisted pleural biopsy has a high diagnostic yield and offers a safe first-line approach in the setting of undiagnosed pleural exudates.

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Highly diagnostic yield of ultrasound-guided pleural biopsy for exudative lymphoctic pleural effusion

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Objectives: To assess the diagnostic value of the US-guided pleural biopsy, we prospectively enrolled 54 patients with nondiagnostic exudative PEs between May, 2010 and January, 2012 at Prathongkuttlak Hospial. Nineteen cases were received traditionally closed pleural biopsy with Abrams needles and the others were performed the US-guided pleural biopsy with the Abrams and Cope’s needles.

Materials and methods: To assess the diagnostic value of the US-guided pleural biopsy, we prospectively enrolled 54 patients with nondiagnostic exudative PEs between May, 2010 and January, 2012 at Prathongkuttlak Hospital. Nineteen cases were received traditionally closed pleural biopsy with Abrams needles and the others were performed the US-guided pleural biopsy with the Abrams and Cope’s needles.

Results: Twenty (63.15%), 6 (31.6%) and 1 (5.3%) cases receiving closed pleural biopsy were diagnosed as malignancy, tuberculosis, and uremic pleurisies, respectively. Twenty five (71.4%) and 9 (25.7%) cases receiving US-guided pleural biopsy were diagnosed as malignancy and tuberculosis, respectively. Twenty five (71.4%) and 9 (25.7%) cases receiving US-guided pleural biopsy were diagnosed as malignancy and tuberculosis, respectively. Twenty five (71.4%) and 9 (25.7%) cases receiving US-guided pleural biopsy were diagnosed as malignancy and tuberculosis, respectively. Twenty five (71.4%) and 9 (25.7%) cases receiving US-guided pleural biopsy were diagnosed as malignancy and tuberculosis, respectively.

Conclusion: US-guided pleural biopsy with Abrams needle is effective for specific diagnosis of exudative lymphoctic PEs.
years). 42 patients underwent tru-cut biopsy of lung and 15 cases underwent FNAC of lung. Mean tumour sizes were 60.2±29.3 mm. Histological/cytological examination provided the diagnosis in 53 cases: lung cancer – 40, other malignant tumours – 3, benign tumours – 2, granuloma – 6, and organizing pneumonia – 2. Adenocarcinoma (22 cases) was the most common lung cancer detected. In three cases the diagnosis was inconclusive. Complications were observed in five patients: mild haemoptysis which improved spontaneously – 2, subcutaneous emphysema – 1 (improved without any intervention), and pneumothorax in two patients, one of whom required tube thoracostomy.

Conclusions: USG guided trucut biopsy/FNAC of lung gives a high diagnostic yield in peripheral lung lesions. Complication rate of the procedure is low.

59. Airway diseases: from invasive to noninvasive biomarkers

P296 Bronchial mucosal dendritic cells and VEGF expression in COPD patients Andrea Zani1, Sabrina Della Patrona2, Federico Gumiero3, Maria Majori1, Danilo Olivarrieri1, Antonio Spanevillo1, Alfredo Chetta1. 1Department of Respiratory Disease, University of Bradford, Bradford, Varese, Italy; 2Division of Pneumology, Salvatore Maugeri Foundation IRCCS Rehabilitation Institute, Tradate, Varese, Italy; 3Cardio-Nephro-Pulmonary Dept, University Hospital, Parma, Italy

Introduction: Dendritic cells (DCs) have a pivotal role in the onset and regulation of innate and adaptive immune responses. A decreased number of mature DCs may occur in the airways of COPD patients, thereby reducing their immune response. Moreover, DCs can affect vascularization process in different physiological conditions. There are no data concerning the relationship between DCs and vascular endothelial growth factor (VEGF) in COPD patients.

Objectives: We evaluated the relationship between the expression of VEGF and the density of DCs in the bronchial mucosa of COPD patients.

Methods: Twenty patients with moderate to severe COPD (age 76±10 yr, 3 F; FEV1 51±9%, FEV1/FVC 48±12%) were studied. Eight healthy subjects represented a control group (CS). Bronchial biopsies were evaluated by immuno-histochemistry and presence of DCs was investigated by using antibody directed against CD207, to mark immature DCs, and against CD83, to mark mature DCs.

Data are presented as mean±SD. In all COPD patients, CD207+ cells were inversely related to FEV1 (r=-0.52, p<0.05) and CD83+ cells were inversely related to VEGF expression (r=-0.45, p<0.05).

Conclusions: Our results show that COPD airways were associated with a decrease in mature DCs and that these cells were inversely related to VEGF expression. Additionally, immature DCs were significantly related to airflow obstruction. We speculate that the DC-VEGF interplay may play a key role both in angiogenesis and in the immune response in COPD patients.

P297 Correlation between airway smooth muscle (ASM) and eosinophilic inflammation in severe non-controlled asthmatics Regina Maria Carvalho-Pinto1,Albertoucker1, Thais Mainaud2, Marisa Dolinhkoff2, Marcelo Gervilla Gregório2, Ray Camargo Pires Neto2, Aila Mirtes Teles1, Klaus F. Rabe1, Reinaldo Stelmach1, 1Pulmonary Division, Heart Institute (InCor) - University of São Paulo Medical School, São Paulo, SP, Brazil; 2Department of Pathology, University of São Paulo Medical School, São Paulo, SP, Brazil.

Background: Airway muscle hypertrophy is a surrogate of airway remodeling and eosinophilia in induced sputum (IS) is associated to lack of asthma control.

Objective: Compare the amount of ASM in endobronchial biopsies with eosinophils % (Eos) in IS in severe asthmatics after optimal treatment.

Methods: 62 severe asthmatics received a 2-week prednisone trial and high inhaled corticosteroid dose (ICS) plus LABA for 12 weeks and were classified according to lung function: 1. the 2-week oral corticosteroid trial. Persistent airflow obstruction (PAO) was defined by FEV1 post BD <80% plus FEV1/FVC post BD <0.70. IS and bronchial biopsies were performed at the end of the 12 weeks. The fractional area of ASM, assessed by quantification of alpha-smooth muscle actin, and Eos % in IS were assessed.

Results: 48 patients were classified as PAO, 14 as non persistent airflow obstruction (NPAO). The fractional area of ASM was higher in PAO (p=0.041), but Neu% and Eos% in IS was not different between groups. There was a strong inverse correlation between IS Eos and total area muscle actin (r = -0.93, p=0.001) in the NPAO and a positive correlation in the PAO group (r = 0.36, p = 0.038). No correlations were found with Neu.

Conclusions: Persistent obstructed severe asthmatics have more smooth muscle hypertrophy than normalize lung function patients. Eos inflammation is inversely associated with ASM mass in the biopsies, whereas the opposite occurs in persistent obstructed patients. These data suggest that structural alterations, in parallel with inflammation, are related to functional abnormalities in the persistent obstructed patients.

P298 The EVA study: Characteristics of the study population Loemen Ziegelb7reich1, Dorothee Buggd1, Marion Heiss-Neumann3, Matthias Wjst6. 1EVA Study Centre, Helmholtz Zentrum München, Garching, Germany; 2Institute for Lung Biology and Disease, Helmholtz Zentrum München, Neuharburg, Germany. The emphysema versus airway disease (EVA) study is an EU-funded project with 15 partners in 8 European countries, which aims at identifying markers associated with subphenotypes of chronic obstructive pulmonary disease (COPD) as defined by CT image analysis. The project has recruited 280 controls (average age 59y, 36% females) and 584 patients (average age 65y, 32% females), who comply with stringent exclusion criteria in that current smoking, oral glucocorticoids, anti-coagulation, FEV1 <30% or long term oxygen therapy is not allowed. Although recruitment selected against asthma post-bronchodilator reversibility >200ml was seen in 184 cases (34%) and 58 controls (21%). Chest CT was done in cases only and this is being used as reference to a series of phantoms- to determine lung density and airway wall thickness as a measure of emphysema and airway disease, respectively. Bronchocscopy was done on 421 cases and 278 controls and here we obtained bronchial epithelium with inflated brushes and alveolar macrophages by lavage with up to 110 mL of fluid. Fluid recovery in lavage in average was 43% for controls and 30% for cases, reflecting the more pronounced airway collapse during fluid retrieval in COPD. Recovery of brush material was similar between cases and controls, in that RNA obtained from the right upper lobe was 5.4 ug and 6.4 ug, respectively. The data show that in a multicentric study sizeable amounts of biological material can be obtained from COPD lungs. This material is currently being analyzed for expression of markers associated with the emphysema-dominant and airway disease-dominant subphenotypes of COPD. Supported by EU FP7 project #206005.

P299 Characterisation of patients with difficult-to-treat and treatment-resistant severe asthma Federica Novell; Federico Lorenzo Dente, Maria Laura Bartoli, Silvana Cianchetti, Antonella Di Franco, Lorenzo Molinosa, Elena Bacci, Perluigi Poggiano. Cardiothoracic and Vascular Dept., University of Pisa, Italy

Background: A recent World Health Organization (WHO) meeting proposed a uniform classification of severe asthma (SA) into 3 groups: untreated SA, difficult-to-treat SA, and treatment-resistant SA (JACI 2010).

Aim: To characterize and compare the demographic, functional and inflammatory parameters and the level of control of patients with difficult-to-treat and treatment-resistant SA.

Method: 12 patients with treatment-resistant SA and 24 patients with difficult-to-treat SA (defined according to WHO document) were enrolled in this study (mean age: 59 yrs). All patients underwent ENT visit to evaluate the presence of pathology of the upper airways (in particular rhinosinusitis and/or polyps).

Results: Patients with treatment-resistant SA had a higher sputum eosinophilia (57.1% (3.7-86.2) Vs 12.5 (0-95.6), p<0.01) and a shorter asthma duration (11.5 (3-40) vs 25 (8-50), p<0.01) than patients with difficult-to-treat SA. The indices of asthma control, as well as FEV1, PD20 methacholine, eNO, and the level of treatment were similar in the two groups.

Conclusions: Patients with treatment-resistant SA have a greater eosinophilic inflammation of lower airways than patients with difficult-to-treat SA, but a similar level of control and pharmacologic therapy, suggesting the need for different treatment strategies in the two groups of patients.

P300 Endogenous hydrogen sulfide (H2S) in serum and sputum as novel biomarker of asthma Muneer Saingi1,2, Qingling Zhang1,2, Christopher Hui1,2, Andrew Menzies-Gow1,2, Pankaj Bhavar1,2, Kian Fan Chung1,2, 1Airway Disease Section, National Heart & Lung Institute, Imperial College London, United Kingdom; 2Respiratory Biomedical Research Unit, Royal Brompton Hospital, London, United Kingdom

Background: Hydrogen sulfide (H2S) is considered to be the third gasotransmitter
to moderate asthmatics and controls, being consistent with the hypothesis that epithelium injury & repair play an important role in this phenotype.

P303 Increased levels of angiotensin 1 & 2 in sputum supernatant in smoking asthma

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Background: Angiotensin-1 (Ang-1), is an essential mediator of angiogenesis by establishing vascular integrity, whereas angiotensin-2 (Ang-2) acts as its natural inhibitor.

Objective: We aimed to determine the levels of angiotensins in sputum supernatants of patients with smoking asthma and to investigate possible associations with mediators and cells involved in both the inflammatory and the vascular remodeling process

Methods: Eighty-seven patients with asthma (42 smokers) and 28 healthy subjects (14 smokers) were studied. All subjects underwent lung function tests, bronchial hyperresponsiveness assessment and sputum induction for cell count identification and Ang-1, Ang-2, VEGF, TFG-β1, MMP-2, IL-13, ECP and IL-8 measurement in supernatants. Airway vascular permeability (AVP) index was also assessed.

Results: Ang-1 (ng/ml) and Ang-2 (pg/ml) levels were significantly higher in patients with smoking asthma compared to patients with non-smoking asthma and both smoking and non-smoking healthy subjects (median, interquartile range) 24 (13-37.3) vs 10 (7.14-21) vs 5.3 (3.7-6.5) vs 4.6 (3.8-5.7) respectively, p<0.001; and 168 (132-205) vs 124 (82-152) vs 94 (78-113) vs 100 (96-108) respectively, p<0.001.

Conclusions: Reduced expression of Ang-1 and Ang-2 in smoking asthma compared to non-smoking asthma and healthy subjects pointing towards a contribution of smoking through these mediators to the asthmatic angiogenesis process.

P304 Short-term and long-term reproducibility of non-invasive clinical and inflammatory parameters in asthma

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Several non-invasive parameters have been proposed to monitor tobacco inflammation in asthma. Aim of this study was to assess the reproducibility of established parameters in asthma within 7 days and after 6 months.

In 83 medically treated asthma patients (51 female, mean±SEM 44±1.5 yrs, FEV1% pred 85±6.2, 20 pts. controlled, 30 partly controlled, 33 uncontrolled) with a constant level of asthma control (GINA) and unchanged medication the following tests were performed at baseline, after 7 days (n=70) and after 6 months (n=37): asthma control questionnaire (ACQ-5), exhaled nitric oxide (eNO), lung function tests, methacholine provocation (PC20), measurement of total serum IgE and sputum induction.

Within 7 days ACQ-5, ENO, FEV1 and total IgE were stable with a Cronbach’s alpha between 0.898 (eNO) and 0.993 (ACQ-5) and intraclass correlation coefficients between 0.898 (eNO) and 0.993 (ACQ-5) and intraclass correlation coefficients between 0.898 (eNO) and 0.993 (ACQ-5).

Reproducibility was good with Cronbach’s alpha [intraclass correlation coefficients] between 0.803 [0.755] (ACQ-5) and 0.997 [0.994] (IgE).

In patients with a constant level of asthma control and unchanged medical treatment clinical parameters are reproducible in a short- and long-term interval.

P305 Increased levels of osteopontin in sputum supernatant in patients with COPD

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Background: Osteopontin (OPN) is a glycoprotein that has been associated with inflammation and fibrosis. Recently published data supports that OPN is upregulated in surgical lung tissue samples of patients with COPD (Schneider F et al FASEB 2010).

Osteopontin (OPN) is a glycoprotein that has been associated with inflammation and fibrosis. Recently published data supports that OPN is upregulated in surgical lung tissue samples of patients with COPD (Schneider F et al FASEB 2010).
Aim: The aim of this study was to determine the levels of OPN in sputum supernatants of patients with COPD, and compare them with healthy subjects and to investigate their possible association with mediators and cells involved in the inflammatory and remodeling process as well as with the extension of emphysema as defined by HRCT.

Methods: Seventy-seven patients with COPD and 40 healthy subjects (20 smokers) were studied. All subjects underwent lung function tests, sputum induction for cell count identification and OPN, TGF-β1, MMP-2, IL-8, LTβ4 measurement in sputum supernatants. A HRCT was performed for quantification of emphysema. Measured and Main results: OPN levels [median (interquartile range) pg/ml] were significantly higher in patients with COPD compared to both healthy smokers and non-smokers [1340 (601-6227) vs 101 (50-69) respectively, p<0.001]. Regression analysis showed a significant association between OPN and sputum neutrophils, IL-8, MMP-2 and the extent of emphysema. The above associations were not observed in healthy subjects.

Conclusions: Our results indicate that OPN levels are higher in patients with COPD compared to both smoking and non-smoking healthy subjects. Moreover, the association of OPN with sputum neutrophils, IL-8 and MMP-2 indicates a role of OPN in neutrophilic inflammation while its association with the extent of emphysema shows a role in the pathogenesis of this particular COPD phenotype.

P306 Reference equation and upper limits of fraction of exhaled nitric oxide (FeNO) in a Chinese population

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Background: Measurement of FeNO has been proposed as a biomarker for monitoring and managing airway diseases. Limiting information is available in regard to the reference levels of FeNO levels in adult Chinese. The aim: To investigate the reference equations and upper limits of FeNO in Chinese adults.

Method: 1093 (577 males) healthy non-smoking subjects with age 18-90 yrs were recruited. FeNO was measured online using a chemiluminescence analyser (NOA 280, Sievers Instruments, Boulder, CO, USA). Other assessments included spirometry, skin prick test, total serum immunoglobin E (IgE) levels and eosinophil count in peripheral blood.

Results: The geometric mean FeNO was 32.6% (95% reference interval [RI] 29.0-36.1) ppb (RI=geometric mean±SD) for all subjects. FeNO value was higher in males than females (geometric mean[95%RI]:38.3[34.8-41.8] vs 27.1[26.3-30.6] ppb). FeNO was positively correlated with height (r=0.20), %-smoking (r=0.18), % eosinophil counts (r=0.18) with p value <0.0001, but not with spirometric parameters. Based on multiple regression modeling, the reference equation of FeNO value was as follows: log[FeNO]=0.781 + 0.0144*(sex =1, male; 0, female) + 0.004*(age in years) + 0.084*(atopic, 1, atopic; 0, non-atopic) + 0.003*(height in cm). Example of a non-atopic man and woman with age 41-50 and height 160-170cm would have their 95% upper limits of FeNO being 32.6 and 25.7 ppb respectively.

Conclusion: It appears that the FeNO level of Chinese adults is higher than the Caucasian population.

Supported by HK Lung Foundation Grant & Respiratory Research Fund of CUHK.

P307 An alternative sampling support for collection of particles in exhaled air

Ann-Charlotte Almstrand, Per Larsson, Anna Bredberg, Ekaterina Mirgorodskaya, Anna-Carin Olin. Sahlgrenska Academy at the University of Gothenburg, Occupational and Environmental Medicine, Gothenburg, Sweden

We have previously reported a method to collect material from the airways in the form of exhaled particles (PEx). In the original set-up, PEx were sampled on silicon wafers to fulfill the conditions for downstream TOF SIMS analysis. Application of analytical techniques, such as immunassay or LC-MS, involves extraction of material from the sampling support. PEx extraction from silicon wafers requires large volumes and generates unwanted silica debris.

The aim of this study was to identify PEx sampling supports suitable for use of wet chemistry on the collected material.

Five individuals exhaled 60L onto different sample supports. All sample supports were commercially available filters (Millipore). Samples were extracted in 200 μl of PBS/0.1%Tween and analyzed using albumin ELISA. Lipid was extracted using chloroform/methanol/water, 3:6:2 v/v/v, and analyzed by MALDI TOF/MS. The six tested sample supports were: (1) LCR Membrane; (2) glass fiber; (3) mixed cellulose membrane; (4) Omnipore Membrane; (5) Durapore Membrane; (6) Isopore Membrane. Silicon wafers were included for comparison. The extraction efficiency was evaluated based on the albumin amount extracted from the filters.

The best results were obtained for Filter1, which gave the highest amount of albumin/PEx, w/v. The filter showed good linearity for observed albumin recovery as function of PEx mass, R²=0.98. The suitability of the filter for lipid analysis was confirmed by MALDI TOF/MS of dipalmitoylphosphatidylcholine.

We conclude that hydrophilic LCR Membrane is a good solid support for sampling PEx, suitable for collection of samples when wet chemistry is involved in the followup analysis.


P308 Endogenous particles in exhaled air – Variability of particle number in healthy individuals

Ann-Charlotte Almstrand, Per Larsson, Anna Bredberg, Ekaterina Mirgorodskaya, Anna-Carin Olin. Sahlgrenska Academy at the University of Gothenburg, Occupational and Environmental Medicine, Gothenburg, Sweden

Endogenous particles in exhaled air (PEx) are formed during airway reopening following airway closure. Analysis of PEx may be used for monitoring biochemical alterations in respiratory tract lining fluid in the small airways. The number of exhaled particles is strongly dependent on breathing pattern but there is also a substantial difference between individuals.

The aim of the study was to assess intra-individual variability of PEx number using a standardized breathing maneuver involving airway closure. 10 healthy subjects participated in the study. They were instructed to exhale slowly and completely, inhale to total lung capacity and exhale at 500 ml/s until functional residual capacity. Particles were counted in the final exhalation of the maneuver using an in-house developed instrument. The maneuver was repeated until 80 liters of exhaled air had been sampled. Sampling was performed 3 times (two mornings and one afternoon) for each subject.

The average total number of PEx varied from 9700 to 93 000 particles/exhalation among individuals. The coefficient of variation of total PEx number/exhalation within individuals was 3.9-36.6%, median 12.9%. The coefficient of variation between individuals was 65%. There was no intra-individual difference in particle numbers between morning and afternoon samplings.

The intra-individual variability of PEx number was substantially higher between individuals than within individuals. The high variability between individuals may be due to differences in lung architecture and possibly to differences in the chemical composition of airway lining fluid. Our results support the fact that it is important to control for mass of PEx for any given concentration of non-volatile analyte.

P309 Microsatellite alterations at 3p and 19q in EBC/DNA of smokers: Are they reversible after smoking cessation?

Giovanna Elisiana Carpagnano, Donato Lacedonia, Roberto Sabato, Piergiuseppe Benedetto, Anna Koutelou, Maria Pia Foschino Barbaro. Medical and Occupational Sciences, Respiratory Section, Foggia, Italy

Microsatellite alterations (MAs) at 3p and 19q are early targets for cigarette smoke and markers of genetic susceptibility to lung cancer. Several susceptible genes modulated by smoking have been found to return to baseline years after smoking cessation. Although great interest has been devoted to the classification of smoking-related genetic alterations as reversible or irreversible, as it seems to influence the different biological functions, none have yet focused on MAs at 3p and 19q.

The aim of this study was to analyse MAs at 3p and 19q in exhaled breath condensate (EBC) and in DNA from smokers before and after smoking cessation. The 63 smokers enrolled in the study participated in a multidisciplinary smoking cessation program with a genetic study. All the subjects fulfilled under EBC and whole blood (WB) collection at baseline. The 28 smokers (20 M, 53±8.5 yrs) who stopped smoking followed up and repeated sample collection after 12 months. All subjects had allelotyping analysis of DNA from EBC and WB from a selected panel of seven microsatellites located in 3p and 19q. MAs at 3p and 19q resulted higher in EBC/DNA than in WB/DNA and dose-dependent from cigarette smoking. These somatic alterations both in EBC/DNA and in WB/DNA resulted as being not modificable after 12 months from smoking cessation.

In conclusion we demonstrated for the first time that MAs at 3p and 19q are not modificable in short term from smoking cessation, although a longer follow-up is needed to better classify MA at these loci. Furthermore, we supported the usefulness of smoking cessation programs based on the information on genotype for its potential ecological health.

P310 Exhaled MMP-9 in lung cancer

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Background: MMP-9 has been recognized in several types of tumour development and markers of genetic susceptibility to lung cancer. Several susceptible genes modulated by smoking have been found to return to baseline years after smoking cessation. Although great interest has been devoted to the classification of smoke-related genetic alterations as reversible or irreversible, as it seems to influence the different biological functions, none have yet focused on MAs at 3p and 19q.

The aim of this study was to analyse MAs at 3p and 19q in exhaled breath condensate (EBC) and in WB/DNA of smokers after 12 months from smoking cessation. The 63 smokers enrolled in the study participated in a multidisciplinary smoking cessation program with a genetic study. All the subjects fulfilled under EBC and whole blood (WB) collection at baseline. The 28 smokers (20 M, 53±8.5 yrs) who stopped smoking followed up and repeated sample collection after 12 months. All subjects had allelotyping analysis of DNA from EBC and WB from a selected panel of seven microsatellites located in 3p and 19q. MAs at 3p and 19q resulted higher in EBC/DNA than in WB/DNA and dose-dependent from cigarette smoking. These somatic alterations both in EBC/DNA and in WB/DNA resulted as being not modificable after 12 months from smoking cessation.

In conclusion we demonstrated for the first time that MAs at 3p and 19q are not modificable in short term from smoking cessation, although a longer follow-up is needed to better classify MA at these loci. Furthermore, we supported the usefulness of smoking cessation programs based on the information on genotype for its potential ecological health.
Participants: We enrolled 40 NSCLC patients and 40 controls affected by transudative pleural effusion.

Measurements: MMP-9 concentrations were measured in the EBC, whole blood (WB) and pleural effusion (PE) of all the subjects under study using ELISA kits.

Results: MMP-9 levels were found to be significantly higher in EBC, WB and PE of NSCLC patients compared with controls. A positive correlation was observed between MMP-9 in EBC, cigarettes smoked and stage of cancer.

Conclusion: Exhaled MMP-9 was elevated in NSCLC patients, especially during tumour progression, and could represent a suitable non-invasive marker in the diagnosis and monitoring of lung cancer.

P311

Influence of oral steroid use in difficult-to-control asthma patients on metabolomic profile of oxidative stress in exhaled breath condensate (EXAIR project)

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Difficult-to-control asthma (DCA) remains a pending clinical problem despite recent advances in therapy. It is supposed that intensity of inflammation and oxidative stress is higher in DCA.

Aims: Our hypothesis was that oxidative stress metabolites in exhaled breath condensate (EBC) differs in oral corticosteroid (CS) dependent DCA patients (group OCS, n=10) versus DCA treated by inhaled CS (group ICS, n=10) from severe asthma center and versus healthy controls.

Methods: We have used metabolomic analysis of EBC using liquid chromatography and mass spectrometry to detect concentrations of 22 markers of oxidative stress (e.g. malondialdehyde, leukotrienes, 8-isoprostane, α-tirosine). EBC was taken by a standardized protocol. Results were analyzed together with FEV1, FeNO50, blood eosinophils and differences in OCS and ICS subgroups were statistically evaluated.

Results: OCS ad ICS did not differ in gender, age (54 vs 53), asthma control test (12 vs 15), FeNO50 (36.5 vs 50) and FEV1 (53 vs 57 % predicted) (all p>0.05). Peripheral blood eosinophils were higher in ICS group (0.46 vs 0.22 x10³/µL, p=0.03). 8-isoprostane was significantly higher in ICS group (101.7 vs 54.5 pmol/L, p=0.002) only. All other measured markers in EBC did not differ between OCS and ICS, however all markers in EBC of ICS and OCS were higher in comparison to control group (all p<0.001).

Conclusion: Our data shows increased liperoxidation and blood eosinophilia in ICS DCA. We speculate that ICS DCA would benefit from earlier chronic oral CS therapy to prevent consequences of oxidative stress, however further data are needed.

Support: PRVOUKP.

P312

Ethnic difference and diagnostic value of exhaled nitric oxide levels for predicting asthma in children

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Exhaled nitric oxide (eNO) has been used as a non-invasive marker of airway inflammation but normal reference data in children are limited. Levels of eNO in a random sample of 1099 Chinese children aged 11-18 years recruited from Hong Kong were measured online by a chemiluminescence analyzer according to ERS/ATS standard. Each student also completed an ISAAC questionnaire. Children who had never been diagnosed to have asthma and did not have any symptoms of wheeze, rhinitis or eczema were considered as normal controls. Ninety-four steroid naïve asthmatics were recruited from the Asthma Clinic for eNO measurement for comparison. Among the control children, there were 369 boys and 373 girls. In control children, the eNO levels (median, interquartile range) were significantly higher (P<0.001) in males (11.4 ppb; 7.7-21.6) than in females (9.0 ppb; 5.9-13.4). For asthmatic males, the median eNO (interquartile range) was 45.5 ppb (28.3-74.1); for asthmatic females, 47.2 (28.6-69.5). Using a cutoff of 15 ppb for girls, the sensitivity and specificity for differentiating asthma from controls are 86% and 78% (AUC of ROC curve =0.84) for boys, the sensitivity and specificity are 80.4% and 79.4% using a cutoff of 25 ppb (AUC of ROC curve = 0.84). This is one of the largest studies of eNO in Chinese schoolchildren and their levels are higher than the reported values for Caucasians. Different cutoff values for boys and girls are needed when eNO is used for supporting the diagnosis of asthma in children.

Supported by HKRGC CUHK4120/06M and CUHK 477110.

We compared the classification ability of two e-noses based on different technologies in asthma and COPD. Ten patients with severe asthma (3/7, males/females, age 47±2 yrs, FEV1 67±7% pred, FVC 82±6±7% pred, P<0.001; 9 non-smokers, 1 current smoker), 9 COPD patients (7/2, males/females, age 69±3 yrs, FEV1 68±5±1% pred, FVC 82±6±5% pred, P<0.001; ex-smokers) and 6 healthy non-smokers (4/2, males/females, age 49±6 yrs, FEV1 109±4±4% pred) were studied in a cross-sectional pilot study. After 5 min of tidal breathing with volatile organic compound-free air, two breath samples were collected from each subject and immediately analyzed with Cyanosense 320 (Smiths Detection, Pasadena, USA) and Ten 2010 (University of Rome Tor Vergata, Italy). Data were analyzed by partial least square discriminant analysis with leave-one-out cross-validation. eNOs were initially used for classifying healthy subjects and patients with pulmonary disease and, then, asthma and COPD patients. Classification capacity between patients with respiratory disease and healthy subjects was as follows: Cyanosense 320, 80%; Ten 2010, 88%; e-nose combination, 92%. Classification rate between asthma and COPD patients was as follow: Cyanosense 320, 92%; Ten 2010, 86%, e-nose combination, 94%.

These preliminary results suggest that a combination of e-noses slightly increases classification capacity in patients with severe asthma and COPD.

68. Late breaking results: Asthma from phenotyping to emerging new treatments

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Developing obstructive change over time is dominant in smallairways in severe asthma

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Background: The clinical features, physiology, and pathology of severe asthma patients has not been fully elucidated.

Objective: To assess the pattern and risk factors of developing airway obstruction over time in severe asthma.

Methods: We examined the data of a retrospective analysis of lung function changes over a 10-year period in 54 patients with severe asthma. The risk factors that might contribute to the progression of obstructive changes were also investigated.

Results: The rate of change in both FVC and FEV1 (forced expiratory volume in one second) was highly variable among the patients with severe asthma. The faster obstructive changes detected by decline in FEV1 were accompanied by excessive loss of FVC (r = 0.85, p < 0.0001) and the reduction in FVC was 1.2 times larger than the FEV1 decline. Age, baseline FVC, annual exacerbation rate and...
use of oral corticosteroids showed significantly negative correlations with the rate of annual change in FVC.

Conclusions: These data indicate that the decline in FVC is more evident than FEV1 in severe asthma, suggesting that small airway susceptibility may be the cause of rapid disease progression. Aging, exacerbations of asthma, and use of systemic corticosteroids are associated with excess FVC decline, particularly if FVC is still normal.

343 Distinct phenotypic and pathophysiologic features of elderly asthma
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Background: Recent epidemiologic evidence suggests that asthma is prevalent in the elderly population. Majority of elderly asthma develops in later life, and thus is considered patho-physiologically distinct from young adult asthma.

Objective: To investigate whether elderly asthmatics may have different phenotypic or pathophysiologic features from young adult asthmatics.

Methods: Young adult (18-45 years) and elderly (≥65 years) non-smoking, treatment-naive asthmatics were compared cross-sectionally. Asthma was defined if they had typical symptoms and methacholine PC20 ≤ 8 mg/mL. They completed baseline spirometry, induced sputum analyses, inhalant allergen skin prick tests, and anthropometric measurements. As indices of small airway involvements, a FEF25-75% and FEF25-75/FVC were used.

Results: A total of 103 young adult (mean age: 29.9 years) and 120 elderly (mean age: 71.1 years) asthmatics were included. Two age groups had similar degrees of airway hyperresponsiveness (methacholine PC20: 2.7 ± 2.2 mg/mL in the elderly vs. 2.7 ± 2.5 mg/mL in young adults). They also did not differ in gender distribution, FVC%, or FEV1%. However, the elderly asthmatics had higher body mass index (24.9 kg/m² vs. 23.3 kg/m², P<0.05), and lower atopy prevalence (40.9% vs. 95.5%, P<0.001), and slightly lower sputum eosinophils (7.1% vs. 10.3%, P<0.1) than young adult asthmatics. In addition, the elderly had significantly reduced FEF25-75% (43.1% vs. 61.6%) and FEF25-75/FVC (0.52 vs. 0.72) than the younger subjects at baseline (all P<0.001).

Conclusions: Elderly asthmatics had different phenotypic and pathophysiologic features from young adult asthmatics, suggesting their distinct pathogenic mechanisms and therapeutic considerations.

344 Asthma phenotypes associated with vocal cord/laryngeal dysfunction
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Aim: To identify asthma phenotypes in patients with refractory and non-refractory asthma in whom inappropriate vocal cord closure and laryngeal dysfunction (LD) may occur (Low et al., AJRCCM, 2011).

Methods: We evaluated 57 patients with mild to moderate non-refractory asthma (N=31) or refractory asthma (N=26). Dynamic 320 slice computerised tomography (CT) of larynx was done and a validated algorithm was used to accurately measure vocal cord lateral diameter during inspiration and expiration. Excessive narrowing of the airways was diagnosed if a predetermined lower limit of normal was exceeded. The asthma groups were compared by semi-supervised cluster analysis to identify asthma phenotypes associated with laryngeal dysfunction.

Results: Overall vocal cord diameter was reduced below the lower limit of normal in 26 of 57 cases (46%). There was no relationship with asthma severity (LD) in refractory asthma: 12/26 (46%) versus non-refractory 14/31 (45%). Laryngeal dysfunction was associated with increased age (P = 0.034) bronchodilator (BD) responses <12% (P < 0.009) and difficult speech when breathless (P < 0.019). There were 3 unique phenotype clusters associated with abnormal vocal cord narrowing and determinants of cluster membership were:

1. age > 40 years, female, bronchodilator response < 12%, difficult speaking when breathless;
2. age > 40 years, bronchodilator response < 12%, BMI > 30 kg/m²;
3. female, bronchodilator response < 12%, BMI > 30 kg/m².

Conclusion: Our results indicate that vocal cord behaviour is abnormal in asthma, irrespective of severity. However, laryngeal dysfunction may often be associated with particular patient phenotypes and contribute to their overall symptomatic burden of disease.

345 Urinary proteomics in asthma: Search for a biomarker
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Background: The use of inflammatory indices such as sputum eosinophilia to guide anti-inflammatory treatment in asthma has been shown to reduce the frequency and severity of exacerbations.

Aims: Sputum induction can be unpleasant for patients and analysis is costly and labour intensive necessitating alternative methods to differentiate inflammatory phenotypes, guide anti-inflammatory treatment and predict exacerbation risk.

Method: Performing Surface Enhanced Laser Desorption/Ionisation Time of Flight Mass Spectrometry utilising 6 different "chips" we analysed spectra from 3 groups, the first (exacerbation vs recovery (n=16), second (prospective patient samples thrice weekly, before, during and after an exacerbation (n=5), and third (patients with different inflammatory phenotypes (eosinophilic, neutrophilic, mixed granulocytic and paucigranular) (n=10).

Results: Differential protein signatures were found between inflammatory phenotypes (p<0.05) and between exacerbation and recovery states (p<0.05). The IMAC Cu chip identified a signature which delineated onset, exacerbation and recovery states. Protein signatures were able to distinguish patients in each comparative group (P<0.05).

Conclusion: Further work is warranted with a larger sample size to corroborate our findings and identify the proteins these signatures represent. This may ultimately identify a urinary marker indicating pre-exacerbation states in asthma enabling early intervention.

346 Nasal and bronchial levels of Th2 cytokines correlate during a virus induced asthma exacerbation
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Asthma is a heterogeneous condition and it is vital to accurately predict responders to targeted therapies. However, difficulties in measuring IL5 and IL13 have forced reliance on indirect markers of Th2 inflammation with limited success. Using the human model of experimental rhinovirus (RV) induced asthma exacerbation (AE) and new techniques to absorb nasal (nasosorption) and bronchial (bronchosorption) nasal washings using an aerosolised low volume fluid (MLF), we explored Th2 inflammation during a RV-induced AE.
Methods: 32 mild-to-moderate asthmatics and 14 healthy subjects were inoculated with RV-16. Bronchoscopies were performed 2 weeks prior to inoculation and on day 0 post inoculation. Cytokines were measured in both bronchial and nasal samples at baseline and on day 4 with further nasal sampling on days 2, 3, 5, 7, 10 and 14.

Results: Nasal IL5 and IL13 were significantly increased in asthma during infection compared to baseline (p<0.001) and increased compared to healthy subjects (p<0.01). In the lung, there were relationships between bronchial IL13 (p<0.05) and IL5 (p=0.059) and total chest symptom score in asthma. Nasal IL5 and IL13 correlated with bronchial levels during infection (p<0.01) whilst baseline levels in the max were correlated strongly with infection levels (p<0.001).

Conclusion: RV induced Th2 inflammation correlated with AE severity. Nasal Th2 inflammation correlated with bronchial levels whilst baseline Th2 levels predicted the magnitude of Th2 induction during the AE. Nosocomia is a non-invasive, rapid technique capable of measuring Th2 inflammation directly. It may be possible to use this technique as a biomarker to guide therapy with anti-IL5 and anti-IL13 mAb treatments.

347 The effects of interferon beta on cold-induced asthma exacerbations
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In vitro studies show that asthmatic bronchial epithelial cells produce insufficient interferon beta (IFNb) when infected with rhinovirus (RV), whilst exogenous IFNb restores their capability to stop viral replication. This has provided pre-clinical proof of concept. In asthma, IFNb is an attractive candidate for a randomised placebo controlled clinical trial of aerosolised IFNb. The trial involved 21 centres and 147 asthmatics, with the sACQ (shortened Asthma Control Questionnaire) as the primary outcome. Patients commenced treatment at the onset of common cold symptoms and, following baseline assessment, were treated daily for 2 wks with IFNb (6MIU) or placebo.134 patients fulfilled the Jackson criteria for a cold (mITT population): in these, respiratory viruses were detected in nasal lavage by PCR in 63% of patients (68% RV+). In the placebo group, cold symptoms correlated strongly with those of asthma and only patients with difficult to treat asthma (BTS steps 4 and 5) had a clinically relevant (>0.5) increase in sACQ, whilst step 2 or 3 asthmatics did not. In the difficult to treat patients the difference in sACQ during the first week was 0.63 (p=0.004) in favour of treatment and the 5% experiencing an exacerbation was significantly (p=0.012) lower. Treatment with IFNb also resulted in significantly faster recovery of PEF and less use of β2-agonists (p<0.05). This trial suggests that treatment with inhaled IFNb significantly attenuates the adverse effects of the common cold in difficult to treat asthma patients whose needs for such treatment are great. The study provides rationale for follow on clinical trials.

The trial was funded by Synarigen plc and supported by NIHR.

348 Increased cytotoxic T cells, CX3CR1+, γδ and IL17+ T cells in severe asthma during exacerbation
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Background: Asthma is a chronic inflammatory disease affecting up to 10% of the general population. In most cases, asthma symptoms are controlled by long term treatment without side effects. However, for severe asthmatics, therapy is often insufficient to gain control of the disease and symptoms progress to exacerbations. Recently, T cells populations such as cytotoxic T cells, CX3CR1+, γδ and IL17+ T cells have been correlated to asthma severity. Our aim was to longitudinally study these cell populations in severe asthma, to better understand immune mechanism that underlies exacerbations.

Methods: 23 severe refractory asthmatics were enrolled in the EXPRESSA study, with a mean follow up of 12 months, comparing blood sampling and nasal swab 40 exacerbations were documented. D cell phenotype was assessed by flow cytometry in samples obtained at baseline, before, during and after exacerbations. Viral colonization was also studied in nasal swab by PCR.

Results: We highlight increased cytotoxic T cells (CD8+perforin+), CD4+CX3CR1+, γδ T cells and IL17+ T cells (p<0.03) associated to increased Th2 cells (IL-5) during exacerbation. This increase in inflammatory profile is associated to decreased T regulatory population and Th1 cells (IFN-γ), which appears before exacerbation (p<0.007). Concerning viral colonization, the lack of virus identification failed to separate exacerbations of viral origins from others.

Conclusion: These results defined a T cell activation profile, specific for exacerbation in severe asthma which seems to be crucial for inflammatory response which develops during exacerbation.

349 Mepolizumab (anti-IL-5) reduces exacerbations in patients with refractory eosinophilic asthma
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Background: Proof-of-concept studies have shown that mepolizumab reduces eosinophilic airway inflammation and asthma exacerbations in patients with refractory eosinophilic asthma. We investigated the effect of three doses of mepolizumab on asthma exacerbations in a larger population of patients.

Methods: This 52-week randomised, double-blind, placebo-controlled study (NCT01000506) compared mepolizumab (75, 250 and 750 mg; intravenous infusion) with placebo in 616 patients (>12 years) with refractory asthma, ≥2 exacerbations in the previous year and evidence of eosinophilic inflammation. The primary outcome measure was the rate of clinically significant asthma exacerbations; defined as episode of acute asthma requiring use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visit. Safety and immunogenicity assessments were also conducted.

Results: The exacerbation rate with placebo (2.4/subject/year) was reduced by 4.8% (75 mg), 5.3% (250 mg) and 7.1% (750 mg) with mepolizumab > placebo (12.2%). No serious life-threatening anaphylactic reactions were reported and the immunogenicity profile was unremarkable.

Conclusion: Mepolizumab, as an add-on therapy in patients with uncontrolled severe refractory eosinophilic asthma, produced a significant reduction in exacerbation rate over one year compared with standard of care, and was generally well tolerated.

69. Asthma and COPD at work: what are the effects of exposure and risk factors?

350 Evolution of immunological occupational asthma depending on the continuation or end of exposure
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Introduction: It is generally agreed that the best treatment after diagnosis of occupational asthma (OA) is avoidance of exposure to the causal agent. However, recent meta-analyses have raised doubts about this conclusion. The aim of the present study is to assess the evolution of OA depending on whether or not the patient avoids exposure.

Methods: Multicentre, cross-sectional clinical follow-up study in patients diagnosed with OA using a specific inhalation challenge (SIC) between January 2000 and December 2009. Patients with this diagnosis received the following examinations on the same day: clinical interview, physical examination, forced spirometry, methacholine test and determination of total IgE and IgE specific to the causal agent. Clinical improvement, deterioration or no change were defined according to the changes seen in the GINA severity scale at the time of diagnosis.

Results: Of the 73 patients finally included, 55 had totally ended exposure and 18 continued. The mean time elapsed since diagnosis was 48 months (range: 12-123). Forty-two per cent of patients who avoided exposure improved clinically, 38% presented no change, and 14% deteriorated. In the patients who did not avoid exposure improvement was recorded in 22%, deterioration in 17% and no change in 61%. No significant differences in methacholine PC20 or FEV1 were detected between both groups.

Conclusions: Avoiding exposure to the causal agent in patients with OA does not seem to improve prognosis in this disease.

Project partially funded by Ciber de Enfermedades Respiratorias (CibeRes).
### 351

**Transfer of wheat allergen and fungal α-amyrase from workplace to home by bakers**

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**Background:** Exposure to flour dust is a leading cause of occupational asthma. Paternal occupational exposure to flour has been associated with childhood asthma, raising the possibility of 'take-home' exposure.

**Aims:** To establish whether workplace contamination of skin/clothing with wheat flour allergen (WFA) and fungal α-amyrase (FAA) is associated with increased levels of these allergens in bakers' homes.

**Methods:** Bakers in north-east Scotland were invited to participate. Controls were recruited from staff students at the University of Aberdeen. Exposure assessment was carried out in bakers' homes using surface wipe and vacuum sampling; samples were analysed for total protein, FAA and WFA.

**Results:** 164 wipe and 49 vacuum samples were collected from 38 bakers (5 bakers and 10 controls). Compared to non-bakers, bakers had higher median levels of FAA and WFA in house vacuum samples; the difference was statistically significant for WFA (total protein 516x10⁻⁶ vs 164x10⁻⁶, p=0.031), FAA (total protein 1.5x10⁻⁷ vs 0.4x10⁻⁷, p<0.001) ratios and FAA loading (median 1.2pg/cm² vs 0.1pg/cm², p<0.001). We found positive correlations between WFA contamination of the bakers' bedrooms and cars (r=0.5, p=0.028), bedrooms and cars (r=0.46, p=0.025), shoes and houses (r=0.45, p=0.029); and between FAA contamination of shoes and houses (r=0.46, p=0.023), and cars and houses (r=0.70, p=0.008).

**Conclusions:** This work demonstrates pathways for 'take home' exposure of occupationally sourced flour. Taken with our previous work, showing that bakers' children are more likely to have asthma, this supports the need for workplace intervention trials to prevent asthma in bakers' children.

### 352

**Incident rhinitis is related to dust and eye exposure among baker's apprentices**

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**Background:** Baker's asthma and rhinitis are related to occupational exposure with an exposure-response relationship for prevalence and incidence. This study was a prospective study to estimate: The dose response relation between new onset asthma and rhinitis and the exposure to personal dust and allergens in baker apprentices during their apprenticeship.

**Methods:** Participants were recruited from baker schools. Baker apprentices without previous occupational exposure to dust, flour, rye and wheat were performed 1 or 2 times in each bakery. Cox proportional methods were used to estimate the hazard ratio (HR).

**Results:** We found 42 cases of rhinitis and 27 of asthma like symptoms.

The dust and allergen levels were: Dust Mean (SD) 1.9 (1.6), rye 0.8 (0.7) and wheat 0.8 (0.5) mg/m³

The HR for high exposure to personal dust controlling for atopy was increased for rhinitis, table 1.

**Table 1.** Cox proportional hazard modelling of Rhinitis with exposure to personal dust

<table>
<thead>
<tr>
<th>Rhinitis during apprenticeship</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal dust Lowest half</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Personal dust 3rd quartile</td>
<td>1.27</td>
<td>0.431, 3.722</td>
</tr>
<tr>
<td>Personal dust 4th quartile</td>
<td>3.07</td>
<td>1.20, 7.87</td>
</tr>
<tr>
<td>Sex (Male = 0)</td>
<td>2.57</td>
<td>1.13, 5.96</td>
</tr>
</tbody>
</table>

We found no association to wheat exposure, but for rye exposure an increased HR for rhinitis symptoms with exposure highest for the 3rd quartile, 2.9 (1.2-7.5) vs 1.6 (0.5-4.8) in the 4th quartile. Only 4 persons developed positive SPT to flour and two to α-amylase during the study.

**Conclusions:** In baker apprentices followed for 36 months, a dose dependent HR for rhinitis symptoms with exposure to dust and rye antigen was seen.

### 353

**Lung function among workers exposed to endotoxins in coffee processing factories**

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**Background:** Occupational exposure to endotoxins causes airway diseases and impairs lung function.

**Objectives:** To measure personal total dust and endotoxin levels and to examine lung function among coffee workers in relation to exposure.

**Methods:** All 159 production workers from four Tanzanian factories processing Arabica and Robusta coffee were invited to participate. Personal total dust was sampled throughout the shift using Sidekick Casella pumps (n=193). Cumulative dust was calculated as mean dust exposure multiplied with the number of years in work in the respective coffee factories. Lung function test was carried out using a portable spirometer (SPIRARE3). Differences in groups were tested by independent t-tests. Linear regression was done to adjust for confounders; age, height and smoking.

**Results:** Robusta (n= 74) and Arabica (n=66) coffee workers had a mean age of 33 years and 38% were current smokers. Total dust levels and endotoxins were significantly higher in the Robusta factories (geometric mean 3.4 mg/m³ and 10800EU/m³, respectively) than in the Arabica coffee factories (2.10 mg/m³ and 1400EU/m³). Mean cumulative dust in both groups was 17mg/m³.

**Conclusion:** Exposures to dust and endotoxins in coffee processing factories are high and might cause decreased lung function.

### 354

**Occupational exposure and lung function in a Dutch general population cohort**

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**Background:** Occupational exposure to vapors, gases, dusts, fumes (VGFD) has been associated with lower lung function, with more pronounced effects in smokers. Less is known about occupational exposure to pesticides, solvents and heavy metals in relation to lung function. We assessed whether these agents negatively affect lung function in a general population cohort.

**Methods:** We included 8,128 subjects aged 18-89 from the LifeLines cohort study (n=2,669 males). Occupational exposures (no/low/high) for current or last held job were estimated with the ALOHA+ Job Exposure Matrix. Associations between exposure and FEV1 were assessed using linear regression, adjusted for sex, age, height, weight and smoking. Additionally we stratified for gender and smoking status.

**Results:** Males were more often exposed than females. VGFD and pesticides had a negative dose-response effect on FEV1 (table 1). Effects were more pronounced in males and ever smokers.

**Table 1.** Associations between exposure and FEV1 (ml) (reference = no exposure)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Low (%)</th>
<th>High (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological dust</td>
<td>–15 (–40; 10)</td>
<td>–85 (–141; –29)</td>
</tr>
<tr>
<td>Mineral dust</td>
<td>–40 (–75; –9)</td>
<td>–102 (–145; –49)</td>
</tr>
<tr>
<td>Pesticides</td>
<td>–90 (–154; –25)</td>
<td>–227 (–346; –108)</td>
</tr>
<tr>
<td>Hericides</td>
<td>–128 (–235; –22)</td>
<td>–413 (–640; –185)</td>
</tr>
<tr>
<td>Insecticides</td>
<td>–93 (–164; –22)</td>
<td>–227 (–348; –108)</td>
</tr>
<tr>
<td>Aromatic solvents</td>
<td>6 (346)</td>
<td>–551 (–172; 61)</td>
</tr>
<tr>
<td>Chlorinated solvents</td>
<td>15 (–31; 62)</td>
<td>–261 (–110; 58)</td>
</tr>
<tr>
<td>Other solvents</td>
<td>18 (–9; 44)</td>
<td>–401 (–121; 41)</td>
</tr>
<tr>
<td>Metals</td>
<td>13 (–39; 45)</td>
<td>–73 (–446; 9)</td>
</tr>
</tbody>
</table>

**Conclusion:** This study confirmed current knowledge on the detrimental effects of occupational VGFD exposure on lung function, especially in males and ever smokers. Additionally we show negative effects of pesticide exposure on lung function.

### 355

**Cross-shift change and subsequent longitudinal changes in FEV1 in a 6 year follow-up study of wood dust exposed workers**

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**Objective:** Cross-shift lung function (LF) changes might predict an accelerated decline in LF. This study investigates the association between cross-shift and annual changes in FEV1 among woodworkers in a 6-year follow-up study.
Methods: 817 woodworkers and 136 controls participated with cross-shift changes of FEV1 at baseline and FEV1 and FVC at follow-up. Height and weight were measured and questionnaire information on respiratory symptoms, employment and smoking habits were collected. Wood dust exposure was assessed from 3,572 personal dust measurements at baseline and follow-up. Cumulative wood dust exposure was assessed by a study-specific job exposure matrix and exposure time.

Results: The median (range) of inhalable dust at baseline and cumulative wood dust exposure was 1.0 (0.2-9.8) mg/m³ and 3.8 (0.7-1.1) mg*year/m³ respectively. Mean (SD) for %ΔFEV1/workday and ΔFEV1/year was 0.2 (6.0)% and -29.1 (41.8) ml. Linear regression models, adjusting for smoking, sex, age, height and weight change revealed no association between cross-shift and annual change in FEV1 (table 1). Including different exposure estimates, atopy or cross-shift change dichotomized or as quartiles did not change the results.

Table 1. Linear regression on the association between longitudinal and cross-shift change in FEV1

<table>
<thead>
<tr>
<th>Longitudinal ΔFEV1 (ml yr⁻¹)</th>
<th>Cross-shift ΔFEV1, %</th>
<th>p</th>
<th>Wood dust exposure mg yr⁻¹</th>
<th>p</th>
<th>Smokers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>β ± SE</td>
<td>-0.38 (0.22)</td>
<td>0.08</td>
<td>-1.54 (0.72)</td>
<td>0.03</td>
<td>-10.48 (2.67)</td>
<td>0.00</td>
</tr>
</tbody>
</table>
| N=881, Model is adjusted for sex, age, height and weight gain. *Cumulative wood dust exposure.

Conclusion: This study among low exposed woodworkers does not support an association between cross-shift changes and accelerated LF decline.

356 Associations between occupational exposure and quantitative computed tomography (CT) measures of emphysema

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Rationale: There is limited knowledge of the effect of occupational exposure on quantitative CT measures of emphysema.

Objectives: To examine the effect of occupational exposure assessed by a job exposure matrix (JEM) on QCT measures of emphysema.

Methods: In the Norwegian GenKOLS study 2003-05, 951 ever-smokers (49% with COPD) aged 40-85 years performed spirometry and CT examination. 941 of them completed a full occupational history. In the current study a JEM was used to assess occupational exposure, and CT measured emphysema (% low-attenuation areas, %LAA) was the main outcome. Quantile regression analyses were used for the multivariate analyses, adjusting for sex, age, smoking, inflation level and FEV1% of predicted.

Results: Quantile regression analyses showed significant associations between occupational exposure to gas/fumes and mineral dust, and %LAA. The unadjusted regression coefficients for %LAA for subjects with occupational exposure in the longest held job, were 0.95 and 1.21 for low and high exposure to gas/fumes, and 1.16 and 1.98 for low and high exposure to mineral dust. For those with low and high exposure to gas/fumes and mineral dust in their latest job, the regression coefficients were 0.90, 1.19, 1.09 and 1.51 respectively. After adjustments, the association's only remained statistically significant for subjects exposed to high levels of gas and fumes in their latest held job.

Conclusions: Subjects with high levels of occupational exposure to gas/fumes in their latest job were found to have higher levels of CT measured emphysema compared to subjects with low or no exposure. A dose-response relationship was suggested.

357 Anti-IgE treatment: An alternative for severe allergic occupational asthma

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Severe work-related asthma remains a difficult problem and new alternative treatment must be evaluated to obtain asthma control and ideally the sustain of the occupational activity.

During 2 years we have enrolled 10 occupational asthmatics (8 men, 2 women, mean age 37, suffering of asthma from 0.5 to 8 years). They were all severe uncontrolled asthmatics (GINA recommendations). The mean dose of inhaled corticosteroids was 3200 μg/day of beclometasone equivalent. All patients had 2 to 8 severe exacerbations/year. Six patients were allergic to a high molecular weight agent (wheat flour: 2, cat: 1, rabbit: 1, storage mites: 1, Alternaria: 1). In 4 patients the causative agent was a low molecular weight compound (isocyanates in 2 cases, acrylates one case, peracetic ethylene one case). Total IgE levels were always above 30 U/mL. The follow-up was performed from 6 to 48 months. Asthma parameters and the occupational status were registered every 6 months.

Results showed a reduction of severe exacerbations in 9 patients. Only one patient was “non responder” after 6 months of treatment. In the 9 “responders” an optimal control could be obtained in 4 patients. Oral daily corticosteroids could be decreased in the 5 (mean initial dose 8.6 mg/day to 1.2 mg/day of equivalent prednisone). Days off-work because of asthma were reduced in the 9 “responders”. 7 could continue to work with amendment of the working place. We suggest that omalizumab could be a potential treatment for severe uncontrolled work-related asthma in 3 conditions, patients who were unable to avoid allergen exposure, persistent asthma after cessation of the offending exposure and work-aggravated asthma symptoms in workers with pre-existing allergic asthma.

70. Mechanisms of asthma

358 The role of histone deacetylase 9 in the imbalance of Th17/Treg in bronchial asthma

Trude Skorle1, Øistein Svanes2, Ane Johannessen3, Thomas Grydeland2,4, Harvey Coxon5,6, Anund Gulsvik7,8, Per Bakke2,4, Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway; 3Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; 4Institute of Medicine, University of Bergen, Norway; 5Department of Radiology, University of British Columbia, Vancouver, Canada; 6James Hogg icAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver General Hospital, Vancouver, Canada

Rationale: Studies have shown that histone deacetylase 9 can affect Tregs function and histone deacetylase inhibitor can inhibit conversion of Tregs into IL-17-producing cells.

Methods: GATA3, IL-4 and HDAC9 mRNA expression level were measured by SYBR Green RT PCR. IL-17 and TGF-β were measured by ELISA. BALB/c mice were randomly divided into three groups, the control group, asthma model group and TSA group. The mice in TSA group were given TSA (1mg/kg) s.p. every other day during sensitization and challenge. The plasma IgE measured by ELISA, observed the inflammation by HE staining, HDAC9, RORγt and Foxp3 mRNA expression in lung tissue were measured by PCR.

Results: HDAC9 mRNA expression was associated with severity of disease (p<0.01). HDAC9 mRNA expression was correlated with GATA3 mRNA expression positively (p<0.01, r=0.482), the same with IL-4 mRNA expression (p<0.01, r=0.432) and IL-17 (p<0.01, r=0.538), but negatively correlated with TGF-β (p<0.01, r=-0.417). In patients with moderate-severe asthma, HDAC9 mRNA expression was negatively correlated with FEV1% (p<0.01, r=-0.657).

Figure 1. HDAC9 mRNA expression was associated with severity of disease.

Conclusions: The relationship between expression of histone deacetylase 9 and imbalance of Th17/Treg has been confirmed in asthma. The histone deacetylase inhibitor TSA can control asthma by regulating activity of histone deacetylase.
Spu...the FEV1 response to oral steroids in non-smokers with asthma. Charl...sputum IL-1RA. We suggest that smoking establishes and aggravates the asthmatic phenotype in mice.

Methods: Sputum was induced from 31 non-smokers and 22 smokers with asthma. Endotoxin was quantified by ELISA (LAL-QCL®, Lonza Biologics plc) and cytokines by luminex (InVitrogen). Spriometry and exhaled nitric oxide measurements were recorded. The response to oral dexamethasone was the change in FEV1, compared with baseline.

Results: Smokers had improved FEV1 after steroids; p<0.015, but smokers were refractory; p=0.591. The steroid response decreased with increasing sputum endotoxin in non-smokers; r=0.479, p<0.015, but not in smokers; r=0.126, p=0.585.

Conclusions: Higher endotoxin in sputum fluid was associated with an impaired FEV1 improvement after steroids only in non-smokers; and was associated with decreased sensitization towards inhaled allergens. Inhalation of DEP increases pulmonary dendritic cell (DC) accumulation and enhances TH2 responses in mediastinal lymph nodes. In inflammatory conditions, DC recruitment is mediated by different CC chemokine receptors (CCR). We hypothesized that CCR2 mediates DC recruitment and TH2 responses upon DEP exposure.

Methods and results: WT and CCR2 KO mice were exposed to saline or DEP, followed by immunological examination. DEP exposure increased pulmonary expression of CCR2 and MCP-1 in WT mice. Exposure induced a pulmonary recruitment of monocytes and inflammatory (CD11b+) DCs in WT mice, which was abolished in CCR2 KO mice. Adoptive transfer of fluorescently labeled bone marrow derived cells from WT and CCR2 KO mice demonstrated the direct involvement of CCR2 in recruitment of blood monocytes towards the lung upon DEP-exposure. Furthermore, analysis of TH2 cytokine production in mediastinal lymph nodes upon DEP-exposure showed an abolished TH2 response in CCR2 KO mice.

Conclusion: These data suggest that monocyte-derived DC, recruited in a CCR2-dependent manner, are critical in inducing TH2 responses upon DEP inhalation.

Funding: Belgian IUAP (P6/35), FWO-Flanders (G.0052.06; G.0329.11N).

363
LSC 2012 Abstract – Monocyte-derived dendritic cell recruitment and allergic TH2 responses after exposure to diesel particles are CCR2-dependent

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Background: Diesel exhaust particles (DEP) inhalation is associated with increased sensitization towards inhaled allergens. Inhalation of DEP increases pulmonary dendritic cell (DC) accumulation and enhances TH2 responses in mediastinal lymph nodes. In inflammatory conditions, DC recruitment is mediated by different CC chemokine receptors (CCR). We hypothesized that CCR2 mediates DC recruitment and TH2 responses upon DEP exposure.

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Funding: Belgian IUAP (P6/35), FWO-Flanders (G.0052.06; G.0329.11N).

364
Cigarette smoke exposure facilitates allergenic sensitization to house dust mite and aggravates the asthmatic phenotype in mice

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Background: Cigarette smoke (CS) exposure has been associated with increased sensitization towards allergens in development in children and adults.

Aims and objectives: We wanted to design a novel mouse model to unravel the impact of CS on the different stages of asthma pathogenesis, specifically during the initial sensitization and acute asthma development.

Methods: Mice were exposed to 25 g house dust mite (HDM) extract (intranasally, i/week) for 3 consecutive weeks, combined with air or CS exposure (3 times/day, 3 days/week) during 3 weeks or only during the first week.

Results: Mice concomitantly exposed to HDM and CS for 3 weeks, showed a significant increase in eosinophils, goblet cells, airway hyperresponsiveness and HDM-specific serum IgG1, compared to sole HDM or CS exposure. Interestingly, exposure to CS only during the first week was sufficient to induce an aggravated asthmatic phenotype after rechallenge with HDM allergens. To further investigate the effect of CS during mucosal sensitization, mice were exposed to HDM (just once) and 3 days of CS, followed by the assessment of DC trafficking and early TH2 responses in the lymph nodes. This CS exposure amplified DC-mediated transport of HDM allergens to the lymph nodes and was sufficient to generate a TH2 response, characterized by IL-4, IL-5 and IL-13 production in the draining lymph nodes.

Conclusions: CS facilitates the development of HDM-induced allergic asthma. Only a few days of smoke exposure are sufficient to facilitate allergic sensitization to common aeroallergens.

Funding: IUAP – Belgian Science Policy P6/35 and BOF/GOA 01251504.

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Increased numbers of alveolar mast cells with an altered phenotype are linked to peripheral airway remodelling in patients with allergic asthma

Cecilia Andersson1, Maria Werstoft Lundström2, Anders Bergqvist1, Michiko Mori1, Leif Bjørner1, Gunilla Westergren-Thorsson2, Jonas Erjefält3.1Dept. of Respiratory Medicine & Allergology, Lund University, Lund, Sweden; 2Lund University, Lung Biology Unit, Lund, Sweden; 3Lund University, Unit of Airway Inflammation, Lund, Sweden

Background: A significant proportion of asthmatics have symptoms despite treatment with inhaled corticosteroids. Recent studies have revealed an expansion of highly FcεRI-expressing alveolar mast cells (MCs) in asthma. The aims were to further phenotype alveolar MCs and explore their connection to peripheral tissue remodelling in different asthma cohorts.

Methods: Bronchial and transbronchial biopsies from controls, patients with rhinitis, mild and uncontrolled asthma were processed for immunohistochemical identification of MC subtypes and expression of pro-fibrotic markers. MC alteration in relation to tissue remodelling (density of collagen, versican, decorin and high affinity IgE receptors) in peripheral lung was studied.

Results: The alveolar parenchyma (AP) in uncontrolled asthmatics had increased densities of MCε (p=0.05) and MC1 (p=0.003). The expression of FcεRI on alveolar MCs was increased in mild (p=0.01) and uncontrolled (p<0.001) asthma compared to controls. The density of collagen (p=0.01) and decorin (p=0.03) was significantly increased in AP of uncontrolled asthmatics compared to controls. The number of alveolar MCε in the uncontrolled asthma was positively correlated to the density of collagen in the AP (r=0.71, p=0.03). MCs in the AP of asthmatics expressed increased levels of pro-fibrotic markers.

Conclusions: Our data show that the alveolar region in patients with asthma is infiltrated by activated MCs that correlate to increased alveolar matrix deposition. This may reflect an important involvement of MCs in the peripheral inflammation in asthma and underscores the need to target peripheral lung inflammation in this patient group.
Mucosal explant induced migration of T-cells from severe asthmatics is inhibited by CCR4 antagonism

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Background: Th2 cells that express chemokine receptor 4 (CCR4) are key to inflammation in asthma. Work in mild asthma patients suggests that CCR4 plays a role in Th2 migration into the lung, making CCR4 a possible therapeutic target. However, little evidence is known on the role of CCR4 on Th2 migration in severe asthma patients on high dose corticosteroids.

Aim: To investigate if chemokines released by mucosal explants, from asthma patients on high dose inhaled corticosteroids, drive Th2 migration and if such a response is CCR4 dependent.

Methods: Bronchial explants, from 11 severe (SA) and 9 steroid naive (SNA) asthma patients, were cultured in media +/- house dust mite extract. The supernatants were used as chemotacticants in migration assays with patient-matched peripheral T-cells. The effects of CCR4 antagonist, GSK494652A, GSK2239633A and GSK2192991A, on T-cell migration were examined.

Results: Bronchial explant conditioned media from SNA induced higher T-cell migration than that from SA (p=0.03). However, house dust mite extract did not enhance chemotaxis in either SNA (p=0.9) or SA (p=0.6). Inhibition of CCR4 reduced T-cell migration in response to unstimulated explanted conditioned media (Table 1).

Table 1. Effects of CCR4 antagonists on T-cell migration

<table>
<thead>
<tr>
<th>Chemotaxis Index</th>
<th>Control</th>
<th>GSK494652A</th>
<th>GSK2239633A</th>
<th>GSK2192991A</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNA Median (range)</td>
<td>2.7 (0.8-17.2)</td>
<td>1.7* (0.6-10.1)</td>
<td>1.7* (0.6-11.2)</td>
<td>1.9* (0.8-7.8)</td>
</tr>
<tr>
<td>SA Mean (semi)</td>
<td>2.0 (0.3)</td>
<td>2.2 (0.4)</td>
<td>1.6* (0.2)</td>
<td>1.4* (0.2)</td>
</tr>
</tbody>
</table>

Control vs CCR4 antagonist: *p<0.05.

Conclusions: Targeting CCR4 may prove to be effective in reducing Th2 recruit-ment into the lung and the subsequent inflammatory response in asthma patients who are on high dose inhaled corticosteroid treatment.

Pulmonary arterial hypertension (PAH) is a rare disease that must be managed in specialized centers integrated in a national network. Availability of epidemiological national data is critical for planning and regulation of healthcare in this field. We conducted a prospective, observational and multicenter registry in 5 portuguese centers. Adults with PAH and chronic thromboembolic PH (CTEPH) confirmed by right heart cath (RHC) were included. Seventy-nine patients were enrolled; 46 (58.2%) classified as PAH and 33 (41.8%) as CTEPH. PAH patients had a mean age of 43±16.4 years and the I/E ratio 1.9±1.1. Idiopathic PAH was present in 17 (37%) patients, followed by connective tissue disease (n=12, 26%), congenital heart disease (n=10, 22%), portopulmonary (n=5, 11%), heritable (n=1, 2%) and other etiologies (n=1, 2%). At baseline most patients were WHO class III or IV (71%). Baseline RHC: elevated RAP (7.7±5.9 mmHg), mPAP (50.6±17.9 mmHg) and mean PVR (11.4±6.5 WU Wood), with a low CI (2.7±1.1 L.min-1.m-2). At baseline patients were medicated with conventional therapies; at follow-up, most were on single (50%), double (28%) or triple (9%) combination of specific therapy. 1-year survival was 93.5%. CTEPH patients were older (60±12.5 years) and had higher RAP (11.0±5.2 mmHg, p=0.015), but 1-year survival (93.9%) was similar to PAH patients. Five CTEPH patients underwent pulmonary endarterectomy. We estimated an annual incidence of 1.5 and 1.1 per million in PAH and CTEPH, respectively.

Our report describes nationwide data on the diagnosis, management and clinical course of groups 1 and 4 PH patients. Clinical presentation, hemodynamics and survival are comparable with those reported on other national registries.

Pulmonary hypertension in patients with lupus: Prevalence, etiology and risk factors

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Background: Pulmonary arterial hypertension has been reported between 0.5 and 14% in systemic lupus erythematosus (SLE). Objectives: To assess PH prevalence, etiology and risk factors in a SLE cohort. Methods: Prospective cross-sectional study of 158 SLE patients. Doppler echocardiographic (DE), diffusion capacity for CO (DlCO), NiprodBNP and dyspnea (Borg scale) were performed in all patients. An echocardiographic exercise test (EE) was conducted in selected patients. When a PAP ≥ 45 mmHg (DE) or a positive EE (>20 mmHg increase in PAPs) a right heart catheterization (RHC) at rest or during exercise was performed. A rest mean pulmonary pressure (mPAP) ≥25 mmHg was accepted as PH. When rest mPAP was less than 25 mmHg, an exercise test was conducted. Patients with resting PH (mPAP ≥ 35 and < 45 mmHg) and obvious cardiac disease were excluded from RHC.

Results: Mean age: 45±12.9 years, 94.3% females. Twenty one patients (13.4%) had dyspnea (Borg scale ≥ 2). Eleven patients (6.9%) showed any degree of PH. Eight patients (out of 11) had PH of left cardiac origin. One patient had thromboembolic disease. Two patients had precapillary PH related with SLE. All 11 patients with PH had dyspnea (Borg scale ≥ 2) vs. those without PH (p<0.001). PH patients showed a significant decrease in DlCO and higher NiprodBNP. There were no differences in SLE clinical characteristics between SLE patients and those without PH. Conclusions: Our data confirm the low prevalence of precapillary PH in SLE. We found a predominance of cardiac etiology. A PH screening program based on DE, NiprodBNP and DlCO does not seem to be cost-effective and should be restricted to SLE patients with unexplained dyspnea.
External validation of the French predictive model to estimate PAH survival: A REVEAL analysis

A French pulmonary hypertension network analysis

Conclusion: The FPHN equation accurately stratified a matched US population according to risk, suggesting its prognostic generalizability in PAH pts.

Introduction: The French Pulmonary Hypertension Network (FPHN) and Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension (PAH) Disease Management (REVEAL) recently developed models to predict survival in PAH patients (pts).

Aims and objectives: The FPHN equation was tested in a REVEAL cohort to assess its generalizability in a different PAH population.

Methods: The REVEAL validation cohort had 436 recently diagnosed (<1 year before enrollment), treatment-naïve, ≥18-year-old patients (pts) with idiopathic, familial, or anorexigen-induced PAH, divided into subgroups with non-missing (n=292) and missing (n=144) data for all FPHN equation parameters.

Results: The FPHN and REVEAL cohorts had similar characteristics. FPHN (n=292) and missing (n=144) data for all FPHN equation parameters.

Conclusion: The FPHN risk score calculator was accurate and well calibrated in the FPHN, suggesting its prognostic generalizability in a different PAH population and in everyday clinical practice.

Introduction: Pulmonary arterial hypertension (PAH) is a disease affecting the vasculature of the lung and is known to decrease carbon monoxide diffusion
capacity (DLCO). Although most patients have a moderately decreased DLCO, a group of patients has severely reduced DLCO. The reason for this low DLCO is unclear. Therefore, the aim of this study is to describe baseline characteristics of idiopathic PAH patients with a low DLCO and compare this group with a group of idiopathic PAH patients with moderate low or normal DLCO.

**Methods:** Patients with idiopathic or familial PAH were included. Patients were grouped based on the finding of a bimodal distribution in DLCO-values.

**Results:** A total of 170 patients were included. DLCO groups were DLCO < 45% (N=58) and ≥ 45% of predicted (N=112). Group characteristics are shown in table 1.

**Conclusions:** Compared with IPAH patients with moderate low or normal DLCO, IPAH patients with a severely reduced DLCO were characterized at baseline by a higher age, increased number of males, more often a history of smoking and coronary disease, and a lower exercise performance. No differences however were found in hemodynamic parameters.

371 'Idiopathic' pulmonary arterial hypertension with preserved lung function but co-existing parenchymal abnormalities: Response to treatment and survival

**Methods:** Methods: All incident cases of IPAH with and without co-existing CT abnormalities diagnosed between January 2001 to December 2009 in all eight PH centres in the UK and Ireland were included. All patients have FEV1, FVC and/or TLC ≥ 60% predicted.

**Results:** Table 1. Baseline characteristics, 6MWD and survival of IPAH

<table>
<thead>
<tr>
<th>With parenchymal abnormalities</th>
<th>Without parenchymal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=146)</td>
<td>(n=482)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>68</td>
</tr>
<tr>
<td>% female</td>
<td>42%</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>209</td>
</tr>
<tr>
<td>6MWD at 3 months, m</td>
<td>52</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>49</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.1</td>
</tr>
<tr>
<td>PVRWT, WU m²</td>
<td>21</td>
</tr>
<tr>
<td>1 year survival</td>
<td>74%</td>
</tr>
<tr>
<td>3 year survival</td>
<td>45%</td>
</tr>
</tbody>
</table>

**Conclusion:** Despite similar baseline haemodynamics and response to treatment, survival of IPAH with coexisting parenchymal abnormalities appears worse compared with IPAH without parenchymal abnormalities. Age and age related co-morbidities may account for the difference in long term outcome between the 2 groups.

372 Hepatopulmonary syndrome: Long-term survival in the Mayo Clinic experience

**Methods:** Survival was assessed using Kaplan-Meier methodology for 106 HPS patients from 1986 through 2010.

**Results:** 49 HPS patients underwent LT Post-LT survival (1, 3, 5 and 10 year) did not differ between groups based on PaO2 at the time of HPS diagnosis. Improvements in overall survival at 1, 3 and 5 years post-LT in those HPS patients transplanted after 2002 (MELD exception era, n=28) (92, 87 and 87%, respectively) as compared to those transplanted prior to that time (pre MELD era, n=21) (71, 67 and 67%, respectively) did not reach statistical significance (P=0.09) (figure 1). Model for Endstage Liver Disease (MELD) exception to facilitate LT was granted to 18 patients since 2002 with post-LT survival of 15/18 patients (83%) and no wait-list mortality.

373 Survival in patients with different groups of pulmonary hypertension

**Methods and results:** Every consecutive patient undergoing right heart catheterization with proven PH was included in the Giesies registry from 1994 to 2011. Differences in survival between the etiological groups were highly significant (p<0.001), with 1-, 3-, and 5-year survival rates of 88.2%, 72.2%, 59.4%, respectively in pulmonary-arterial hypertension (PAH, N=685) as compared to 79.5%, 52.7%, and 38.1%, respectively in lung disease associated PH (PH-LD, N=546). Chronic thromboembolic pulmonary hypertension (CTEPH, N=449) had the best survival rates with 89.2%, 77.4%, and 66.7%, pulmonary venous hypertension (N=307) was intermediate. Age also differed between the groups: mean age at diagnosis was 51.3 (PAH), 67.0 (PVH), 63.7 (LD-PH), 61.9 (CTEPH) years, respectively. In multivariate analysis, age, gender, NYHA functional class, uric acid, urea, brain natriuretic peptide, heart rate, sodium, six-minute walk test distance, cardiac output, and systolic blood pressure at baseline were significantly associated with survival.

**Conclusions:** In this report we present data on long term survival and its determinants from patients with pulmonary hypertension mostly focus on the subgroup of pulmonary arterial hypertension (PAH). Data on other subgroups is rare.

374 Survival after liver transplantation with hepatopulmonary syndrome

**Methods:** Several markers have been suggested to be associated with severity and/or prognosis of disease in patients with pulmonary hypertension (PH). Reports on survival and its determinants in patients with pulmonary hypertension mostly focus on the subgroup of pulmonary arterial hypertension (PAH). Data on other subgroups is rare.
# 72. Functional imaging of the lung parenchyma, tumours and circulation

## 374

**Quantifying lung function in COPD with hyperpolarised ³He MRI**

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**Introduction:** Hyperpolarised ³He MRI can identify regional lung defects and has been found more sensitive than spirometry to early changes in smokers lungs. We aim to quantify change in lung function in response to bronchodilator in COPD using ³He MRI.

**Method:** 10 patients with moderate to severe COPD (per NICE) were scanned pre and post bronchodilator at FRC+1L. Lung volume (LV) was defined by region growing algorithms (Slicer 3D, Harvard) on conventional ¹H MRI. Ventilated volume (VV) was defined by a threshold on ³He MRI. Percentage ventilation (PV) was defined as VV/LV. Lungs were segmented into 4 regions on each slice with large airways removed.

**Results:** Change in ventilation, including recruitment of newly ventilated areas, was seen post treatment.

**Conclusions:** Global MRI measures and spirometry simplify lungs to one unit. Regional analysis showed patterns of change in different lung areas which may be hidden in global measures. FEV₁% significantly increased post treatment (p<0.02) suggesting geographical variation of lung recruitment significantly affects FEV₁, as opposed to global change in gas flow.


## 375

**MRI of delayed-ventilation perfusion matching in COPD**

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**Introduction:** Delayed ventilation in COPD may be caused by collateral ventilation, partial obstruction, lung hyperinflation or a mixture of such mechanisms, and allows initially-unventilated lung regions to become ventilated over time. Recently hyperpolarised gas MRI has been used to directly visualise delayed and collateral ventilation in COPD over the period of a single breath-hold. Delayed ventilation will only contribute to gas exchange if there is blood perfusion in these regions.

**Objective:** To image the perfusion matching of lung regions with delayed ventilation in COPD.

**Methods:** Ten patients with moderate to severe COPD as defined by NICE guidelines were scanned using ³He and proton MRI. Delayed-ventilation images were acquired at six time-points during a single breath-hold.

**Results:** Regions of delayed-ventilation were perfused in some cases and were not perfused in others giving an indication of which areas remained active in gas exchange.

**Conclusions:** Hyperpolarised gas and proton MRI allow the visualisation of ventilation and perfusion matching, and may aid in the understanding of delayed-ventilation in COPD and its role in gas exchange.

Lung qS0 maps were reproducible with reduced values seen in regions comparable to CT detected emphysema regions. The mean and 15th, 50th, 75th percentile qS 0 value of 378 0.4 ml/g in UL and 0.6 ±0.3 ml/g in LL; 3) of the 4D-CT dataset was registered onto the reference (phase 0, i.e. end inspiration) and compared with the patients' diagnosis. In addition of the comparison of the parameters between the groups, Receiver Operating Characteristics analysis was used to assess sensitivity, specificity, positive predictive value, negative predictive value of EP and MP parameters.

Results: Most of the malignant nodules showed stronger enhancement with higher EP and MP values. There were significant differences between benign and malignant lesions. Sensitivity, specificity, positive predictive value and negative predictive value were 75%, 93%, 92% and 76% for EP and 93%, 86%, 88% and 95% for MP, respectively.

Conclusion: A combination of kinetic and morphological evaluation in dynamic MRI provided accurate differentiation between benign and malignant pulmonary lesions. It was a useful and noninvasive method of evaluating pulmonary nodules.

Key Words: Pulmonary nodules, dynamic MRI, kinetic parameters.

380 Non-invasive estimation of pulmonary artery pressure and resistance with CMR imaging: Derivation and prospective validation cohort study

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Background: The role of the right atrium (RA) is under-researched within pulmonary hypertension (PH). The aim of this study was to develop a cardiac magnetic resonance (CMR) imaging model for non-invasive estimation of mean pulmonary arterial pressure (mPAP) and total pulmonary resistance (TPR).

Methods: A derivation cohort of 64 consecutive patients with known or suspected pulmonary hypertension underwent right heart catheterization (RHC) and CMR within 12 hours. Cardiac volumes and function and pulmonary arterial (PA) flow were quantified. The strongest statistical model to predict mPAP from the derivation cohort was identified. Total pulmonary resistance (TPR) was estimated utilising the physiological model: TPR= pressure (CMR-derived mPAP) divided by flow (CMR-derived PA flow).

An independent prospective validation cohort of (n=40) tested the accuracy of the model.

Results: The multivariate regression CMR model gave the following equation: mPAP = 33.4 + [right ventricular end-diastolic mass index (g/cm²) x 1.21] – [PA average velocity (cm/s) x 0.99]. In the prospective validation cohort, predicted and invasively measured mPAP were strongly correlated (R²=0.74; p<0.0001). For detection of mPAP ≥ 25mmHg the area under the receiver operator curve (ROC) was 0.91 (p<0.0001). CMR-estimated TPR correlated strongly with RHC-derived TPR (R²=0.75; p<0.0001) in the validation cohort. CMR estimated TPR reliably identified TPR > 5WU with a high degree of accuracy, the area under the receiver operator curve (ROC) was 0.96 (p<0.0001).

Conclusions: A CMR Imaging derived model can accurately estimate mPAP and vascular resistance in patients with PH.

381 MRI assessment of right atrial volume and function in pulmonary hypertension

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Background: The role of the right atrium (RA) is under-researched within pulmonary vascular disease. The aim was to investigate the use of magnetic resonance imaging (MRI) derived RA volume and function in the diagnosis and management of pulmonary hypertension (PH).

Methods: Patients attending the pulmonary vascular clinic were retrospectively assessed. Inclusion criteria were cardiac MRI and right heart catheterisation within 48 hours. Standard cardiac-gated balanced steady state free precession sequences were used. End-systolic volume (ESV) and diastolic volume (EDV) were calculated using Simpson’s numeric integral applied to manual RA area tracings in the 4-chamber stack sequence.
Results: 71 PH patients were included, mean age was 65 ± 15.5 years and 67.6% (48) were female.

RA function was shown to correlate with cardiac index (R = 0.69) and mean RA pressure (R = 0.64), P < 0.001.

RA ejection fraction ≤ 28.3% was shown to have moderate sensitivity (90%) and specificity (71%) for identifying patients who met diagnostic criteria. RA ESV > 28.0 ml was useful (sensitivity 96%, specificity 78%) for identifying patients with a high RA pressure, see figure 1.

![Figure 1. Receiver operator characteristic curves showing the diagnostic accuracy of (a) RA ejection fraction to detect a mean pulmonary artery pressure of ≥ 25 mmHg. (b) RA ESV to detect a mean RA pressure of > 10 mmHg.](image)

Conclusion: RA pressure is a known prognostic indicator; this study suggests high RA pressure can be detected using cardiac MRI. RA function has been shown to correlate well with haemodynamic measurements and clinical data. Further research into the natural history of RA volume change in PH is needed.

73. Update on neutrophil and macrophage function in COPD

382 Identification of pathogenic macrophage subpopulations in lung disease

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Residential macrophages may exist in discreet subpopulations which subserve specific roles in the maintenance of tissue and immunological homeostasis. In lung, alveolar macrophages (AMφs) comprise of > 95% cells in the alveolar airspaces, where they act as the primary sentinels of pathogens. Increased alveolar macrophage numbers are observed in many animal models of COPD and also clinically in COPD patients. Currently, M2 macrophage polarization is thought to be a contributor of lung disease, although this in vitro-derived macrophage paradigm may not completely explain the complex behaviour of AMφs in vivo.

Using flow cytometry, we have developed an approach which shows that mouse residential macrophages may exist as M1-like (classically-activated) or M2-like (alternatively-activated) states. In COPD, M1-like macrophages may appear “hyper-inflammatory” regardless of environment suggesting lack of plasticity. Altering COPD Mφ plasticity may be a therapeutic target.

384 Chemokine characterization in human lung macrophages following stimulation with Th2-type cytokines IL-4 or IL-13

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Background: Macrophages may acquire polarized phenotypes, the two extremes being the proinflammatory (M1) and immunoregulatory (M2) phenotypes characterized by surface markers and chemokine profiles. Reprogramming of AM toward a partially M2-polarized phenotype has been suggested to contribute to COPD pathogenesis. We thus sought to characterize the phenotype of human lung macrophages (LM) following stimulation with the Th2-type cytokines IL-4 and IL-13.

Methods: LM were isolated from human resected lungs challenged for 24 or 48hrs with IL-4 or IL-13 (1-150 ng/mL). Cytokines transcript expression was assessed with RT-qPCR, whereas proteins of M1 (TNFα, CCL3, CCL4 and CXCL8) and M2 cytokines (CCL13, CCL17 and CCL22) were quantified in supernatants.

Results: Unstimulated LM exhibited a rather undifferentiated phenotype, with weak M1/M2 cytokines expression. On the other hand, transcriptome analysis of 80 cytokines gene revealed that only four M2-type transcripts levels were increased (> 4- to 8-fold) following stimulation with IL-13 (CCL13, CCL17, CCL22 and CCL26). M2-type cytokine production at the protein level was also concentration-dependently increased (> 3- to 20-fold), whereas LM cytokines were unaffected. CCL13 and CCL22 increase was maximal at 48hrs, while the maximum was reached at 24hrs for CCL17. The results obtained with IL-4 were similar, except that IL-4 potency was greater than IL-13 since the low 10 ng/mL concentration provided submaximal cytokines increases.

Conclusions: Our data demonstrate that IL-4 and IL-13 favours LM polarization toward the immunomodulatory M2 phenotype characterized by the expression of CCL13, CCL17, CCL22 and CCL26.

385 Lipids in the lung: Respiratory inflammation in COPD

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Background: There is strong association between COPD and metabolic co-morbidities involving lipids. Abnormalities of lipid metabolism are associated with increased inflammatory responses. The aim of this study was to identify abnormalities of lipid content in the lungs of COPD patients, focusing on lung macrophages.

Methods: Resected lung tissue from patients undergoing surgery for cancer was used; isolated macrophages and macrophages within formalin fixed paraffin embedded (FFPE) tissue were examined. Comparisons were made between 5 subject groups, never smokers (NS), current smokers with normal lung function (S), ex-smokers with normal lung function (E), COPD current smokers (COPDS) and COPD ex-smokers (COPDE). The presence of lipid laden macrophages was identified using oil red o stain (ORO) where positive staining is expressed as % mean (SD).

Results: The number of ORO positive macrophages was increased in COPD patients and controls who were current smokers (COPDS and S) compared to the other groups of ex- or never smokers, in both isolated macrophages and FFPE tissue.

Discussion: We have shown an increase in lipid laden macrophages in the lungs of...
S and COPDS. Current smoking appears to cause dysfunctional lipid metabolism within lung macrophages that may contribute to respiratory inflammation. Smoking cessation may have benefits in returning lipid metabolism to normal in these cells.

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Effect of neutrophil supernatants on ex vivo small airway contractility in COPD
Natasha J. Madge, Louise E. Donnelly, Duncan F. Rogers. Airway Disease, National Heart & Lung Institute, Imperial College London, United Kingdom

Airway neutrophilia is a significant feature of COPD. Neutrophils release a variety of cytotoxic products (e.g. proteases) that degrade components of extracellular matrix. This may result in destruction of the lung and impendence of airflow characteristic of COPD. Small airways are the main site of airflow obstruction in COPD. Our aim was to study the effects of products from activated neutrophils on the contractility of small airways. Rat precision cut lung slices (PCLS) were obtained and videomicroscopy used to assess contractility of small airways. Neutrophils were isolated from whole blood of non-smokers, smokers and COPD patients, stimulated with 1μM (100μM) and supernatants collected. PCLS were incubated overnight in neutrophil supernatants, and the contractility of small airways assessed by addition of increasing concentrations of carbachol. PCLS incubated in supernatants from COPD patients caused a significant leftward shift in EC50, compared with untreated controls (13±2 vs 34±8μM, n=6, p<0.01). Conversely, PCLS incubated in supernatants from smokers had no effect on EC50, but significantly reduced maximal contraction compared with untreated controls (65±1% vs 88±3%, n=6, p<0.05). PCLS incubated in supernatants from non-smokers showed small but significant reductions in both EC50 (16±3 vs 32±8μM, n=6, p<0.05) and maximal contraction (79±4 vs 87±2%, n=6, p<0.05), compared with untreated controls. Elastase content of supernatants correlated with maximal contraction, but not with EC50. We conclude that neutrophil supernatants from COPD patients increase the sensitivity of small airways to cholinergic stimulation, which may contribute to the airflow limitation characteristic of the disease.

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Reduced phagocytosis of pathogenic bacteria by neutrophils from COPD patients
Catherine Thomas, Peter Barnes, Louise Donnelly. Airway Disease, National Heart and Lung Institute, Imperial College, London, United Kingdom

Acute exacerbations of COPD are the commonest cause of acute medical admissions in the UK, with ~50% associated with bacterial infection. An acute bacterial insult is usually associated with increased recruitment and activation of neutrophils. COPD is characterized by airway neutrophilia; however, despite increased numbers of these cells, bacterial colonization persists. This study examined whether neutrophil phagocytosis was altered in COPD. Neutrophils were obtained from COPD, smoking and healthy subjects and phagocytosis of fluorescently-labelled polystyrene beads, Haemophilus influenzae (HI) or Streptococcus pneumoniae (SP) measured by flow cytometry. Neutrophils from all subjects ingested beads similarly showing that all cells were capable of phagocytosis. Neutrophils from all subjects phagocytosed SP with a maximum response at 5 min, however COPD neutrophils ingested significantly less SP (p<0.05) than those isolated from non-smokers (NS) and smokers (S) (NS: 17±1±1.7 MFI, n=19 vs S: 14±8±1.2 MFI, n=19 vs COPD: 12±8±0.5 MFI, n=20). Approximately 95% of cells phagocytosed HI, but the capacity of COPD neutrophils to ingest HI was significantly attenuated (p<0.01) compared with control neutrophils for all time points up to 30 min. Neutrophils from S phagocytosed HI similarly to cells from NS initially (NS: 18±0±1.8 MFI, n=19 vs S: 19±3±0.6 MFI, n=20 vs COPD: 5.2±0.5 MFI, n=20). However, after 10 min this response became blunted. These effects were not associated with differences in expression of CD11b, TLR2 or TLR4 or in cell viability. Therefore, neutrophils from COPD patients exhibit reduced phagocytosis of pathogenic bacteria which could account for persistent airway colonization.

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Short term effects of alpha-1-antitrypsin substitution therapy on the degradation of neutrophil granulocytes
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Introduction: Alpha-1-antitrypsin-deficiency (AATD) is a hereditary, co-dominant condition which results in low levels of circulating alpha-1-antitrypsin (A1AT), unbalanced protease activity and frequent development of emphysema. The concept behind substitution therapy with human plasma A1AT is to normalize the concentration in blood and tissue and thereby protecting the lungs from progressive destruction by proteases.

Aim: To better understand the influence of weekly augmentation therapy on polymorphonuclear neutrophils (PMNs) we examined direct effects on chemokine release and degradation of matrix metalloproteinase-9 (MMP-9) and matrixmetalloproteinase (MPO).

Methods: PMNs were isolated from peripheral blood of ten AATD-patients (PIZZ, mean age 55±8±7, FEV1[%] 38±1±14±33, pre) and two hours post substitution infusion. The release of IL-8, MMP-9 and MPO was quantified in neutrophil supernatants via ELISA. Standard inflammation markers as well as MMP-9, MPO and the tissue inhibitor of metalloproteinase-1 (TIMP-1) were evaluated in patient sera.

Results: PMN-stimulation experiments displayed no differences on chemokine release or degradation between pre and post substitution infusion. Two hours after substitution we measured increased MMP-9 (p=0.002) and MPO (p=0.0034) concentrations in sera of patients, whereas TIMP-1 decreased drastically (p=0.002). IL-8 levels in sera of these patients were within normal range and no changes were detectable due to substitution.

Conclusions: We conclude that elevated MMP-9 and MPO concentrations after substitution depend on rapid degradation of PMNs whereas the decline in TIMP-1 concentration possibly depends on a feedback loop.

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Lung inflammation is significantly reduced by recovery of neutrophil apoptosis in vivo
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Introduction: Neutrophil apoptosis is considered to be a major regulator of neutrophil driven lung inflammation. The compatible solute ectoine has been described to act preventive against lung inflammation induced by environmental particles (Sydlik et al., Am J Respir Crit Care Med 2009). As a therapeutic approach, here, we investigated the influence of this compound on neutrophil apoptosis in the inflammatory microenvironment.

Methods: Human neutrophils were treated ex vivo with particles or inflammatory mediators in the presence or absence of ectoine in order to study apoptosis rates and pro-apoptotic signalling. Lung inflammation was induced in rats by intra-tracheal application of 2.5 mg/kg environmental particles and studied in lung lavages after control or ectoine intervention.

Results: Apoptosis rates of human neutrophils from COPD patients and volunteers, which were significantly reduced by the inflammatory stimulus, recovered significantly in the presence of ectoine. Mechanistic analyses demonstrated the preventive effect of ectoine on pro-apoptotic signalling events via Akt and Mecl-1. The in vivo relevance of the data was shown by significantly reduced neutrophil inflammation after ectoine intervention which correlated with restored neutrophil apoptosis rates in the lung.

Conclusions: The current studies demonstrate the effective to prevent anti-apoptotic signalling in neutrophils by the compatible solute ectoine. This effect led to recovered apoptosis rates and a reduction of environmentally induced lung inflammation. The relevance of ectoine treatment for humans is demonstrated by the EFECT study which will be presented on the same meeting.
74. How to use technology to provide better critical care

The musculoskeletal ultrasound in critical care: Longitudinal evaluation (UK-MUSCLE) study: Severity of acute critical illness determines the degree of muscle wasting

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Acute muscle wasting in critical illness is a major cause of disability amongst intensive care survivors. Limited data exists detailing sequential loss of muscle mass and histological changes. We hypothesised that loss of Rectus Femoris Cross-Sectional Area (RFCSA) would be determined by illness severity and paralleled by reduction in myofibrillar cross-sectional area.

Methods: Critically ill patients were recruited within 24 hours of admission. Serial RFCSA measurements were taken using B-mode ultrasound and stratified by numbers of failed organ systems. Serial vastus lateralis muscle biopsies were performed.

Results: 63 patient were analysed. The greatest RFCSA reduction was observed in patients with multi-organ failure (MOF) 21.5 ± 10.5% in MOF patients vs. 7.2 ± 5.7% in patients with single organ failure (SOF); p < 0.001.

439 Can lung ultrasound predict prone positioning response in ARDS?

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Introduction: Prone positioning (PP) is an alternative in the management of patients with severe ARDS. Among patients treated with that technique: only 70% are responders as they improve their P/F, but at present we are not able to predict the patient’s responsiveness. The aim of our study was to determine whether the lung aspect observed with US before PP can predict or not the prone positioning response.

Patients and settings: Prospective monocentric study (medical ICU university hospital Brest France) including patients with severe ARDS (P/F < 200 with FiO2 ≥ 0.7). A standard lung US exam with 12 lung areas to explore (superior/inferior, anterior/lateral/posterior, right/left) was practiced before prone positioning (12 hours according unit’s procedure). Before PP, after 2 hours of PP and 2 hours after turning back the patient supine, haematosis parameters were collected.

Lung aspect was evaluated a posteriori by 3 physicians and graded in 4 stages (normal aspect, and 3 stages of lung compression)

Observation of the P/F ratios course permitted to classify patients as responders or non-responders.

Statistics: Fisher’s exact test

Results: 17 patients were enrolled in the study.

– For the early response: the absence of lung compression in anterior and supero-rider organs is associated with an improvement of P/F ratio > 20 mmHg, whereas posterior areas aspect is not predictive of the response to PP.

– For the late response, we have not found any relationship between the lung aspect and the pp response.

Discussion: The first analysis showed that lung’s US aspect could predict the patient’s response to PP and could help physician in routine practice to place or not sever ARDS patient in PP.

392 Treatment of hypercapnic respiratory failure with a novel extracorporeal CO2 removal system

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Background: Extracorporeal CO2 removal (ECOO2R), a potentially valuable technique, has not been systematically evaluated in patients with hypercapnic respiratory failure. We describe the application of a novel single venous catheter, low blood flow, ECOO2R device (Hemolung® Respiratory Assist System, ALANG Technologies, Inc.).

Methods: Twenty three hypercapnic patients received ECOO2R. Group 1 (n=7) consisted of patients with chronic obstructive lung disease on non-invasive ventilation with a high likelihood of requiring invasive ventilation, Group 2 (n=2) were patients who could not be weaned from noninvasive ventilation, Group 3 (n=11) were patients who could not be weaned from invasive ventilation, and Group 4 (n=3) were patients on invasive ventilation requiring lung protective ventilation techniques.

Results: The device was well tolerated, with complications and rates similar to those seen with central venous catheterization. Blood flow through the system was 430.3 ± 73.7 ml/min, and ECOO2R was 82.5 ± 15.6 ml/min. Invasive ventilation was avoided in all patients in Group 1 and both patients in Group 2 were weaned; PaCO2 decreased significantly (p <0.003) with application of the device. In Group 3, three patients were weaned, in 3 patients ventilatory support was reduced, and one patient died due to a retroperitoneal bleed following catheterization. In Group 4, lung protective ventilation was enhanced by the ECOO2R device.

Conclusions: This single catheter, low blood flow ECOO2R system provided clinically useful levels of CO2 removal in these hypercapnic patients. The system appears to be a potentially valuable additional modality for the treatment of hypercapnic respiratory failure.

393 Effect of a closed loop ventilation strategy on the duration of ICU stay: A randomized controlled trial (interim analysis results)

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Background and aim: There are some studies suggesting that adaptive support ventilation (ASV), a closed loop ventilation mode, shortens the weaning duration in some patient groups. We aimed to investigate the effect of ASV on total duration of mechanical ventilation (MV), weaning and intensive care unit (ICU) stay when compared to pressure controlled ventilation (PCV), a conventional mode.

Materials and methods: Patients who were mechanically ventilated longer than 24 hours were randomized into ASV and PCV. Demographic data and total duration of MV, weaning and ICU stay, number of manipulations, need for sedation and complications (self-extubation, ventilator associated pneumonia) were compared.

Results: Data are expressed as median (IQR). 96 patients (73 COPD) were enrolled between December 2011 and February 2012. Duration of weaning was 2 hours (2–7) in ASV and 4 hours (2–26) in PCV (p=0.013). Number of manipulations were 1 (2–3) in ASV and 3 (1–6) in PCV (p<0.001). When a subgroup analysis was done only on patients who could be weaned, in addition to the results above, duration of ICU stay was 4 days (3–7) in ASV while it was 7 days (5–10) in PCV (p=0.039).

Conclusion: ASV seems to decrease the staff’s workload, duration of weaning and ICU stay when performed from intubation until extubation. The present study is continuing until the targeted sample size is reached in order to detect the effects of

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this mode on secondary outcomes such as total duration of mechanical ventilation and need of sedation.

394 Diaphragm electromyographic activity as a predictor of weaning failure
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Purpose: To compare breathing pattern descriptors and diaphragm electromyo-
graphic activity (EAdi)-derived indices obtained from a Neuromuscular Ventilator
Assessment (NVA) catheter during a spontaneous breathing trial (SBT) in patients
successfully (SP) and unsuccessfully (UP) separated from the ventilator and to
assess their performance to discriminate these two categories of patients.

Methods: 57 ready-to-wean patients were included in a prospective observational
study (35 SP and 22 UP separated from the ventilator). During a 30 minutes SBT
pressures, flow, work, zero of expiratory pressures, tidal volume (VT) and
respiratory rate (RR) were obtained from the flow signal at 3, 10, 20 and
30 minutes. EAdi-derived indices were simultaneously computed: maximum of
the EAdi (EAdmax), area under the inspiratory curve of EAdi (EAdIAUC), the difference
during EAdmax and EAdmin (AEAdi), EAdmax/VT, EAdIAUC/VT and AEAdi/VT.

Results: At baseline, breathing pattern was similar in the two groups whereas
EAdmax and EAdIAUC were significantly lower in the success group (p<0.05). In
the failure group, RR and RR/VT increased significantly during the trial, VT
decreased, whereas EAdmax and EAdIAUC did not change. At 3 minutes, the ar-
cas under the receiver operating characteristic-curve of RR/VT and EAdi-derived
indices to predict weaning outcome were: RSBI (0.83), EAdmax/VT (0.84),
EAdIAUC/VT (0.80) and AEAdi/VT (0.82). During the SBT, the coefficient of
variation of VT decreased in the failure group while the one of EAdmax remained
unchanged.

Conclusion: EAdi-derived indices provide reliable and early predictors of weaning
outcome. However, the performance of these indices is not better than the RR/VT.

395 Usefulness of selective neutrophil elastase inhibitor, sivelestat, in ALI patients
with SIRS
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Background: Neutrophil elastase is known to be an important mediator of acute
lung injury (ALI) in systemic inflammatory response syndrome (SIRS). Sivelestat
is a neutrophil elastase inhibitor, but the clinical efficacy of sivelestat in patients
with lung injury (ALI) in systemic inflammatory response syndrome (SIRS). Sivelestat
in Japan

Purpose: To evaluate the clinical efficacy of sivelestat in the treatment of acute lung
injury (ALI) in patients with systemic inflammatory response syndrome (SIRS).

Methods: 40 patients (17 men and 23 women) aged 66 ± 10 years old were included
in the study, 20 patients were in the treatment group and 20 were in the placebo
control group. Both groups were monitored for 72 hours. The change in VFD (day 3-
day 0) and P/F ratio were compared between the two groups.

Results: Among the 20 patients in the treatment group, 8 patients (40 ± 10 years old)
showed a significant improvement in VFD and P/F ratio compared to the control
group (p=0.01). In the placebo control group, 12 patients (40 ± 10 years old) showed
no significant improvement in VFD and P/F ratio.

Conclusion: Sivelestat might have beneficial effect on the respiratory condition of the
ALI patients with SIRS. Furthermore, sivelestat administration tends to associate with survival in patients with ALI with sepsis.

75. Clinical management of lung diseases: from bronchi to pleura

P397 Respiratory muscle strength and physical performance in elderly hospitalized
patients
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Age-related changes in pulmonary function increase respiratory muscle work. In
front of this increased demand, sarcopenia frequently associated with age and
multimorbidity, can reduce endurance and strength of respiratory mus-
cles. Furthermore, sarcopenia may per se contribute to reduction of physical perfor-
mance.

Aim of the study: To evaluate the correlation between the respiratory muscle
strength and physical performance in elderly.

Population: 65 patients (30 men and 40 women) aged between 65-80 years.

Methods: A retrospective data analysis of 110 ALI patients with SIRS was con-
ducted to investigate the effects of sivelestat. The clinical efficacy of sivelestat
was evaluated based on the survival rate and ventilator free days (VFD) and changes
between before and 7 days after administration of sivelestat in PaO2/FiO2 (P/F)
ratio, white blood cell count, levels of C-reactive protein and procalcitonin (PCT).

Results: Sivelestat group included 70 patients, and control group included 40 pa-
tients without administration of sivelestat. VFD was significantly higher, and P/F
ratio significantly improved in the sivelestat group compared to the control group.

Conclusions: Sivelestat significantly increased VFD and P/F ratio, and reduced the levels of
PCT in septic patients.

This result suggests that sivelestat might have beneficial effect on the respiratory condition of the ALI patients with SIRS. Furthermore, sivelestat administration tends to associate with survival in patients with ALI with sepsis.

396 Biological effects of nanostructured lipid carriers
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Nanostructured lipid carriers (NLC) are a type of drug delivery system offering
improved performance in terms of drug loading and long-term stability. Our aims
were to test mechanisms of NLC uptake into endothelial cells (EC) and evaluate
possible biologic effects of these compounds.

NLC were prepared with triglycerides Miglyol and Softisan and egg-
phosphatidylcholine (1:1 by weight) by the double emulsion technique. Cul-
tured mouse lung microvascular endothelial cells (LMVEC) were incubated with
curcumin-loaded NLC and uptake was quantified as fluorescence detected in the cell
homogenate or by FACS. To test biologic effects, we challenged human LMVEC
with thrombin with or without NLC and measured endothelial permeability as flux
rate of fluorescent albumin across endothelial monolayers grown on transwell in-
serts. Alterations were tested in thrombin-induced endothelial Lipid raft-Regulated
Kinase (ERK) activation by immunoblotting and endothelial actin remodelling by fluores-
cence microscopy. Finally, NLC were delivered intravenously as pre-treatment in
a mouse model of hydrochloric acid (HCl) aspiration lung injury.

Using cultured mouse LMVEC we observed that NLC are incorporated into cells
more efficiently when caveolin-1, the structural protein of caveolar vesicles, is
expressed. Upon challenge of cultured EC with thrombin, NLC attenuated the
permeability increase, activation of ERK, cytokine production and actin stress
fiber formation. In the HCl-aspiration model, NLC attenuated the increase in bron-
choalveolar lavage protein content, inflammatory cells and histological alterations.

Conclusion: Systemically delivered NLC are taken up by EC via caveolae and
have endothelial-protective effects of potential relevance to acute lung injury.

P398 Plasma homocysteine is associated with low diffusion capacity (DLCO) in
COPD patients
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Introduction: Chronic obstructive pulmonary disease (COPD) is associated with

cardiovascular events, however, its underlying pathophysiological mechanism is unknown. Elevated total plasma homocysteine (tHcy) levels is considered to be a cardiovascular risk factor. Several studies show that COPD may be associated with high tHcy.

Objective: To identify possible clinical variables associated with high tHcy in COPD patients.

Methods: We performed an observational study of 88 consecutive smokers or ex-smokers older than fifty years and with more than 10 pack-years smoking history. We used Mann Whitney test to compare COPD with controls. Step wise logistic regression analysis was used to determine the association between tHcy and different clinical, analytical and physiological variables in COPD patients.

Results: Of the subjects evaluated, 62 had COPD (70.5%) and 26 (29.5%) did not, and served as controls. COPD patients had higher tHcy than controls: median (±SD) 14.2±6.6 vs 11.7±4.5 μmol/L, p=0.025. In COPD patients, using tHcy >14 μmol/L as an independent variable, logistic regression analysis including age, gender, smoking history, creatinine clearance, FEV1, DLCO and daily alcohol intake, only lung diffusion capacity for carbon monoxide (DLCO) was significantly associated (Odds Ratio (95% confidence intervals) 0.947 (0.904 – 0.992); p=0.023).

Conclusions: COPD patients had higher tHcy than controls and they were associated with a low DLCO. Therefore, we conclude that COPD patients with low DLCO may have a higher risk of cardiovascular events; however, further studies are needed to confirm this hypothesis.

P399

Inflammatory mediators associated with bone metabolism in patients awaiting lung transplantation

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Aims: to evaluate the association between systemic inflammation, markers for bone turnover and bone mineral density (BMD) in 105 candidates for lung transplantation.

Methods: BMD, bone biomarkers, inflammatory mediators were determined in 105 patients with end-stage of chronic respiratory failure and 85 age and sex matched controls.

Results: We identified a osteoporotic syndrome in 82/105 patients, 10/85 controls were osteoporosis. Procollagen type 1 amino-terminal propeptide (P1NP), markers of bone formation, was higher in lung diseases and osteoclast was similar between patients and controls. Type 1 collagen C-tepeptide (CTX), a marker of bone resorption, was higher in candidates for lung transplantation and was inversely correlated with P1NP. Bone density (BMD) values were lower in candidates for lung transplantation (BMD lung 0.70±0.1 cm2, BMD N 0.78±0.1 cm2, p=0.01). TNF-a and its receptors level, interleukin-6, receptor of nuclear factor kappa b (RANK) were higher, osteoprotegerin level was low in lung pathology. Vascular endothelial growth factor was lower in patients with emphysema and correlated with BMD (t=0.06, p=0.002) only in with end-stage of emphysema.

Conclusions: Patients with end-stage lung diseases had a greater prevalence of osteoporotic syndrome. Results shows possibly role of systemic inflammatory in the increasing of bone loss at the terminal stage of lung disease.

P400

Administration of lisoflavan in the treatment for enogenic allergic alveolitis (EAA)

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Aims: To evaluate efficacy of continuous treatment for subacute variant of EAA with inhalation lisoflavan.

Materials and methods: We studied 27 patients with subacute course of morphologically confirmed EAA. Group 1 (10 patients) received the standard treatment with prednisolone (20 mg/day). Group 2 (17 patients) received prednisolone (15 mg/day) plus inhalation lisoflavan. We evaluated clinical symptoms (cumulative index), 6-minute walk test, spirometry, diffusion capacity of the lung (DLCO), computed tomography (CT) of the lungs using Kazeromi modification, before and after the treatment. The reliability of differences was estimated using the Mann-Whitney test.

Results: There were no reliable differences between the groups. The analysis of the data within the both groups revealed reliable improvement of clinical symptoms, LVC, distances of the 6-minute walk test, the alveolar component of CT. In group 2 we also observed increased DLCO.

Conclusion: Nebulizer administration of lisoflavan in the complex treatment for subacute course of EAA allows decreasing corticosteroids doses.

P401

Review of health-related quality of life and patient-reported outcome in patients receiving EPs 7630 treatment for acute bronchitis

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Background: Health-related quality of life (HRQL) and patient-reported outcome (PROM) are important outcome parameters for the evaluation of both medical treatment within clinical trials and efficacy in clinical practice. For EPs® 7630 (Umcalanob®) treatment, clinically relevant improvements in HRQL/PROM have been reported recently (Matthys, H. et al. Wien Med Wochenschr 2010;160:564-70; Matthys, H. et al. Eur Respir 2011;38(Suppl 55):18s-19s).

Aims: We systematically reviewed randomised controlled trials (RCTs) in order to assess the impact of EPs 7630 treatment on HRQL and PROM of patients with acute bronchitis (AB).

Methods: Trials published 2010 or earlier were included for the review if they were RCTs investigating EPs 7630 vs placebo (PL) in adults or children suffering from AB and assessing HRQL and PROM by means of the EQ-5D questionnaire and the Integrative Medicine Patient Satisfaction Scale (IMPSS).

Results: 6 trials with a total of 1164 patients (EPs 7630: 586; PL: 578; 53% 1-18 yrs) were identified. After 7 days of treatment, clear and mostly statistically significant advantages were seen for EPs 7630 compared to PL in the EQ-5D dimensions (mobility, usual activities, pain/discomfort and anxiety/depression: p<0.01; self-care: p=0.02) and in the health status of patients (EQ VAS: p<0.01). 7630 for EPs 7630, twice as many patients were satisfied or very satisfied with treatment outcome compared to PL (82.1% vs. 40.0%; p<0.01).

Conclusions: There are encouraging evidence from currently available data derived from placebo-controlled trials that EPs 7630 treatment improves HRQL and PROM in both children (>1 year) and adults with acute bronchitis.

P402

Efficacy of corticosteroids in hospital treated community-acquired pneumonia

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Aim: The aim of the study was to evaluate beneficial effect of corticosterides in short treatment of community acquired pneumonia (CAP).

Patients and Methods: We enrolled a total of 149 hospitalized patients, for a period of an year (January 2011 to December 2011). The diagnosis of CAP was made using standard clinical and radiological criteria. Disease severity was scored using Pneumonia Severity Index. Age, antibiotic treatment and PSI adjustment has been done between the groups. Patients received 50 mg prednolone for 7 days, along with antibiotics.

The outcomes were clinical cure at day seven, defeverescence, length of stay, time to clinical stability.

Results: Mean age of patients enrolled in study was 63±16.7 in prednolone and 53±18.6 in group without prednolone Therty (40%) patients in prednolone group and 16 (22.2%) in without prednolone group were in Pneumonia Severity Index class I-II. Clinical cure at day 7 was 81(75) (82.6%) in the prednolone group and 44/72 (61.1%) in other group (P<0.008). Patients on prednolone had faster defeverescence compared with other group, (P<0.0002). Length of stay was significantly lower in patients with prednolone compared with nonprednolone group, 9.4±4.3 and 12.3±6.4 respectively, (p=0.0011). Adverse events were few and not different between the two groups.

Conclusions: In this study we show that Prednolone (at 50 mg) once daily for a short time, (a week), have a beneficial effects in patients hospitalized with mild to severe CAP, improving outcomes without adverse events.

P403

Nurse practitioner insertion of Seldinger chest drains. A pilot study

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Background: In 2008 the National Patient Safety Agency encouraged UK hospitals to develop local policies that reduced the risks associated with chest drain insertion. A key theme that emerged from the 2008 Rapid Response Report was...
that the inexperience of junior doctors and inadequate supervision increased the risk of complications associated with the procedure.

Aims: We proposed that a ward based nurse practitioner, trained in thoracic ultrasound and chest drain insertion, was the nurse practitioner. Various aspects relating to chest drain insertion including consent practice, use of thoracic ultrasound and incidence of any adverse events were audited. Data was collected over a four month period (June to September 2011).

Results: All 10 chest drain insertions performed by the nurse practitioner were correctly sited, written consent was obtained in 100% of procedures undertaken, thoracic ultrasound was used to guide drain placement in 100% of cases and there were no adverse incidents or complications related to chest drain insertion.

Conclusion: Training of specialist nurses in the procedure of chest drain insertion for elective patients with uncomplicated pleural effusion is an acceptable model within the district hospital setting and has the additional benefit of providing appropriate support and supervision for junior doctors undertaking this procedure.

P404
Outcomes of bronchial artery embolisation in the management of clinically significant hemoptysis
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Objectives: Bronchial artery embolisation (BAE) has been established as an effective technique in the emergency treatment of massive hemoptysis. Aim of the study has been to evaluate immediate and long-term outcomes of BAE and to identify factors influencing outcomes.

Methods: A retrospective analysis was carried out of the medical records and angiograms of 120 patients who underwent BAE between January 2005 and December 2009. 79 patients were men and the mean age was 54.5 years.

Results: The patients were divided 3 groups including recurrent hemoptysis (<100ml/day: n=49), (100-400ml/day: n=49), massive hemoptysis group (>400ml/day: n=24). The common underlying diseases of hemoptysis were pulmonary tuberculosis and related disorders (51%), bronchiectasis (21%) and aspergillosis (21%). In this series, immediate success rate to control bleeding within 24 hours was 89% (106 cases), long-term success in 62.5% (75cases) and recurrence rate was 26% (31cases). Five patients died from massive hemoptysis. Among initial radiographic findings, pleural lesions (P<0.05) and aspergillus (P<0.05) were significantly associated with hemoptysis recurrence. A good clinical outcome was significantly associated with hemoptysis recurrence.

Conclusion: BAE after non-cardiac thoracic surgery are common and lead to increased morbidity and prolonged hospital stay in our setting. We identified pre-existing chest disease, prolonged anaesthesia and emergency surgery as common predictors of PPC.

Aims & Objectives: To study factors predicting PPC in our setting.

Methods: Prospective study of consecutive 404 patients undergoing non-cardiothoracic surgery under GA with tracheal intubation from Jan 2009 to Dec 2010. Chi-square was used for univariate analysis and forward stepwise logistic regression for multivariate analysis.

Results: The mean age was 51±18 years with 54% males. 22% were smokers, and mean BMI was 23±4.5 kg/m² with 35% overweight & obese. 4% of subjects had chronic lung conditions while 23% had non-pulmonary chronic conditions. 70% of the surgeries were done electively and the mean duration of GA was 78±44 min. The overall PPC rate was 8%; atelectasis (4%) followed by bronchospasm (25%) and pneumonia (16%) being the commonest complications. The mean duration of hospital stay was significantly longer in patients with PPC (11±9 days, p<0.001) and 29% of them required mechanical ventilation. Logistic regression analysis identified chronic chest condition, emergency surgery and prolonged duration of GA as significant predictors of PPC while age, gender, BMI, smoking history and non-pulmonary premorbid was not of any significance.

Conclusion: PPC after non-cardiothoracic surgery are common and lead to increased morbidity and prolonged hospital stay in our setting. We identified pre-existing chest disease, prolonged anaesthesia and emergency surgery as common predictors of PPC.

P405
Changing serum cytokines levels in patients with idiopathic pulmonary arterial hypertension treated with bosentan
Tamila Martynyuk, Kirill Zykov, Olga Arkhipova, Ekaterina Kobal, Irina Chazova. Department of Systemic Hypertension, Russian Cardiology Research-and-Production Complex, Moscow, Russian Federation

Aim: To investigate the influence of Bosentan on serum cytokines levels in pts with idiopathic pulmonary arterial hypertension (IPAH).

Methods: In the single-center comparative study we included 35 pts aged 35,2±0,6 yrs with IPAH confirmed by RHC (WHO Functional Class (FC) II-IV) without systemic inflammation signs. On top of chronic bosentan therapy (250 mg/day) we randomized 1:1 by the envelope method to have bosentan 125 or 250 mg/day. At baseline, at wk4 and wk12 the pts underwent the clinical and laboratory assessment (FC, 6-minute walking test (6-MWT), Echo, RHC, routine lab measurement of high sensitivity C-reactive protein (hsCRP) and serum pro-inflammatory serum cytokines (interleukin (IL) 1β, 8, TNFα).

Results: At baseline the groups did not differ in age, disease duration, functional, and hemodynamic parameters, hsCRP levels were normal in both groups.

Conclusion: The influence of Bosentan 125 and 250 mg/day on some cytokines levels to wk12 showed its anti-inflammatory effect in IPAH pts.

P407
Bosentan influence on cellular immunity parameters in patients with idiopathic arterial pulmonary hypertension
Tamila Martynyuk, Kirill Zykov, Olga Antonova, Olga Arkhipova, Ekaterina Kobal, Valery Masenko, Sergey Nakonechnikov, Irina Chazova. Department of Systemic Hypertension, Russian Cardiology Research-and-Production Complex, Moscow, Russian Federation

Aim: To assess the influence of endothelin receptor antagonist Bosentan on cellular Immunology parameters in pts with idiopathic pulmonary arterial hypertension (IPAH).

Methods: In the single-center comparative study we included 35 pts aged 35,2±0,6 yrs with IPAH confirmed by RHC (WHO Functional Class (FC) II-IV) without systemic inflammation signs. On top of chronic bosentan therapy (250 mg/day) we randomized 1:1 by the envelope method to have bosentan 125 or 250 mg/day. At baseline, at wk4 and wk12 the pts underwent the clinical and lab assessment (FC-6 minute walking test (6-MWT), Echo, RHC, routine lab+ measurement of high sensitivity C-reactive protein (hsCRP) and serum pro-inflammatory serum cytokines (interleukin (IL) 1β, 8, TNFα).

Results: At baseline the groups did not differ in age, disease duration, functional, and hemodynamic parameters, hsCRP levels were normal in both groups.

Conclusion: The influence of Bosentan 125 and 250 mg/day on some cytokines levels to wk12 showed its anti-inflammatory effect in IPAH pts.

Abstract P406 - Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (bosentan 125 mg)</th>
<th>Group 2 (bosentan 250 mg)</th>
<th>Normal control</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10 (pg/ml)</td>
<td>1.8 (1.5-2.8)</td>
<td>0.6 (0.3-0.8)*</td>
<td>0.8 (0.7-1.1)</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>10.6 (5.1-16.2)</td>
<td>16.2 (8.8-18.7)</td>
<td>8.1 (7.6-11.0)*</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>19.4±6.5</td>
<td>19.6±3.9</td>
<td>20±1.9</td>
</tr>
</tbody>
</table>

*p<0.05 IPAH pts vs control, *p<0.05 vs baseline, †p<0.05 group 1 vs group 2.

Abstract P407 - Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (bosentan 125 mg)</th>
<th>Group 2 (bosentan 250 mg)</th>
<th>Normal control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19*</td>
<td>10.3±2.8</td>
<td>10.9±3.1*</td>
<td>7.8±4.4</td>
</tr>
<tr>
<td>CD3+HLA-DR*</td>
<td>5.5 (2.2-7.5)</td>
<td>4.0 (2.5-9.0)</td>
<td>6.2 (5.6-9.2)</td>
</tr>
<tr>
<td>CD3+HLA-DR+*</td>
<td>11.2±2.4</td>
<td>10.8±2.5</td>
<td>9.3±2.6</td>
</tr>
<tr>
<td>CD4+CD45RA*</td>
<td>37.2±12.7*</td>
<td>29.9±18.9*</td>
<td>47.5±9.3</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline, †p<0.05 group 1 vs group 2.
Results: All cellular immunity parameters of IPAH pts remained within normal limits.

Conclusion: 12wk therapy with Bosentan changed CD-markers levels. The daily dose of 125mg resulted in the increase of B-lymphocytes and slight decrease of activated T lymphocytes. In patients treated with Bosentan 250 mg we found decreased numbers of activated B- and T-lymphocytes.

P408
High-dose inhalation corticosteroids in conjunction with plasmapheresis in the treatment of patients with acute variant of exogenous allergic alveolitis (EAA)
Natalya Markaryants, Larisa Lepeshka, Eugene Shmullev. Respiratory/Pathology Department, CTRI RAMS, Moscow, Russian Federation

Aim: To evaluate efficacy of high-dose inhalation corticosteroids in conjunction with plasmapheresis in the treatment for acute variant of EAA.

Materials and methods: We studied 16 patients with acute course of morphologically verified EAA. The main group (8 patients) received high-dose fluticasone (2500 µg) and plasmapheresis. The control group (8 patients) received the standard dose of prednisolone (0.25 mg/kg). The both groups received the treatment during one month. We performed cytology and morphology studies of lung biopsies from all the patients. We evaluated clinical symptoms (cumulative index), 6-minute walk test, spirometry, diffusing capacity of the lung, computed tomography (CT) of the lungs by Kazerouni, before and after the treatment.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Main group (n=8)</th>
<th>Comparison group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Cumulative index (scores)</td>
<td>2.4±0.3</td>
<td>1.0±0.3*</td>
</tr>
<tr>
<td>6-minute walk test (m)</td>
<td>446.5±20.6</td>
<td>510.0±24.5*</td>
</tr>
<tr>
<td>FEV 1 (% of the due values)</td>
<td>59.8±8.4</td>
<td>109.9±8.4*</td>
</tr>
<tr>
<td>DLCO (% of the due values)</td>
<td>102.3±7.6</td>
<td>108.1±7.5</td>
</tr>
<tr>
<td>LCV (% of the due values)</td>
<td>80.9±2.6</td>
<td>83.7±2.5*</td>
</tr>
<tr>
<td>CT alveolar component (scores)</td>
<td>3.1±0.4</td>
<td>1.8±0.4*</td>
</tr>
<tr>
<td>CT interstitial component (scores)</td>
<td>0.3±0.2</td>
<td>0.3±0.2</td>
</tr>
</tbody>
</table>

To analyze the data we used the non-parametric methods of the Statistica program, and the Wilcoxon criterion.

Conclusion: High-dose inhalation corticosteroids in conjunction with plasmapheresis may be used to treat patients with acute variant of EAA as alternative to the standard corticosteroid therapy.

P409
Pleural drain management – A clinical practice improvement project
Baloor Ran, Vinod Ayappa, Jeff Bowden, Anand Rose, Adriana Thanh-Thao Le. Respiratory, Flinders Medical Centre, Adelaide, SA, Australia

Introduction: An audit performed in Year 2010 at Flinders Medical Centre showed significant number of complications with intercostal chest drain insertion and management, with only 28% of patients being complication free.

Aims and objectives: Our mission was to reduce the incidence of complications associated with management of pleural drains, in respiratory unit at Flinders Medical Centre, by 80% within 6 months.

Methods: We used validated tools, introduced by Deming, Shewart, Juran et al., customized to the health environment to tackle this problem. We assembled a team and undertook diagnostics. This included brainstorm sessions, cause and effect diagram and prioritized problems using a pareto graph. We then designed interventions and evaluated the outcome.

Results:

Audit: Pre and Post project

<table>
<thead>
<tr>
<th>Complications</th>
<th>Audit 1</th>
<th>Audit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drain falling out</td>
<td>2/14 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Tubing disconnected</td>
<td>1/14 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Tube kinked</td>
<td>2/14 (14%)</td>
<td>2/16 (12.5%)</td>
</tr>
<tr>
<td>Issues with suction/UWSD</td>
<td>1/14 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Ongoing air leak</td>
<td>2/14 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>2/14 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Severe Pain</td>
<td>4/14 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>1/14 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate anchoring sutures</td>
<td>1/14 (7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

We found that the three main issues impacting on pleural drain management was a lack of protocol, lack of patient information and Nursing education. This was followed by targeted intervention. Already available protocol was reviewed and customized to our local setting. A formal patient information sheet was adapted from British Thoracic Society and American Thoracic Society guidelines. A nursing education session was undertaken and a continuous refresher course was set-up.

Documentation sticker was prepared. Subsequently a re-audit was performed, which showed a reduction of complications from 72% to 12.5%.

P410
Risk factors in elderly patients with acute respiratory failure
Balam Er Dedekarginoglu, Elif Kupeli, Gaye Uzunay. Chest Diseases, Basent University Hospital, Ankara, Turkey

Introduction: Acute respiratory failure is a condition that may cause morbidity in not only patients with systemic disorders but also healthy people.

Aim: To determine risk factors in elderly patients with acute respiratory failure (ARF).

Method: Cases over 65 years old with (ARF) that applied to the Department of Chest Diseases of our hospital between years 2011 and 2012 were included in the study prospectively.

Findings: 47 cases (M=25.22, median age:74.7±10 years) were included in the study. Computed thorax tomography was conducted in 38 cases. Multiple pulmonary pathology was established in 18 cases (41.9%) while 4 cases (9.3%) only had lung bullaeles, 3 cases (7%) only had honeycomb appearance, and in 1 case (2.3%) only had pneumonia. It was established that 25 cases (53.2%) had type 1 respiratory failure (RF), 22 cases (46.8%) had type 2 RF. Intensive Care (IC) monitoring was necessary for 18 cases. Average term of stay in IC was 10.7±4 days. Need of intubation developed in 13 patients (27.7%). Oesaltamivir was administered in 23 cases with suspicion of influenza. Only 3 out of 23 cases administered Oesaltamivir were intubated and 9 out of other 24 cases were intubated (p<0.05). Intubation period was average 6.5 days in cases intubated and treated with Oesaltamivir and 7.8 days in untreated ones (p<0.05).

Result: Influenza related respiratory failure should be borne in mind in patients that alert with acute respiratory failure and that do not have classic radiological or pathologic findings.

In these patients supplementation of antiviral agents in the treatment particularly in the high risk group in terms of influenza complications may reduce the need of IC, duration of stay in IC and duration of intubation.

P411
The use of pulmonary embolism severity index (PESI) score in identifying patients suitable for ambulatory treatment or early hospital discharge following diagnosis of pulmonary embolism
Veronica Smith, Rossena Salinas-Abadalaz, Muriel Shannon, Brendan Madden. Cardiothoracic Medicine, St. George’s Hospital, London, United Kingdom

Introduction: International treatment guidelines for pulmonary embolism (PE) recommend that patients with low-risk of mortality should be considered for early discharge or ambulatory care. The Pulmonary Embolism Severity Index (PESI) has been validated to assess probability of 30 and 90 day mortality post PE. The aim of this study was to determine whether avoiding hospital admission, or facilitating early discharge, in low-risk patients could be achieved safely using the PESI score.

Methods: Since May 2010, St George’s Hospital has implemented a PE Assessment pathway. The PESI score was used to identify low-risk patients in order to determine suitability for early discharge or ambulatory care. A dedicated PE specialist nurse collected patient data and selected appropriate patients. Low-risk patients with PESI score I-II were given education, and taught self-administration of low molecular weight heparin.

Results: Over a twenty-one month period, 119 of 346 patients with confirmed PE on computed tomography pulmonary angiogram (CTPA) were discharged within 24-48 hours of diagnosis. A further 25 patients were able to avoid hospital admission, on the basis of early discharge, in low-risk patients could be achieved safely using the PESI score.

Conclusions: The PESI score can be utilised effectively by a specialist nurse to treat patients with low-risk PE (PESI score class I-II) in the community.

P412
The rise in carboxyhemoglobin and methemoglobin concentration from repeated five second breath-hold maneuvers
Gerald Zavorsky, Allison Straub, Kaleen Lavir, Kathleen Uhranowsky. Human Physiology Laboratory, Marywood University, Scranton, PA, United States

The measurement of pulmonary diffusing capacity for carbon monoxide (DLCO) raises the carboxyhemoglobin concentration in the blood, [COHb]. The standard 10 s breath-hold technique increases [COHb] by about 0.7% per test, which results in a 1% decrease in DLCO for every 1% rise in [COHb] (Respir Physiol, 1990, 81: 303-12). However, few data exist on the rate of increase in [COHb] or methemoglobin [METHb] from the modified Roughton and Forster one-step technique in which 0.28% CO and 40 to 50 ppm NO is inhaled simultaneously for 5 s. The combination of CO and NO inhaled together allows for determination of pulmonary capillary blood volume in a single breath-hold maneuver. Nine healthy subjects [24 (SD 4) yrs, hemoglobin concentration 13.2 (1.7) g/dL] performed repeated DLCO testing on two separate days. The days were randomized to provide either the standard 10 s breath-hold maneuver (0.30% CO), or the 5 s modified Roughton and Forster technique (0.28% CO, 55 ppm NO). Twenty-two 5 s breath-hold maneuvers, each separated by 4 min rest raised [COHb] to 11.1 (1.4)% and minimally raised the [METHb] to 0.8 (0.2)%.

After the 22nd test, DLCO was reduced by 3.6 (2.9) mL/min/mHg. This equates to a 0.44 (SEE

SUNDAY, SEPTEMBER 2ND 2012
0.08% increase in [COHb] per s vs breath-hold maneuver and a concomitant 0.35 (SEE 0.31%) decrease in DLCO. Pulmonary diffusing capacity for nitric oxide (DLNO) was not altered after 22 tests. On another day, the 10 s single breath-hold maneuver increased [COHb] by 0.64 (SEE 0.13%) per test, and reduced DLCO by 0.40 (SEE 0.26%) per test. In conclusion, the 5 s modified one-step technique does not appreciably raise [METHb], and DLCO is only significantly reduced after 10 tests.

### P413

Impact of a hand held ultrasound machine (HHUSM) in pulmonologist’s clinical hospital practice: Experience of nine months

**Michèle Gallo, U.O.C. Pneumologia I, A.O.Ospedali Riuniti Villa Sofia Cervello, Palermo, PA, Italy**

**Introduction:** HHUSM utilization is spreading outside radiology department at the point of care to guide some procedures and to assist clinical evaluation.

**Objectives:** The aim of this study was to evaluate the impact of HHUSM utilization in the pulmonologist’s hospital practice.

**Methods:** An ultrasound report was written by the P after each examination. Thoracic ultrasound evaluation (TUSE); a database was created after nine months. This database was analyzed to deduce the impact of HHUSM utilization in pulmonologist’s practice.

**Results:** Data are summarized in Table 1: 146 TUSE were analyzed: 108 were used in the clinical setting of lung opacities in the chest X ray and ultrasound assisted thoracocentesis. According to the pulmonologist’s Knowledge, 38 TUSE were applied in critical care setting.

**Conclusion:** HHUSM utilization is really important in several clinical situation. Limitations of technique were the operator’s knowledge and the standardization of the skillfulness outside radiology department. Waiting for gold standard exam-ination HHUSM utilization could help in clinical procedures and decisions when applied at point of care.

### P414

Premature adult lung study (PALS): Spirometry and lung clearance index are impaired in adult survivors of bronchopulmonary dysplasia

**Steven Caskey1, Aisling Gough2, Stephen Rowan1, Katherine O’Neill3, Judy Bradley4, Michael Tunney5, Chris Patterson6, Stuart Elborn1, Mi-kael Shields1, Henry Halliday5, Lorcán McGarvey1, Centre for Infection and Immunity, Queen’s University Belfast, United Kingdom; 2Nursing and Midwifery Research Unit, Queen’s University Belfast, United Kingdom; 3Health and Rehab Sciences Research Institute, University of Ulster, Belfast, United Kingdom; 4Cystic Fibrosis and Airways Research Group, Queen’s University Belfast, United Kingdom; 5Centre for Public Health, Queen’s University Belfast, United Kingdom; 6Regional Neonatal Unit, Royal Maternity Hospital, Belfast, United Kingdom; 7Health and Rehabilitation Sciences Research Institute, University of Ulster, Belfast, United Kingdom**

**Introduction:** We have previously reported increased respiratory symptoms in adult survivors of bronchopulmonary dysplasia (BPD) compared with very low birth weight (VLBW) (<1500g) and term controls. Here we report preliminary findings from spirometric and Lung Clearance Index (LCI) measurements.

**Objective:** To investigate whether adult survivors of BPD have greater impairment of lung function and LCI than age and gender matched VLBW and term controls.

**Methods:** Spirometry measurements (MicroLab ML3500 Mikhs®) were obtained in 16 BPD (male: mean (SD) age 24.9 (3.9) y, 9 VLBW [Mean (SD) age 25.5 (7.73) y] and 55 term controls [30 male; mean (SD) age 26.0 (4.0) y]); LCI measurements (Innocom™ device) obtained in BPD and VLBW participants were compared to 17 healthy controls (6M, mean (SD) age 30.5 (7.5) y).

**Results:** For all spirometry end points (FEV1, FVC, FEV1/FVC and FEF25-75%), BPD adults had significantly lower values than term controls (p<0.001). Mean FEV1 and FVC/FVC measurements were lower in BPD adults than VLBW (p<0.05). Mean LCI measurements were higher (more impaired) in BPD (mean (SD) 6.99 (0.78)) versus healthy controls [mean (SD) 6.36 (0.362)]. p<0.001. LCI measurements were also higher in BPD than VLBW but this was not statistically significant. Three BPD subjects had entirely normal spirometry but abnormal LCI values (value: > healthy control mean +2SD).

**Conclusion:** Our preliminary findings suggest existing lung function impairment in adult survivors of BPD. LCI may be a useful tool in detecting early small airways disease in adult survivors of preterm birth.

### P415

Diagnostic performance of the interferon gamma release assay in elderly patients and clinical factors to support the diagnosis of active tuberculosis

**Hiroyuki Kamiya1, Soichiro Ikushima, Keisuke Kondo, Kota Satake, Minoru Inomata, Atsuko Moriya, Tsunehiro Ando; Respiratory Medicine, Japanese Red Cross Medical Center, Tokyo, Japan**

**Background and objective:** The understanding of the diagnostic performance of the interferon gamma release assay in elderly patients is crucial in a country like Japan, where the higher rate of a prior history of tuberculosis can affect the test result.

**Methods:** From a total of four hundred twenty five patients screened, who were suspected of having active tuberculosis and received the Quantiferon-TB Gold In-Tube test (QFT-GIT), 65 patients in younger age group with the age less than 70 years, and 52 patients in elderly age group were eligible for the analysis. The diagnostic performance of the test was compared between two age groups, and the possible clinical factors to discriminate active tuberculosis cases from elderly patients with positive results of the test were also evaluated.

**Results:** Although the number of patients diagnosed to have active tuberculosis was similar among both age groups, the number of false positive results was significantly higher in elderly patients (4.6% compared to 23.1%). The specificity, positive predictive value and positive likelihood ratio were significantly lower in elderly patients, at 72.7% compared to 93.8%, 36.8% to 83.8%, and 3.21 to 14.12, respectively although other values were almost similar. Radiological findings, such as small nodules and infiltrates, were noted in more cases with active tuberculosis in elderly patients with positive results of the test than with other diseases.

**Conclusions:** The QFT-GIT test may be less accurate in elderly patients in the diagnosis of active tuberculosis, and radiological findings may be helpful in the clinical evaluation of positive results of the test.

### P416

New skin test with recombinant protein CFP10-ESAT6 in patients (children and adults) with tuberculosis, non-tuberculosis disease and latent TB infection

**I. Shorokhay3, 1, V. Litvinov1, Ya. Kochetkov1, B. Ovsyankina1, K. Kudlay2, P. Selsotovsky1, N. Nikolenko2, D. Ivanova1, 1Clinical Research, Scientific and Clinical Antituberculosis Center of Moscow Government Health Department, Moscow, Russian Federation**

**Aim:** To determine sensitivity & specificity of DIASKINTEST in children & adults with pulmonary, extrapulmonary TB, non-tuberculosis disease, latent TB infection (LTBI) and BCG vaccinated.

**Method:** 2609 patients received Mantoux test with 2 TU PPD-L and DST 0.2 mg/kg 1 ml.

**Results:** 97.3% (178/183) children & adolescents and 84.2% (208/247) adults with pulmonary TB & 89.7% (26/29) with extrapulmonary TB were DST-positive. Among 88 adults with TB/HIV 41 had <200 CD4 + T-lymphocytes (DST-positive were 22.0% & 47 >200 count (DST-positive were 55.3%) 94.6% (105/111) with pulmonary and 98.5% (67/68) with extrapulmonary non-tuberculosis disease were DST-negative. All 19 patients with non-active extrapulmonary TB had negative DST reactions. Among 1636 children & adolescents with LTBI the highest percentage of positive DST reactions - 94.9% (37/39) were observed in patients with converted tuberculin reactions and household spumum positive TB contacts, the lowest LCI = 22.5% <16(718) & with close social spumum negative TB contact. In adolescent students with close social spumum positive contact 77.9% were Mantoux - positive & only 5.6% (8/143) were DST-positive - among them 5 TB cases & 3 individuals with LTBI were detected.

DST was not positive in all 228 BCG-vaccinated. Among all children & adolescents 93.8% were Mantoux-positive.

**Conclusion:** DST demonstrated high sensitivity for both active TB and LTBI & high specificity in BCG vaccinated & non-tuberculosis disease.
Faheem Khan, Orla Cotter, Jim Clair, David Curran, T O'Connor. Respiratory Department, Mercy University Hospital, Cork, Ireland

We sought to determine whether the intensity of response in patients with a positive QuantiFeron-TB Gold assay (QTF) was predictive of active over latent tuberculosis, and whether other factors determined the intensity of response. We analyzed positive QuantiFeron assays (Cellexis, Carnegie, Australia) performed between July 2009 and April 2011 in the Mercy University Hospital, Cork. The group consisted of 94 patients with latent tuberculosis and 35 patients with active tuberculosis. There was no difference in the intensity of response between patients with latent and active tuberculosis (p=0.1589). In patients with latent tuberculosis, there were no correlations between age (p=0.353), sex (p=0.476), smoking status (p=0.323), contact history (p=0.612), Mantoux response (p=0.055), Irish nationality (p=0.768), previous BCG vaccination (p=0.504), WCC (p=0.187), peripheral lymphocyte count (p=0.786), neutrophil count (p=0.157) and the intensity of QTF response. Similarly in active TB group there is no correlation found between mentioned variables and QTF response.

The intensity of QTF response does not help to differentiate active from latent tuberculosis. In adults with tuberculosis, the intensity of QTF response is not influenced by age, sex, smoking, remoteness of contact history, Mantoux response, nationality, CXR abnormalities, BCG vaccination and peripheral lymphocyte count.

The persistency of positive or negative IGRA results does depend on the concentration observed in the first IGRA. This further underlines the need for a grey zone (e.g. 0.2 – 0.7 IU/mL) for IGRA interpretation in the serial testing of HCWs.
P422 Diagnostic value of gamma interferon assay in tuberculosis pericardial effusion: Study on a cohort of Iranian patients

Soorekh Sefid1, Setarab Davoudi2, Reihaneh Mohsenipour2, Farzad Masoudkabir1, Abbas Salehi Omran1.

Endocrinology and Metabolic Research Institute, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran; 2Department of Infectious Diseases, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

Background: The efficacy of interferon-gamma (INF-gamma) and adenosine deaminase (ADA) for diagnosing tuberculosis pericarditis in a cohort of Iranian patients presenting with pericarditis were evaluated.

Methods: Thirty eight patients with presentation of pericarditis underwent diagnostic and therapeutic pericardiostomy with drainage and biopsy. Adenosine deaminase and Interferon-gamma levels were determined in pericardial fluid samples of all patients. Pericardial tissue samples were submitted for histopathologic and microbiologic studies. Polymerase chain reaction (PCR) was performed on all pericardial fluid samples to detect Mycobacterium tuberculosis.

Results: Among 38 patients with pericarditis, 7 cases were diagnosed as tuberculosis pericarditis (18.4%). Mean concentration of Interferon-gamma in tuberculosis group was significantly higher compared to non-tuberculosis group (692.57 ± 434.27 vs. 329.03 ± 437.7, P < 0.001). ROC showed a value of 14400 pg/ml as cutoff point for INF-γ with a sensitivity of 100% and specificity of 100% for diagnosing tuberculosis pericardial effusion. Adenosine deaminase was not found to be significantly higher in tuberculosis group in comparison with non-tuberculosis causes of pericardial effusion (35.7 ± 23.8 vs. 36.03 ± 72.27, P = 0.28).

Conclusions: According to the results of this study Interferon-gamma showed to be a valuable diagnostic test for detection of tuberculosis pericarditis, while adenosine deaminase measurement did not prove to have the characteristics of an accurate diagnostic test for tuberculosis pericarditis.

P423 Concordance between tuberculin skin testing and interferon-gamma release assays in diagnosis of latent tuberculosis infection among HIV-infected individuals

Adriana Soraci1, Gheorghe Nini2, Voicu Tudorache3, Teodora Moisil3, Erdin Borgaz4, Ana Fernandez-Quiroga5, Henar Villar5, Manuel Martinez-Muñiz1, Jose-Manuel Fernandez-Carreira5, Kaoutar El Boutaibi Faiz1, Fernando Alvarez-Navascues1, Ana Fernandez-Quiroga5, 1Area Gestión, Hospital San Agustín, Aviles, Asturias, Spain; 2Unidad Referencia Micobacterias, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain; 3Department of Infectious Diseases, Clinical Hospital "Dr. V Babes", Timisoara, Romania; 4Department of Pulmonology, West University "Dr. V Babes", Arad, Romania; 5Department of Infectious Diseases, Clinical Hospital "Dr. V Babes", Timisoara, Romania; 6Department of Pneumology, Clinical Hospital Pneumophysiologico, Constanta, Romania

Introduction: Detection and treatment of latent TB infection (LTBI) in HIV infected individuals is strongly recommended to decrease morbidity and mortality in countries with high levels of HIV. Interferon gamma release assays (IGRA) are now available alternatives to tuberculin skin test (TST) to detect LTBI.

Aims: This study compared QuantiFERON-TB Gold In-Tube (QFT-IT) with the TST for the detection of latent tuberculosis infection among HIV-infected individuals in an area with a high prevalence of tuberculosis (120/100000), where BCG vaccination is mandatory.

Methods: A prospective study of HIV-infected individuals with received the TST and an IGRA, the QFT-IT.

Results: Of 147 participants, 106 (72.1%) returned for an evaluable TST. Concordance between QFT and TST was 88.8% (kappa = 0.37, P < 0.001). However, in subjects with positive test results by either TST or QFT, only 27% (4/15) had positive test results by both modalities. TST-positive/QFT-negative discordant results were found in 5.1% of subjects and TST-negative/QFT-positive discordance in 6.1%. Indeterminate QFT results occurred in 5.4% (8/147), all due to a failure to respond to the phytohemagglutinin-positive control. Subjects with a CD4+ count of less than 100 cells/mm3 had a relative risk of an indeterminate result of 4.24 (P = 0.003) compared with those with a CD4+ count of 100 or more.

Conclusions: Overall concordance between QFT and TST in HIV infection was high and similar to that seen in an immunocompetent population, but QFT testing may be limited by an elevated rate of indeterminate results in subjects with CD4+ cell counts of less than 100 cells/mm3.

P424 Cut-off point for tuberculin skin test (TST) and QuantiFERON (QFT) in the diagnosis of tuberculosis infection (TI) in a study of contacts of tuberculosis (TB)

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Aim: To determine the cut-off for TST assuming a diagnosis of TI when QFT was ≥ 0.35 IU/mL. Moreover, we calculated the cut-off for QFT assuming the diagnosis of TI when TST was ≥ 5 mm.

Methods: We studied prospectively 414 close contacts from 82 TB patients. We performed "QuantiFERON TB GOLD in Tube" (according to the manufacturer’s instructions, Cellestis, Australia) and the same day after venous blood puncture for QFT, TST (Mantoux technique with 2 UI of PPD RT23 with lecture 72 hours later). We studied sensitivity, specificity and analysis "Receiver Operator Characteristics" (ROC). The positive and negative predictive values (PPV, NPV) were calculated based in our proportion of TI of 52.9%.

Results: Assuming as "gold standard" of TI a value of QFT 0.35, the best cut-off of TST was 5mm.

P425 Evaluation of cut-off values of QuantiFERON-TB Gold, interferon gamma inducible protein-10 and tuberculin skin test in active tuberculosis diagnosis

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Aim: The diagnostic accuracy of interferon-gamma-based assays for Mycobacterium tuberculosis infection may be improved by using lower cut-off values for the tuberculin skin testing (TST), QuantiFERON-TB Gold (QFT) and Interferon gamma inducible protein (IP)-10.

Methods: A total of 70 adult TB patients and 81 healthy controls were included for this study. Three assays, TST, QFT and IP-10, were evaluated for their diagnostic performance with respect to different cut-off values. Test cut-offs were established based on receiver operating characteristic curve analysis.

Results: The sensitivities of the assays were: TST 40%, QFT 87% and IP-10 85%, while their specificities were TST 58%, QFT 71% and IP-10 74%. Both QFT

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and IP-10 were significantly more specific than TST (both P < 0.001), but were similar to each other (P > 0.5). Receiver operating characteristic analysis revealed that a cut-off value of 0.29 IU/ml for QFT and 1857 IU/ml for IP-10 maximizes specificity with significant loss of test sensitivity. Using lower cut-off values for TST, however, also increased the sensitivity of the assay but resulted in a significant decrease in specificity.

Conclusions: Lower cut-off values for TST, QFT and IP-10 increased the sensitivity of each assay, but a lower cut-off value for QFT and IP-10 could specificity be maintained.

P426
Sensitivity of the QuantiFERON-TB Gold test in culture-verified NTM disease and TB in a Danish setting
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Introduction: Previous studies have suggested that the QuantiFERON®-TB Gold (QFT) test can be used to discriminate between tuberculosis (TB) and non-tuberculous mycobacterial (NTM) disease. The QFT-test has a higher specificity and sensitivity for infection with mycobacterium tuberculosis (MTB) compared to the tuberculin skin test, but only few studies have included a large number of patients on a nation-wide basis.

Methods: We have studied 12000 QFT-tests obtained between 2009-2011 from a Danish national database. Results of mycobacterial cultures were available for 300 patients. Performance of the QFT-test in the group of patients with active TB and NTM disease was evaluated.

Results: 202 patients had positive culture for M. tuberculosis complex (MTC) and a QFT done. We found 165 positive, 29 negative and 8 indeterminate results, resulting in a specificity of 81.7%. In total 98 patients had culture verified NTM infection (species known to share the ESAT6 and CFP10 antigens were excluded). n=60. We found 15 positive, 68 negative and 9 indeterminate results. The causative microorganisms of NTM pulmonary disease were: M. avium (52%), M. gordonae (17%), M. catarrhalis (7%), M. Mucogenic (6%), M. xenopi (4%), M. intracellulare (4%), M. kansasii (4%).

Conclusion: The sensitivity of the QFT-test in Denmark, a low-burden TB setting, corresponds well with earlier findings. In a large population of patients with NTM we found a specificity of 74% for infection and a relatively high indeterminate rate. The impact of prior BCG vaccination, MTB exposure and immunodeficiency on specificity and indeterminate rate in the NTM group will be further explored.

P427
Treatment in inflammatory bowel disease affects IGRA performance
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Introduction: The detection of LTBI in patients with inflammatory bowel disease (IBD) before treatment with anti-tumor necrosis factor α must be made with chest radiograph and TST. In immunocompromised patients the limitations of this strategy are well known, therefore it is advisable to use new diagnostic methods based on the release of interferon-γ (IGRA).

Material and methods: 204 IBD patients underwent screening for detection of LTBI where T-SPOT.TB (T.SPOT) and Quantiferon-TB Gold In Tube (QFT) determinations were performed simultaneously, also lymphogram, TST and chest X-ray were performed. TST was defined when the TST and/or any IGRA was positive.

Results: 156 patients had Crohn disease, 42 ulcerative colitis and 6 non-specific colitis. 34 were treated with 5-aminosalicylic acid, 63 with immunomodulators, 32 anti-TNF-α, 27 corticosteroids and 47 a combination of them. 14 were positive TST, 24 for the T-SPOT and 3 for the TST. The lymphogram showed an association between TSPOT + and QFT + and the amount of circulating CD8 (≥ 500 cells) while QFT-SPOT + results have the amount of CD8 reduced (<500). Moreover, their treatment modified all lymphocyte populations particularly the ICS and Treg cells.

Conclusion: The immunomodulatory treatment of patients with IBD altered lymphocyte profile which, in turn, is related to the result of testing LTBI. A correct interpretation of the results for the study of LTBI needs to know the treatment received and requires an assessment of lymphocyte populations that verifies its normality. If the lymphocytes are low, particularly CD8, the effectiveness of IGRA (specially the QFT), is very small and require every test possible to rule out LTBI.

P428
Application of intracellular cytokine flow cytometry in the diagnosis of active tuberculosis
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Background: Intracellular cytokine flow cytometry (ICCFC) has been introduced to detect the T cell response to M. tuberculosis antigen (MTB Ag). However, it could not overcome the limits shown by whole blood interferon-gamma (IFN-γ) release assays (IGRA). Given the important role of CD4+T cells as well as IFN-γ and TNF-α in pathogenesis of TB, we compared the diagnostic accuracy between ICCFC measuring frequencies of MTB-specific Ag stimulated IFN-γ+CD4+ and CD4+ cells and IGRA to confirm the usefulness of application of ICCFC for TB diagnosis in clinical practice.

Methods: Both Quantiferon® TB Gold In-tube (QFT-IT) test and ICCFC analysis were performed in 80 patients who were suspected of having pulmonary TB or TB pleurisy and 10 controls with no known exposure to TB. Results: (1) Sixty one and 19 out of total 80 patients were diagnosed with active TB and non-TB, respectively. (2) Double IFN-γ+TNF-α+CD4+T cell among all T cell subsets analyzed by ICCFC showed the highest sensitivity (90%) for diagnosis of TB. (3) Sensitivity of QFT-IT test and ICCFC assay were 77% and 90%, respectively (p = 0.021). (4) Specificity of QFT-IT and ICCFC assay were 73.7% and 89.5%, respectively. (5) There was a good correlation between the quantity of IFN-γ, as detected by the QFT-IT test, and the frequencies of IFN-γ+TNF-α+CD4+T cell measured by the ICCFC assay in TB patients (p=0.012). (6) The frequencies of IFN-γ+TNF-α+CD4+T cells were significantly decreased after 6 months of treatment compared with pretreatment (p=0.026).

Conclusions: The ICCFC assay with T cell stimulation by MTB-specific Ag may be a useful additional tool for the diagnosis of active TB, although further study is needed for more convincing data.

P429
Immune responses in the lungs of patients with tuberculous pleural effusion without parenchymal tuberculosis
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Background: Tuberculous pleural effusion (TPE) is one of the most common forms of extrapulmonary tuberculosis. Because most studies of TPE focussed on the pleural space, little information regarding lung parenchyma is available. We therefore aimed to investigate immune responses in the lung parenchyma of TPE patients without active parenchymal tuberculosis.

Methods: Patients with any evidence of active parenchymal tuberculosis, either from radiologic or bacteriologic evaluation, were excluded. Bronchoalveolar lavage fluid (BALF) was collected from 10 newly diagnosed, untreated, HIV-negative TPE patients and 10 healthy controls. We analyzed T-lymphocyte subpopulations and measured 10 cytokines in BALF. Cytokine levels in BALF were standardised using urea.

Results: The concentrations of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and the CD4+/CD8+ ratio of lymphocytes were significantly higher in TPE patients without active parenchymal tuberculosis than in the controls. Of the cytokines measured in BALF, VEGF showed the highest concentration. No difference was observed in T-helper type 2 cytokines between the 2 groups.

Conclusion: There were significant immune responses and increases in IFN-γ, TNF-α, and VEGF in the lung parenchyma of TPE patients without active parenchymal tuberculosis. This result suggests that TPE may induce a significant immune response in lung parenchyma.
a moderate agreement: 90% (45/50); (k=0.611). Active TB was detected in 4% (2/50) subjects.

**Conclusion:** Despite the intense exposition of immunocompetent household TB contacts to a highly symptomatic index case, transmission of M. tuberculosis rarely occurred. The data indicate that a previous BCG vaccination and/or TST testing could be a reason for the false positive TST results. Two tests can be used in the diagnostic algorithm of TB infection in household contacts. In order to apply the TST a higher cut off values (≥15 mm) should be used for positivity. The QFT assay could replace the TST in BCG vaccinated population.

**P341**

**Experience of using Diaskintest by tuberculosis patients**
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This is a study of Diaskintest (DST) - a new diagnostic test for tuberculosis (TB). It is an additional method of TB diagnosis and of evaluation of activity of the TB process. The objective of the study was to evaluate the sensitivity and specificity of the test on a sample of TB patients treated at the TB hospital in Saratov (Russia) in 2010 - 2012. A total of 95 subjects participated: newly diagnosed - 69.5%, with relapses - 11.6%, chronic forms - 18.9%. HIV co-infection in 22.1%

In most TB patients (71.6%) DST was found to be positive. Test average value was 9,8±8,85, including M 9,0±8,21 in newly diagnosed subjects, 11,5±11,71 in subjects with relapses, and 11,6±9,41 in chronic patients. In subjects with limited processes, DST was 7,4±4,91, and in subjects with wide-spread and destructive processes - 10,6±9,77 (p ≥ 0.05). Only 42.9% subjects with HIV infection, were DST-positive. Out of the 95 participants, 27 subjects with clinically confirmed TB, 28.4% were DST-negative. Of these, 12 had HIV infection which could have caused suppression of DST sensitivity. Of the remaining 15 subjects with TB, 10 were confirmed by bacterioexcretion, one – by histological examination of surgical specimens, and only 4 subjects did not have such confirmation. In other words, in 11 cases (11.6%) the presence of tuberculosis was not revealed by DST.

**Conclusion:** DST was positive in 71.6% of TB cases, but only 42.9% among HIV-positive subjects, and in 79.7% in subjects without HIV infection. In 11.6% of the cases, DST did not reveal the presence of TB.

**77. CPAP: beneficial effects on different aspects of health**

**P342**

**ncCPAP’s functional effects on ciliary function of nasal respiratory epithelium**
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Continuous positive airway pressure (CPAP) is the gold standard in therapy of obstructive sleep apnea (OSA) but is associated with numerous side effects often related to the nose and the upper airway. Humidified CPAP may, in part relieve these symptoms. Nevertheless, little is known regarding the effects on ciliary function (CF).

In this prospective, randomized, crossover trial patients with OSA (AHI ≥20) were included and randomized to one of two treatment arms, nCPAP with or nCPAP without humidification, for a period of eight weeks. At the end of the eight-week period patients were swapped to the alternative treatment arm for a further eight week period. CF (beat frequency [CBF] and mucus transport time [MTT]) were assessed before and one day after the beginning of nocturnal ventilation and again at the end of each treatment arm.

The baseline CBF was 4.7 ± 0.07 Hz. The MTT 568 ± 185s. Short-term changes without humidification (CBF +0.7 ± 0.08 Hz; MTT -152 ± 158s) and with humidification (CBF +0.7 ± 0.08 Hz; CBF +0.20 ± 0.08 Hz; MTT +192 ± 208s) were not statistically significant. The long-term effects, CPAP without humidification significantly increased the CBF above the baseline level by v.5.±0.4 Hz and -107±175s (p<0.01) and even more so with humidification (+4±0.71Hz, -286±49s; p<0.01).

Independent of airway humidification, nCPAP has limited effects on short-term ciliary function of the nasal respiratory epithelium that is not statistically significant. However, long-term effects showed a significant increase in ciliary function both in terms of an increased beat frequency and an increase in mucus transport time that has not been described previously. The effect was more pronounced when humidification was used during nCPAP.

**P343**

**CPAP therapy in OSA patients: The effects on healthcare use and medical costs related to cardio- and cerebrovascular diseases**
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**Background:** Obstructive sleep apnea (OSA) is a major risk factor for cardio- and cerebrovascular diseases, however, CPAP treatment could reduce the occurrence and healthcare costs of these complications.

**Aim:** To assess the impact of CPAP therapy on healthcare use and medical costs related to cardio- and cerebrovascular diseases.

**Methods:** By analysing the patient database of the Hungarian Health Insurance Fund Administration in a one-year period starting from July 2007, OSA patients with newly initiated CPAP therapy were identified. Hospital admission rates, hospital treatment days, and the use and costs of relevant medications of these patients were evaluated from 3 years before to 3 years after CPAP therapy.

**Results:** In the study period, 993 OSA patients started CPAP therapy in Hungary. In comparison to the 3-year period on CPAP therapy (post-CAP), the numbers of pre-CAP cardio- and cerebrovascular disease related hospital admissions and treatment days were higher by 22.4% (205 vs. 159 admissions) and 25% (2254 vs. 1968 days), respectively. Mean hospital treatment costs were 34% lower in the post-CAP than in the pre-CAP period (238 vs. 156 €). The reduction in post-CAP hospital admissions, treatment days and costs was more prominent in a subgroup analysis in patients fully complying with the follow-up care (112 patients). Interestingly, the use and costs of relevant medications were nearly identical in the pre- and post-CAP therapy periods.

**Conclusion:** Our study suggests that CPAP therapy could reduce healthcare costs of OSA patients by lowering hospital admission rates, treatment days and costs related to cardio- and cerebrovascular diseases.

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**Long-term CPAP compliance in women with obstructive sleep apnoea**
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**Objectives:** We sought to analyze long-term CPAP compliance and predictors of CPAP dropout, in a large female cohort with a prolonged follow-up.

**Methods:** Consecutive women diagnosed with OSA (apnoea-hypopnoea index [AHI] ≥10) and started on CPAP treatment in two Spanish Sleep Units between 1999-2007 were included in the study. Women were followed-up until December 2009. The Kaplan-Meier method was used to calculate the probability to continue on CPAP treatment, and a multivariate Cox regression analysis was used to identify baseline predictors of CPAP dropout.

**Results:** We analyzed 708 women with median (IQR) age 60 years (52-67), AHI 43 (27-66.8), and Epworth Scale 13 (9-16). Women were followed for a median period of 6.2 years (4.2-7.7) and average compliance with CPAP was 6 hours/day (4-7). During follow-up, there were 129 CPAP dropouts (18.2%), and the probability of being still on CPAP at 5 and 10 years was 82.8% and 79.9%, respectively. Baseline predictors of CPAP dropout in the multivariate analysis were age (OR 1.01, 95%CI 1.00-1.03), use of sedative/antidepressant medication (OR 1.47, 95%CI 1.03-2.08) and CPAP pressure (OR 0.89, 95%CI 0.82-0.97).

**Conclusions:** Long-term CPAP adherence in women with OSA is good. Increasing age and use of sedatives/antidepressants were independent predictors of CPAP dropout, whereas higher CPAP pressures were associated with continued treatment.

**P345**

**Titration of continuous positive airway pressure in Chinese patients with obstructive sleep apnea**
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**Objective:** Whether CPAP pressure derived from manual titration is the same as pressure titration by automized CPAP devices is unknown. The purpose of this study was to compare the pressure derived from manual titration with pressure from automatic titration. We also attempted to establish a formula to determine the appropriate CPAP pressure for Chinese individuals.

**Methods:** Fifty-one patients with OSA (mean apnoea-hypopnoea index [AHI] = 50.6±18.6 events/hour) who were newly diagnosed after an overnight full polysomnography and who were willing to accept CPAP as a long-term treatment were recruited for the study. Manual titration was performed by the method of nocturnal ventilation for 8 weeks with full polysomnography monitoring and untreated automatic titration with an automatic CPAP device
Conclusion: nGER is a common clinical symptom of OSA and often related to the Icelandic Sleep Apnea Cohort (ISAC) Prevalence of restless legs syndrome among patients with obstructive sleep No.81120108001). REMstar-auto, is usually higher than the pressure derived from manual titration. Our results suggest that automatic titration pressure derived from methods:
The OSA subjects (n=822) were newly diagnosed with moderate or severe OSA (665 males,157 females). The control subjects (n=742) were randomly chosen Icelanders (394 males, 348 females) who participated in another epidemiological study (www.boldcopd.org). Measurements included a standardized RLS rating scale, questions about sleep and the Ewthorp Sleepiness scale. The change with CPAP treatment was assessed after 2 years (n=558).

Results: Among OSA males 23.3% reported RLS but 12.9% of control males (p<0.001). 35.8% of OSA females reported RLS but 24.4% of control females (p=0.03). Both among OSA patients and controls those with RLS more commonly reported insomnia, daytime sleepiness, nocturnal sweating, snoring and gastro esophageal reflux (<p>0.05). No relationship was found between RLS and age, BMI, hypertension or respiratory disease. Subjects using CPAP had a decreased prevalence of RLS from 25.7% to 13.8% while no change was observed in those without RLS (p=0.04 for difference between groups).

Conclusion: RLS is more prevalent among OSA patients than controls. CPAP treatment decreases RLS symptoms significantly.

P437
Nocturnal gastro-esophageal reflux and respiratory symptoms in patients with obstructive sleep apnoea, before and after CPAP treatment, compared to the general population: The Icelandic Sleep Apnea Cohort (ISAC) study. Thórarinn Gislason1,2, Oscar Inggi Emísson1,2, Eina Sif Arnardottir1,2, Christur Jansson1, Bryndis Benediksdottir1,2, Sigurður Júlíusson1, Allan Pack1,4, Respiratory Medicine and Sleep, Landspílsstaður University Hospital, Reykjavík, Iceland; 2Faculty of Medicine, University of Iceland, Reykjavik, Iceland; 3Department of Medical Sciences, Respiratory Medicine & Allergology, Uppsala, Sweden; 4Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, United States

Introduction: To estimate the prevalence of reported restless gastro-esophageal reflux (nGER) and respiratory symptoms in obstructive sleep apnoea (OSA) subjects compared to the general population. Also change in nGER with CPAP treatment. Methods: 826 OSA patients referred for CPAP treatment. 623 subjects have had a 2 year follow-up visit (n=412 CPAP users, n=211 nonusers). The control group consisted of 939 subjects randomly selected from the general population (81% response rate). Both groups answered the same questionnaires on nGER, sleep, respiratory symptoms, general health and quality of life measured by SF-12.

Results: Altogether 18.6% of OSA females and 13.6% of males (p=0.07) compared to 7.5% of controls (p<0.01) reported nGER (> 1x a week). Where a more common among OSA subjects with nGER compared to those without nGER (42.5% vs. 29.3%, p<0.05). Bringing up phlegm in the morning was also associated with reporting nGER (35.7% vs. 24.8%, p=0.02). Among OSA patients nGER was not related to smoking, obesity, hypertension, diabetes or OSA severity. SF-12 showed that among those with nGER both physical component scores (40.7±10.9 vs. 37.4±10.3, p=0.003) and mental scores (49.9±10.8 vs. 44.1±11.1, p<0.001) were significantly lower. At two year follow-up nGER was only reported by 6.2% of those followed and was lowest (3.8%) among full CPAP users (p<0.001).

Conclusion: nGER is a common clinical symptom of OSA and often related to respiratory symptoms. Prevalence of nGER decreases with CPAP treatment in a majority of OSA patients.

P438
Control of breathing in obstructive sleep apnoea patients: Role of CPAP therapy Antónia Re, Flaminio Mornole, Alessandro Di Marco Berardin, Dina Visca, Bruno Iovene, Salvatore Valente. Pneumologia, Università Cattolica del Sacro Cuore, Roma, Italy

Aim: Control of breathing during wakefulness in obstructive sleep apnea (OSA) and the role of CPAP therapy is an ongoing controversy. We studied the ventilatory response of healthy controls and OSA patients before and after at least 1 year of CPAP therapy. Methods: 17 never treated OSA patients (16 M, 53.1±12.3yrs; BMI=34.5±8.1; AHl=45±14.7) underwent nocturnal cardipulmonary monitoring, spirometry and blood gas analysis. Read’s rebreathing test was used to evaluate hypercapnic ventilatory response (HVR CO2); hypoxic ventilator response (HVR O2) was studied by both progressive and transient methods, to explore both peripheral oxygen chemoreceptors and the central modulation. The relationship between minute ventilation (VE) or mean inspiratory flow (VTi) or PET CO2 or PET O2 was expressed in terms of slope of linear regression for HVR CO2 and of parameter A of hyperbolic function for HVR O2. Results: OSA patients showed an increased responsiveness to transient, but not to progressive, hypoxemia, and a reduced response to hypercapnia when compared to controls. Transient HVR CO2 showed a significant reduction during CPAP therapy (p<0.01), whereas HVR CO2 increased only slightly. Progressive HVR O2 was not modified by CPAP [Tab 1].

Conclusions: The daytime glycomic reactivity to transient hypoxia is increased by repeated nocturnal hypoxic stimulus; CPAP significantly restores the ventilatory stability during sleep.

Table 1. Chemosensitivity in Controls and in OSA pre and post CPAP

P439
Differences between commercial vehicle drivers and other patients in symptoms of obstructive sleep apnoea and response to CPAP therapy Werner Stekel, Daisana Steks, Michael Tamm. Pneumologie, University Hospital, Basel, Switzerland

Introduction: Among patients with obstructive sleep apnoea (OSA), commercial vehicle drivers (CVD) should be treated with special care, since untreated OSA is a well established risk factor for traffic accidents. However, little is known whether symptoms and course of treatment of OSA in CVDs are similar to those of other OSA patients.

Method: We analysed the course of diagnosis and treatment in CVDs diagnosed with OSA in 2009 and 2010 and compared these data with a control group of non-CVD patients.

Results: We identified 37 CVDs treated with CPAP and compared their results with a control group of 74 patients. Both groups were well matched with respect to age, BMI, apnoea-hypopnoea index and oxygen desaturation index. However, the Ewthorp Sleepiness Score (ESS) was significantly lower in the CVD group (8.1±2.8 vs. 11.0±2.7, p<0.001) and this difference was unchanged after 6 months of CPAP therapy (4.8±2.1 vs. 7.7±2.2, p<0.001). The adherence to CPAP therapy was lower in CVDs than in the control group: daily usage was 4.5±1.1 vs. 5.0±1.4 hrs (p=0.02), % of days used was 75±14 vs. 83±19% (p=0.012). CVDs had significantly more unscheduled visits in the first 6 months of treatment than control patients: 1.5±0.6 vs. 0.7±0.4 (p<0.001).

Conclusions: Despite similar baseline characteristics, CVDs report significantly lower values in the Ewthorp sleepiness score at diagnosis and under CPAP treatment. CPAP compliance is lower in CVDs than in control patients and CVDs have more unscheduled clinical visits than other CPAP patients. These points should be taken in consideration when starting OSA treatment in CVDs.
Patients with apnoea-hypopnoea index (AHI)<5/hour served as controls. Serial measurements of exhaled NO after PSG were performed in 21 OSA patients and 8 control subjects.

**Results:** CANO was significantly higher in OSA patients (n=71; 4.07±1.7ppb) as compared with controls (n=24; 2.24±1.06ppb; p<0.0001) whilst maximal bronchial NO flux and fractional concentration of exhaled NO did not significantly differ between the two groups. In patients with OSA, CANO was strongly associated to AHI (r=0.70; p<0.0001) and to recoding time with SatO2<90% (ST-90%; r=0.659; p<0.0001). The area under ROC curve for screening patients with OSA and significant nocturnal oxygen desaturation (ST-90%>15%) was 0.855 (0.777-0.933) (p<0.0001). CANO at 4.49ppb could detect these patients with sensitivity of 46% and specificity of 94%. Increased CANO variation after PSG was significantly related to oxygen desaturation index (TS-90%).

**Conclusions:** Increased alveolar NO concentration was related to the severity of nocturnal oxygen desaturation in patients with OSA, linking the distal lung inflammation to intermittent hypoxia. CANO could be used to screen for severe OSA in suspected and symptomatic patients.

**P441**

Predictors of long-term PAP-adherence in obstructive sleep apnea syndrome

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**Introduction:** Few studies have assessed long-term adherence to positive airway pressure therapy (PAP) in OAS. The aim of this retrospective study was to determine adherence and its potential predictors.

**Methods:** All patients (pts) treated at the St.Gallen sleep centre from 11/2001 to 4/2011 were included for analysis of baseline data and follow-up information. The primary dependent variable of interest was continued use of PAP. Kaplan-Meier estimates and Cox-proportional hazards regression were used to model the risk of loss of adherence. A multivariate regression analysis was performed for age, gender, Epworth sleepiness score (ESS), BMI, apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) at baseline.

**Results:** During the study period, of 2160 pts started on PAP, 42 (2%) died on PAP; 91 (4%) no longer needed PAP (weight reduction, alternative treatments) and 311 (14%) were lost to follow-up. In 1716 pts, adherence at 1y was 74.8% CI: 71-76%), at 5y 56 (53-59)%, and at 8y 52 (49-56)%. Results of univariate and multivariate analyses are summarized in the figure.

**Conclusion:** Adherence is independently associated with clinical (ESS) and polysomnographic (ODI, AHI) measures of OAS severity, but not with BMI, age, gender. Most pts who stopped PAP were lost to follow-up. With a relatively low long-term, intensified efforts and alternative or novel follow-up options (e.g. telemetry) to support such patients should be tested.

**P442**

Utility of a nurse-led visit program for patients with obstructive sleep apnea syndrome treated with CPAP

**Amara Ateca, Izar Arizmendi, Sonia Herrero Martin, Jose Antonio Casacante Rodrigo, Pilar Cebollero Rivas, Victor Manuel Eguía Astibia, Javier Hueto Pérez de Herdia, Isabel Andrade Vela, Respiratory Department B, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain**

Obstructive Sleep Apnoea Syndrome (OSAS) is a frequent cause of visit in our clinic’s environment. In order to diminish its impact in the physician’s agenda we created a specific nurse-led individual consultation for their follow-up visits.

**Aims:** We want to analyze the characteristics of patients and changes made in terms of treatment or even medical discharge.

**Methods:** We have analyzed IAH, BMI, Epworth sleepiness scale (ESS), CPAP compliance and satisfaction grade in patients attended from June to December 2010.

**Results:** We attended 243 patients, 88% of them were men, the age average was 56.6±11.6 years. At the moment of the diagnosis the IMC was 33.2±5.4 and the ESS 10.3±4.9. At nurse-led visit IMC was 33.4±5.6 and ESS 9.8±4.2. We found an average of use of 6.0±3.2 hours per hour and 6.4±1.6 days per week. We detected a good level of compliance in 78% of them, quite good in 8.5% and bad in 13.5%. They fulfilled a satisfaction test (scale 0-10) and the mean value obtained was 7.2±2.4. We needed to change the Mask model because of bad tolerance in 20% of patients. Because of good follow up, we could discharge from medical control 37.9% of the cases, they are followed now only in the Nurse unit and almost 60% remained control by both medical and nurse but medical one are their regular follow-up visit. We only give definitive discharge because of low compliance in 1.2%.

**Conclusions:**
- Our patients showed a good level of satisfaction
- We have found a good level of CPAP compliance
- We had to change mask model in a substantial number of cases
- We could discharge from medical follow up an important number of patients, optimizing the use of health care resources.

**P443**

Impact of a respiratory rehabilitation program in the functional capacity of the patients with obstructive sleep apnea-hypopnea syndrome (OSAHS)

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**Objectives:** Determine the basal exercise capacity in patients with severe OS-AHS.Determine the exercise capacity modified after 3 months of treatment with CPAP or with CPAP and Respiratory Rehabilitation program.Analyze the impact of these changes on the quality of life,physical activity and psychological impact.

**Methods:** A prospective study with a consecutive inclusion of healthy patients with the polysomnographic diagnosis of severe OS-AHS.We evaluated the exercise capacity of these patients by means of a cardiopulmonary test in a cyclogrime–submaximal exercise capacity before the beginning of the treatment in both groups.

**Results:**

<table>
<thead>
<tr>
<th>CRAP BASAL ml 30</th>
<th>3M CRAP</th>
<th>CRAP+PAP 30 days</th>
<th>1M CPAP+R</th>
<th>1M CRAP+R</th>
<th>28th BLOOD</th>
<th>3M CRAP+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPRAWH1H1</td>
<td>11.84±4.6</td>
<td>7.64±2</td>
<td>11.64±3.1</td>
<td>7.10±3.4</td>
<td>11.22±2.4</td>
<td>7.10±3.4</td>
</tr>
<tr>
<td>ANEMONY (Hb%)</td>
<td>5.74±4.42</td>
<td>5.94±3.42</td>
<td>5.42±2.16</td>
<td>4.52±3.75</td>
<td>5.74±3.75</td>
<td>5.74±3.75</td>
</tr>
<tr>
<td>DEFICENCY (Hb%)</td>
<td>2.62±4.49</td>
<td>2.56±3.77</td>
<td>1.2±4.17</td>
<td>1.2±4.17</td>
<td>1.2±4.17</td>
<td>1.2±4.17</td>
</tr>
<tr>
<td>ASH (%)</td>
<td>76.7±25</td>
<td>78.5±25</td>
<td>80.7±25</td>
<td>80.7±25</td>
<td>80.7±25</td>
<td>80.7±25</td>
</tr>
<tr>
<td>WAMM (%I)</td>
<td>184.4±1.5</td>
<td>133.2±3.5</td>
<td>133.2±3.5</td>
<td>133.2±3.5</td>
<td>133.2±3.5</td>
<td>133.2±3.5</td>
</tr>
<tr>
<td>WAMM (%)</td>
<td>65.35±4.5</td>
<td>65.35±4.5</td>
<td>57.35±4.5</td>
<td>57.35±4.5</td>
<td>57.35±4.5</td>
<td>57.35±4.5</td>
</tr>
<tr>
<td>V02 max (ml/kg)</td>
<td>10.36±4</td>
<td>5.9±4</td>
<td>17.36±5</td>
<td>17.36±5</td>
<td>17.36±5</td>
<td>17.36±5</td>
</tr>
<tr>
<td>V02 max (l/min)</td>
<td>1.70±3.47</td>
<td>1.9±2</td>
<td>1.70±3.47</td>
<td>1.70±3.47</td>
<td>1.70±3.47</td>
<td>1.70±3.47</td>
</tr>
<tr>
<td>V02 max (%)</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
</tr>
<tr>
<td>SUBMAX (%)</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
<td>70.43±1.2</td>
</tr>
</tbody>
</table>

The average age was 48.5±12.55 years old,90.9% male,40% smokers,30.9% ex-smokers and 29.1% non-smokers (17.6±26.26 packet/year).The average BMI was 32.27±5.56.

**Conclusions:** There is a slight decrease of the basal exercise capacity in both groups.There are no differences between submaximal test and the maximum load (W).After 12weeks of treatment in both groups,we obtained a significant decrease in E胸怀work scale,without differences between groups,There is an increase in submaximal effort results in both groups,although in CPAP group increases 29.71% and CPAP+R 116.84% with no differences.

**P444**

Nasal inflammation and compliance with nasal CPAP therapy in obstructive sleep apnoea (OSA)

**Noura AlAhmari; Raymond Sapsford, Jadwiga Wiedzicha, John Hurst. Academic Unit of Respiratory Medicine, Academic Unit of Respiratory Medicine, UCL Medical School, London, United Kingdom**

**Background:** CPAP is the standard therapy for treating OSA (1). However, CPAP can cause undesirable nasal side effects that compromise compliance (2).

**Aims and objectives:** Over a six month period, we assessed the association between nasal inflammation using nasal wash interleukin (IL-6) concentration and compliance with therapy.

**Methods:** Twenty-two patients were recruited with new confirmed OSA. Daily CPAP use was prospectively recorded on diary cards. Nasal wash IL-6 and diary cards for compliance were performed at no CPAP and at 1, 3 and 6 months
post-CPAP Pearson correlation was conducted to assess the relationships. A P value < 0.05 was considered a statistical significance.

**Results:** The twenty-two patients (mean age±SD: 59.5±7.5 years) had AHI of mean (SD) 30.2±19.9.

**Characteristics of the OSA patients**

<table>
<thead>
<tr>
<th>Details of subjects studied (n=22)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective (MF)</td>
<td>159 (99.4)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>39.5</td>
<td>7.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.6</td>
<td>8.6</td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>50.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Neck circumference</td>
<td>37.2</td>
<td>1.5</td>
</tr>
<tr>
<td>CPAP (cm H2O)</td>
<td>7.84</td>
<td>0.87</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>22.7</td>
<td></td>
</tr>
</tbody>
</table>

*1At recruitment to the study.

We found a significant relationship between increased nasal IL-6 and decrease in compliance at baseline and six month of CPAP therapy, Pearson [r = -0.57; P=0.014].

**Conclusion:** Our results show that nasal inflammation relates to compliance with CPAP therapy in OSA.

**References:**


**P445**

Residual sleepiness in obstructive sleep apnea (OSA) patients on CPAP: Not only a symptom but rather a true syndrome?

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**Background:** Hypoxic brain damage might explain persistent sleepiness in some CPAP compliant OSA. Since residual sleepiness (RES) on CPAP remains not fully understood, wake promoting drugs in RES are no longer allowed by the European Medicines Agency.

**Aim:** To describe RES phenotype in a large prospective sample of OSA patients.

**Methods:** RES was defined by an Epworth Sleepiness Scale (ESS) ≥ 10. Hypoxic insult is probably not the explanation for RES since OSA severity does not seem to be critical. Residual symptoms are not limited to sleepiness and this true “CPAP resistant syndrome” may justify treatment by wake promoting drugs.

**P446**

Home-based evaluation in patients with high risk for moderate to severe OSA

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Obstructive sleep apnea (OSA) is a disorder characterized by recurrent obstruction of the upper airways during sleep. The high prevalence of this disease led to propose new strategies based on the home evaluation and management of patients. The aim of this study was to compare unattended home-based protocol with ambulatory in-laboratory analysis, in a sample of patients with high risk for moderate to severe OSA.

We enrolled 131 patients, who were randomly divided into 2 groups: group 1 (n=60) was diagnosed and titrated at home; group 2 (n=65) was analyzed in the sleep lab of our hospital. Diagnostic evaluations were carried out with portable monitoring at home, and with polysomnography in the sleep lab. Titation was performed with the same autoCPAP device in both groups.

At the end of the study, 13 (19%) subjects had dropped out in the group 1, and 9 (14%) in the group 2 (p= not significant). There were no significant differences among groups in both basal and with CPAP values of apnea-hypopnoea index (AHI), oxygen desaturation index (ODI), and total sleep time with oxyhemoglobin saturation below 90% (TST90). In the home group, therapeutic pressure values reached at the end of each unattended home titration night were similar. Home diagnosis and titration approach should be considered in a subset of patients with OSA. A single unattended titration night is sufficient to determine the therapeutic pressure.

**P447**

The heterogeneity of obstructive sleep apnoea: Congestion leads to longer respiratory cycle lengths in heart failure

Christina Efken, Thomas Bitter, Britta Körker, Kevin Bullert, Dieter Horstkotte, Olaf Oldenburg, Department of Cardiology, Heart and Diabetes Center North-Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

It is controversial if heart failure (HF) can influence obstructive sleep apnoea (OSA) per se. Previous studies documented increased cycle lengths (VL), ventilation lengths (VL), and circulatory delays (CD) of OSA in HF patients. Aim of the present study was to verify these results in a cohort of well-defined HF patients and to investigate possible interactions of HF and OSA.

**Methods:** 39 patients with OSA (apnoea-hypopnoea index, AHI > 10h) with (NYHA ≥ II, LV-EF ≤40%; n=26; male 18, 67.2±9.4 years) and without (EF ≥50%, NT-proBNP <400; n=13, 6 male, 72.7±8.5 years) HF underwent simultaneous right- and left-heart catheterization within 12h of cardiorespiratory polygraphy.

**Results:** AHI as well as obstructive apnoea-index (OA) were comparable in both groups (AHI: 32.3±26.5 vs. 32.3±18.0; p=n.s.; OA=5.7±5.8 vs. 10.0±10.8; p=n.s.). We were able to verify increased CL, VL, time to peak ventilation (TTPV) and circulatory delay (CD) in patients with HF (CL: 32.8±10.6 vs. 46.0±10.0s, p=0.024; VL: 25.1±4.6 vs. 35.4±6.3, p=0.044; TTPV: 9.3±2.5 vs. 10.6±3.0s, p=0.021; CD: 22.6±7.7 vs. 28.5±7.5s, p=0.005). Apnoea length (AL) was higher in HF patients (16.5±3.9 vs. 20.5±4.9s, p=0.013). Positive and robust correlations between parameters of OSA and degree of congestion were found in OSA patients with HF exclusively. CL, VL, and TTPV increased with elevation of PCWP (CL: r=0.53; p=0.006; VL: r=0.55; p=0.004; TTPV: r=0.47; p=0.015).

**Respiratory parameters of OSA (CL, VL, TTPV) correlate with the degree of congestion in patients with OSA and HF, but not in non-HF patients with OSA. These results point to a reciprocal relationship of HF and OSA severity.

**P448**

Coexistence of central sleep apnea or periodic breathing pattern in patients with congestive heart failure and obstructive sleep apnea

Michael Arzt1, Gerhard Weinreich2,3, Olaf Oldenburg1, Andrea Graml1, Helmut Teschler1, Karl Wegscheider2, Erland Erdmann2, Holger Woehrle3,4, for the SchlafHF Investigators. 1Dept. of Internal Medicine II, Pneumology, University Hospital, Regensburg, Germany; 2Dept. of Pneumology, RuhrlandKlinik, University Hospital Essen, Germany; 3Science Center, ResMed, Martinsried, Germany; 4Dept. of Cardiology, Heart and Diabetes Center North-Rhine Westphalia, University Hospital, Ruhr University Bochum, Bad Oeynhausen, Germany; 5Dept. of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 6Clinic III for Internal Medicine, Heart Center, University Hospital, Cologne, Germany; 7Sleep and Ventilation Center Blaubeuren, Respiratory Center Ulm, Ulm, Germany

**Background:** The presence of altered ventilator control instability in congestive heart failure (CHF) patients with obstructive sleep apnea (OSA) may have signif-
ificant therapeutic implications. Indicators for ventilator control instability can be significant proportions of central sleep apnea (CSA) and/or a periodic breathing (PB) pattern. The aim of the present study was to determine the prevalence of such indicators in CP patients with OSA.

Patients and methods: The ongoing German multi-center SchlaFHF registry prospectively included 7007 stable CHF patients (NYHA class ≥II and LVEF ≤45%) from cardiology practices and cardiology departments of hospitals. Patients were studied with a two-channel screening device (nasal airflow, pulse oximetry, ApnoeaLink, ResMed, Sydney, Australia) that detects PB patterns based on an algorithm. The pattern recognition was performed with suspected SBH detected polysomnography (PSG) with certified scoring.

Results: Of the 2183 PSG-patients 1583 (73%) had an AHI ≥15/h, of whom 49% had OSA (±50 apneas and hypopneas were obstructive). In such CP patients with OSA the prevalence of a significant proportion of central apneas and hypopneas (20-49%) was 35%. The prevalence of objectively assessed PB was 44% in OSA patients. 358 (59%) heart failure patients with OSA presented with either a significant proportion of CSA and/or a PB pattern.

Conclusions: The high prevalence of a significant proportion of CSA and objectively assessed PB pattern in CHF patients with OSA suggests ventilator control instability that may have an impact on the appropriate modality of positive airway pressure therapy to suppress apneas and hypopneas.

P449 Pulmonary diffusion capacity is not associated with severity of Cheyne-Stokes respiration in heart failure patients

Oldf Oldenburg, Britta Korber, Thomas Bitter, Thomas Fischbach, Dieter Horskotte. Department of Cardiology, Heart and Diabetes Center North Rhein-Westfalia, Ruhr University Bochum, Bad Oeynhausen, Germany

A recent study in severe heart failure (HF) patients indicates a possible pathophysiological role of an impaired pulmonary diffusion capacity and respiratory disturbance during sleep, especially the degree of Cheyne-Stokes respiration (CSR). The aim of the present study was to verify this hypothesis in a larger cohort of HF patients.

In 87 patients (male, age 68±9 years) with polysomnography confirmed and untreated CSR due to cardiac failure (NYHA ≥ II, LVEF ≤45%), pulmonary diffusion capacity (TLCO and KCO) were prospectively investigated using the single-breath method. Apnoea-hypopnoea-index (AHI) was 38.4±7%, TLCO 67±20% of normal, and alveolar-volume corrected diffusion capacity (KCO) 85±20% of normal. Correlation analysis using Spearman rank order correlation revealed no significant correlation of AHI and TLCO (r = 0.071, p = 0.516) or AHI and KCO (0.019, p = 0.863).

In our cohort of HF patients with untreated CSR no correlation of respiratory disturbance during sleep and pulmonary diffusion capacity was found. Thus, a significant role of an impaired pulmonary diffusion on CSR genesis seems to be unlikely.

P450 Prevalence and under-diagnosis of airflow limitation and other lung function abnormalities in patients with ischaemic heart disease: an interim analysis of the ALACE study

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1Fondation Cauchet-CIMERA Ile de Balleurs, CIMERA, Banyuls, Spain; 2Program Development Centre, CIRO, Hong Kong; 3Respiratory and Intensive Care Medicine, Bichat-Druze Hospital, University Hospital of the Descartes, Paris, France; 4Wales Heart Research Institute, Cardiff University School of Medicine, Cardiff, United Kingdom; 5Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; 6Department of Oncology Haematology and Respiratory Diseases, Section of Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; 7Multidisciplinary Cardiovascular Research Centre, University of Leeds Medical School, United Kingdom; 8Department of Internal Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; 9Department of Medicine, University Kiel, Germany; 10Respiratory Centre of Excellence, ClaccsmithKline, Uxbridge, United Kingdom; 11Hospital Lu Dec, IdiPAZ, Madrid, Spain; 12Excellence Medicale, GSK France, Marly Le Roi, France

Background: Although ischaemic heart disease (IHD) and chronic pulmonary diseases, eg COPD, share similar risk factors, the prevalence and rate of diagnosis of airflow limitation (AL) and other lung function abnormalities, in patients with IHD are largely unknown.

Methods: In a cross-sectional study conducted in 15 sites across nine European countries (Belgium, France, Germany, Greece, Ireland, Italy, the Netherlands, Spain, and Sweden), we investigated the prevalence of airflow limitation compatible with COPD (defined as post-bronchodilator (BD) FEV1/FVC <0.70) and other lung function abnormalities in outpatients with documented IHD who were ≥40 years, and current or former smokers. Each participating center completed a core questionnaire and performed full pre- and post-BD spirometry. Quality control of spirometry readings was performed by a centralized system.

Results: Up to April 2012, we studied 1803 evaluable IHD patients, 86.0% male, mean±SD age of 65±9.8 years. The prevalence of AL was 30.6% (95% CI 28.5%-32.8%, n=552) and, from 547 with available data, only 29.4% (n=161) of these had a prior diagnosis of COPD. In addition, we found a restrictive lung disease prevalence of 11.0% (defined as pre BD FVC<80% predicted and post BD FEV1/FVC<70% predicted) in a subset of 1685 patients with available data.

Conclusions: Airflow limitation, compatible with COPD, and spirometry results suggestive of restrictive lung disease are frequent in individuals with IHD and are largely under-diagnosed, which has implications for the treatment and prognosis of both respiratory and cardiovascular diseases.

P451 Prevalence of osteoporosis in steroid naive postmenopausal women with COPD in Indian subjects

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Study objective: Osteoporosis in elderly female COPD on inhaled or systemic corticosteroids had been reported. We looked into prevalence of osteoporosis by BMD analysis in steroid naive COPD patients presenting to COPD clinic for first time.

Material & Method: Retrospective analysis done by computerized search of patient’s OPD records between Jan 10 & Dec 10. 1084 patients visited clinic for COPD and 411 underwent DEXA scan within 2 weeks. 253 post menopausal women identified COPD. 122 were steroid naïve (on rescue salbutamol and no records of using labelled systemic or local steroids). Severity of COPD was classified as per GOLD. Statistical analysis done using one way ANOVA.

Results: Of 122 patients with COPD 61 (50%) had osteoporosis. 6/20 (30%) GOLD stage I patients, 23/35 (66.7%) stage 2, 17/27 (62.9%) stage 3 and 15/22 (68.1%) in stage 4 had osteoporosis. Low BMD (T-score at AP spine < -1) was observed in 17/20 (85%) stage 1, 44/53 (83.01%) stage 2, 21/27 (78.5%) stage 3 & 19/22 (86.36%) stage 4. Significantly lower BMD were observed in stage 1 (0.88±0.11 gm/cm²), Stage 2 (0.84±0.19 gm/cm²), Stage 3 (0.83±0.18 gm/cm²) & Stage 4 (0.78±0.16 gm/cm²) compared to normal age matched postmenopausal women (1.04±0.22 gm/cm², p-value <0.003, p-value <0.001, p-value <0.001 and p-value <0.001 respectively.

Conclusion: In our subset of postmenopausal steroid naive COPD women low BMD is seen in 86% of patients being lowest in most severe COPD. Hence, it would be prudent to do DEXA scan at initial visit of such patients particularly in stage 3 and 4 COPD, where add-onICS could worsen BMD.

P452 The prevalence of chronic obstructive pulmonary disease (COPD) in individuals with diabetes, hypertension, asthma, or mood/anxiety disorders: A Canadian population study

Pat Camp,1 Darcy Marcuniak2,3, Mariouc Doucet1, Teresa Tr5, Robert Prosser4, Anita Kozersky5, Nancy Garvey2, Kim Reznier4, S. Vanderloos5, Charles Gilbert5, Louise McRae9, Andrea Gershon4.

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There is little information on the prevalence of COPD among people with other chronic conditions. We determined the cross sectional prevalence of COPD among Canadians with diabetes, asthma, hypertension, and mood/anxiety disorders. We also compared the all-cause mortality between individuals with these other diseases without COPD.

Methods: Using the Canadian Chronic Disease Surveillance System (CCDSS), we analyzed 2008/2009 administrative health data for Canadians aged 35 years.
and older, from 12 of 13 provinces/territories. COPD, diabetes, hypertension, mood/anxiety disorders and asthma were identified using ICDC/10 codes from physician billing and hospitalization records.

Results: The prevalence of COPD among Canadians aged 35 years and older was 8.2%. The prevalence of COPD among people with diabetes, hypertension, mood/anxiety disorder and asthma was respectively 11.4% (95% confidence interval (CI) 11.1, 11.7), 11.0% (95% CI 10.9, 11.1), 11.6% (95% CI 11.5, 11.7), 11.6% and 26.3% (95%CI 26.20, 26.35). In addition, a diagnosis of COPD was associated with a 140% increase in mortality among people with diabetes and a 154% increase in mortality among people with hypertension (compared to mortality among people with asthma or mood/anxiety disorders could not be calculated because the data were not available).

Conclusions: COPD is a prevalent comorbid condition for individuals with asthma, mood/anxiety disorder, diabetes and hypertension and comorbid COPD is associated with higher mortality. An integrated care approach to these patients may optimize health outcomes and reduce the burden of chronic disease.

P453 Comorbidity between chronic obstructive pulmonary disease and type 2 diabetes in adult twins Howraman Meteran1, Bocker Vibeke1, Kyvirk Kirsten Ohn2, Axel Skythle1, Simon Francis Thomsen1, 1Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen NV, Denmark; 2Institute of Regional Health Services Research & Odense Patient Data Explorativ Network, University of Southern Denmark, Odense, Denmark; 3The Danish Twin Registry, University of Southern Denmark, Odense, Denmark.

Aim: To examine the relationship between chronic bronchitis and chronic obstructive pulmonary disease (COPD) and type 2 diabetes in adult twins.

Methods: Questionnaire data on chronic bronchitis and hospital data on diagnosed COPD on 13,649 twins, 50-71 years of age, from the Danish Twin Registry, were cross-linked with hospital discharge diagnosis data on type 2 diabetes from the Danish National Patient Registry.

Results: The type of type 2 diabetes was higher in subjects with symptoms of chronic bronchitis compared with subjects without symptoms of chronic bronchitis (3.5 vs. 2.3%), OR=1.5 (1.09 - 2.15), p<0.012; and in subjects with diagnosed COPD compared with subjects without diagnosed COPD (6.6 vs. 2.3%), OR=2.97 (1.95-5.3), p<0.000. The results were significant after adjusting for age, sex, and smoking. Correlations between genetic effects on chronic bronchitis and type 2 diabetes; and between genetic effects on diagnosed COPD and type 2 diabetes, respectively, were 0.25 (0.00-0.59), p=0.130 and 0.35 (0.00-0.72), p=0.134.

Conclusions: Patients with chronic bronchitis and COPD have an increased risk of type 2 diabetes independently of sex, age, and smoking. Furthermore, comorbidity between these diseases seemed not to be explained by shared genetic factors. The increased risk of type 2 diabetes must be accommodated in the management of patients with chronic bronchitis and COPD.

P454 Angiotensin II receptor blockers, ACE inhibitors, lung function and percent emphysema: the MESA lung study John Austin1, Kevin Rolston2, Gina Lovasi6, Karol Watson7, Karen Hinkley3, Bonnie Klibanski1, 1Department of Radiology, University of Iowa, Iowa City, IA, United States; 2Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States; 3Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY, United States; 4Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, IL, United States; 5Department of Social and Economic Research and Policy, Columbia University, New York, NY, United States; 6Division of Cardiology, UCLA School of Medicine, Los Angeles, CA, United States; 7Department of Biostatistics, University of Washington, Seattle, WA, United States

In a murine model of emphysema, angiotensin receptor blockers (ARB) improved airway and airspace architecture and lung function. We hypothesized that use of ARBs and angiotensin-converting enzyme (ACE) inhibitors would be associated with higher lung function and less emphysema compared to ARB and ACE inhibitor use in the Multi-Ethnic Study of Atherosclerosis (MESA) recruited participants age 45-84 yrs, free of clinical cardiovascular disease. Percent emphysema was estimated on full-inspiration cardiac CT scan using a threshold of -910 HU. Spirometry was measured following ATS/ERS guidelines. Linear regression models adjusted for age, sex, race/ethnicity, body mass index, smoking status, pack-years, exposure to second-hand smoke, educational attainment, hypertension, diabetes, asthma, family history of emphysema, statin use, female hormone replacement therapy, fish oil use and scanner type. Among 3,599 participants (mean age 61±10 years, 51% female; 35% white, 26% black), 22% Hispanic, 16% Chinese), the proportion of participants using ARBs or ACE inhibitors was 5.5% and 11.8%, respectively. The mean square root transformed percent emphysema was 3.85±1.52, the mean FEV1 (L) was 3.54±0.7. Participants using ARBs or ACE inhibitors had slightly less square root transformed percent emphysema (0.12, 95% CI, -0.31, 0.07; P=0.22) and participants using ACE inhibitors had slightly higher levels of FEV1 (19 ml; 95% CI, -35, 73; P=0.50) compared to others, but neither difference was statistically significant. In cross-sectional analysis, adjusting for various confounders, there was no evidence that use of ARB or ACE inhibitors was associated with less emphysema or better lung function.

P455 Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease Marcie Thomas1, Morten Dahl1, Peter Lange2, Jorgen Vestbo4, Birge Noodenstedt1, 1Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark; 2Respiratory Section, Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark; 3Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 4Respiratory Research Group, Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, Manchester, United Kingdom

Background: Patients with chronic obstructive pulmonary disease (COPD) have evidence of systemic inflammation that may be implicated in the development of comorbidities. We tested the hypothesis that elevated levels of three inflammatory biomarkers are associated with increased risk of comorbidities in COPD.

Methods: We measured baseline C-reactive protein (CRP), fibrinogen, and leukocyte count in 10,052 COPD patients from two large population studies. During a median 5-years follow-up we recorded hospital admissions due to ischemic heart disease, myocardial infarction, heart failure, type II diabetes, lung cancer, pneumonia, pulmonary embolism, hip fracture, and depression as endpoints.

Results: Multifactorially adjusted risk of ischemic heart disease was increased by a factor of 2.19 (95% confidence interval 1.48 to 3.23) in individuals with three biomarkers elevated (CRP above 3 mg per liter, fibrinogen above 14 μmol per liter, and leukocyte count above 9 x10^9 per liter) versus individuals with all three biomarkers at or below these limits. Corresponding hazard ratios were 2.32 (1.34 to 4.04) for myocardial infarction, 2.63 (1.71 to 4.04) for heart failure, 3.54 (2.03 to 6.19) for diabetes, 4.00 (2.12 to 7.54) for lung cancer, and 2.71 (2.03 to 3.63) for pneumonia. There were no consistent differences in risk of pulmonary embolism, hip fracture, or depression as a function of these three biomarkers.

Conclusions: Simultaneously elevated levels of CRP, fibrinogen, and leukocyte count are associated with a 2 to 4-fold increased risk of major comorbidities in COPD. These findings may enable clinicians to conduct stratified management of comorbidities in COPD patients.

P456 Comorbidity in chronic obstructive pulmonary disease (COPD): Data from the fourth Korean National Health and Nutrition Examination Survey (KNHNES IV) Chunoong Moon, Saey Byol Kim, Kyung Soo Chung, Seo Cheol Park, Won Jai Jung, Eun Young Kim, Ji Ye Jung, Young Ae Kang, Moo Suk Park, Young Sam Kim, Se Kyu Kim, Chul Min Ahn, Joon Chang. Division of Pulmonology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction: Many comorbidities frequently coexist with chronic obstructive pulmonary disease (COPD) and they could influence on poor prognosis. We tried to determine which comorbidities frequently coexist in individuals with COPD using population based nationwide survey.

Methods: We used data obtained in the first (2007) and second year (2008) of the Fourth Korean National Health and Nutrition Examination Survey (KNHNES IV) and included participants aged ≥40 years. Subjects with FEV1/FVC<0.7 was defined as individuals with COPD. Participants with history of asthma, pulmonary tuberculosis and bronchiectasis were excluded.

Result: Baseline characteristics were not significantly different between COPD group (n=357) and control group (n=357) except spierometric findings. COPD group was associated with increased risk of low BMI (<18.5 kg/m²) (OR 3.53, 95% CI 1.29-9.68; p=0.014) and associated with decreased risk of hypertension (OR 0.73, 95% CI 0.54-0.99; p=0.042) and hypercholesterolemia (OR 0.59, 95% CI 0.37-0.93; p=0.022). The incidence of low BMI uniquely increased with the severity of airflow obstruction (1.4% in control subjects, 3.6% in GOLD stage I, 4.5% in GOLD stage II and 30% in GOLD stage III; p<0.0001). However, the incidence of hypertension and hypercholesterolemia did not.

Conclusion: Incidence of low BMI uniquely increased with the severity of airflow limitation. However, more study is needed to confirm whether low BMI is the cause of COPD or the result of COPD.

P457 Ventilatory function and markers of metabolic disorders in adults Vanessa Garcia Larsen1, Peter Burney1, Joannis Bakolis1, Hugo Amigo2, Patricia Bustos3, Roberto Rona1, 1Respiratory Epidemiology & Public Health, National Heart and Lung Institute, Imperial College London, London, United Kingdom; 2Department of Nutrition, Faculty of Medicine, University of Chile, Santiago, Chile; 3Department of Psychological Medicine, Weston Education Centre, King’s College London, United Kingdom

Background: Metabolic disorders are related to poor lung health in adults but...
there is limited evidence of this effect in young adults. Early identification of these risk factors could contribute to improve lung function and to prevent COPD later in life. In this study we investigated the relationship between measures of ventilatory function and markers of metabolic disorders in young adults.

**Methods:** A cross-sectional study was performed in 1000 subjects aged 22-28 years old from a semi rural area in Chile. Forced vital capacity (FVC) and the ratio FEV1/FVC were the outcomes. Serum levels of fasting insulin, high-density lipoprotein, triglycerides and plasma glucose were also measured. Insulin resistance status (Homeostatic Model Assessment (HOMA-IR)) and metabolic syndrome (MS) were calculated.

**Results:** 970 participants had valid lung function data and complete information on exposures. The mean value of HOMA-IR was 2.59 in males and 2.48 in females (reference cut off point 2.53). 12% of males and 11% of females had MS (defined according the ATP III guidelines). After adjusting for potential confounders, FVC (L) was statistically negatively related to high HOMA-IR (difference of means -0.11 [95% Confidence Interval CI] -0.17 to -0.05, P value <0.0001). FVC was also statistically negatively associated with MS (difference of means -0.18 [95% CI -0.27 to -0.09, P value <0.001]. No association was found between FEV1/FVC and these markers.

**Conclusion:** Presence of metabolic disorders had a deleterious effect on ventilatory function in the young adults studied.

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**P458**

**Waist circumference and lung function parameters: The PLATINO study**

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**Background:** Obesity is a known risk factor for chronic diseases. Recently, studies have shown that abdominal fat, measured by waist circumference, rather than BMI, is a more important predictor for the development of non-communicable chronic diseases.

**Objective:** To evaluate the association between waist circumference (WC) and lung function parameters among adults.

**Methods:** A cross-sectional study was performed in five Latin America countries (Brazil, Chile, Mexico, Uruguay and Venezuela), named the PLATINO study. The data was collected from 1999 to 2002 and 2008 among 1000 adults. WC and FVC were measured using spirometry pre and post bronchodilator. WC was measured by trained interviewers. Data analyses were performed using multiple linear regression models and were stratified by sex.

**Results:** The correlation coefficients (r) between WC and FVC and FEV1 were negative, although for WC and FEV1/FVC the coefficients were positive. After adjusting for age, height, weight, BMI and smoking, the increase of 1 cm in WC decreased FEV1 by 0.018 liters [95%CI -0.023, -0.013] in males, and 0.009 liters [95%CI -0.011, -0.006] in females. For FVC, the results showed the same direction, but were more expressive (males β = -0.024 [95%CI -0.057, -0.018] and females β = -0.016 [95%CI -0.031, -0.001]). When we evaluated the predicted values for FEV1 and FVC, an inverse relationship with WC was also found. For FEV1/FVC, only females showed a direct relationship with WC (values for FEV1 and FVC, an inverse relationship with WC was also found. For females β = 0.018; 0.114).

**Conclusion:** WC is an important risk factor for chronic diseases. The effect of WC on lung function is more pronounced in females.

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**P459**

**Effects of BMI changes on lung function in COPD subjects from two longitudinal general population studies**

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**Background:** Nocturnal gastroesophageal reflux (nGER) is associated with asthma and obstructive sleep apnea in observational studies, but prospective epidemiological studies are lacking. Our aim was to investigate whether nGER is a risk factor for onset of asthma, respiratory and OSA symptoms in a prospective population based study.

**Methods:** We invited 2640 randomly selected subjects from Iceland, Sweden and Belgium for two evaluations with a nine years interval (participation rate 66.7%). They participated in a structured interview, answered a questionnaire regarding respiratory symptoms and were underwent spirometry and a methacholine challenge. Blood samples were analysed for specific IgE.

**Results:** Subjects with persistent nGER (n = 123) had an increased risk of asthma and OSA follow-up after 9 years, independent of gender, age, location, smoking history, BMI at baseline and change in BMI (OR (95% CI): 2.3 (1.1-4.9). Persistent nGER was also independently related to the onset of various respiratory symptoms (OR (95% CI): 3.0 (1.6-5.6). The risk of developing symptoms of OSA was increased in subjects with new onset ≥ 2.01 and persistent ≥ 2.01 (95% CI): 2.2 (1.3-1.6) and 2.0 (1.0-3.7), respectively). No significant independent association was found between nGER and lung function or bronchial responsiveness.

**Conclusions:** Persistent nocturnal gastroesophageal reflux contributes to the development of asthma and respiratory symptoms. The risk of new onset of OSA symptoms is also higher among subjects with nGER. These findings further support the conclusion that nGER may play a causative role in the genesis of respiratory symptoms and diseases.

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**P461**

**Patients with depressive symptoms presenting to the emergency department for asthma have worse clinical status**

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**Background:** Depressive symptoms are associated with worse long-term asthma but less is known about their effects on acute exacerbations.

**Methods:** This analysis compared clinical characteristics according to depressive symptoms among 296 patients presenting for asthma to emergency departments (EDs) in New York City. At presentation patients completed valid surveys measuring asthma variables and depressive symptoms. Patients received follow-ups for 16 weeks.

**Results:** Mean age was 44 years, 72% were women, and 23% had a positive screen for depression. Compared to those with a negative screen, those with a positive screen were more likely to know what triggered the exacerbation (11% vs 22%, p<0.01), and to report worse asthma-related quality of life (<0.001), worse asthma control (p=0.002), and worse asthma self-efficacy (p<0.001). These relationships persisted in multivariate analysis when controlled age, sex, and long-term asthma severity (p<0.05). There were no differences in hospitalization rates for the current exacerbation based on depressive symptoms, but among those admitted (n=184), more patients with a positive screen had a length of stay that exceeded the median of 3 days (45% vs 71%, p=0.004). At 4 weeks (n=269) and 16 weeks (n=281) patients with a positive screen were more likely to have taken rescue beta agonists (67% vs 84%, p=0.01) and to have had a repeat ED visit for asthma (17% vs 27%, p=0.09).

**Conclusions:** Asthma ED patients with a positive screen for depression had worse self-report clinical status and more short-term resource utilization. Depres-
sive symptoms may be modifiable and should be addressed in relation to acute exacerbations.

### P462

The combined association of anxiety or depression symptoms and obesity with incident asthma: The HUNT study

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Anxiety and depression may increase the risk of developing asthma. We conducted a prospective study to test this hypothesis and additionally investigate the potential joint effect of these symptoms and obesity. We studied 23,199 adults who were 19-55 years old at baseline in the Norwegian Nord-Trøndelag Health Study (HUNT). The participants were followed for 11 years. The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety (HADS-A ≥ 8, range 0-21) and depression (HADS-D ≥ 8, range 0-21) symptoms. Obesity was defined as having a body mass index of ≥30.0 kg/m². Incident asthma was self-reported. Odds ratios (ORs) for incident asthma associated with anxiety or depression were calculated using logistic regression models. To test the joint effect of anxiety or depression and obesity we calculated the relative excess risk due to interaction (RERI).

At baseline, 4,151 participants (17.9%) had anxiety or depression symptoms. There was a significant association of anxiety or depression with incident asthma (OR 1.36, 95% CI 1.15-1.61). Compared to non-obese without anxiety or depression, obese women with anxiety or depression had a significantly higher risk of incident asthma (OR 2.13, 95% CI 1.44-3.15). The relative excess risk due to interaction for obese women with anxiety or depression and obesity was 1.08 (95% CI 3.02-3.15). This study suggests that anxiety and depression symptoms contribute to incident asthma in adults. Obesity may interact with anxiety and depression symptoms in increasing the risk of asthma.

### P463

Asthma in pregnancy and risk of preterm delivery

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The effects of asthma on pregnancy outcomes differ between studies. A recent review indicates that the conflicting results are related to study design, where larger database studies have reported increased risks, and smaller clinical prospective cohort studies have not found significantly increased risks. We study the effects of asthma within a large study of air pollution and preterm birth; is there an increase in preterm birth and how common are exacerbations in pregnancy resulting in outpatient hospital visits?

Our study cohort from Stockholm, Sweden, is constructed by matching live births 1998-2006 from the Medical Birth Registry with information on the mother from the Patient Registry (1987-2010 for hospital admissions and 2001-2010 for outpa- tients). Compared to the population from this area, we define all mothers who had at least one hospital visit for asthma or had asthma medication as having asthma. We used logistic regression to assess the relation between asthma and preterm birth. We adjusted the model for education, previous preterm birth, origin, parity, date of conception and maternal age. The prevalence of preterm birth was 5.4% among mothers with asthma (n=13,261) and 4.4% in the rest of the population (n=111,931). The odds ratio for giving birth preterm was 1.27 (p < 0.01) for women with asthma compared to non-asthmatic mothers. 1.9% of the asthmatic mothers had a hospital contact for asthma during pregnancy, and 4.8% of them delivered preterm. Asthma is associated with an increased risk of preterm birth, particularly in women with exacerbations of the asthma during pregnancy.

### P464

Respiratory function in elderly with ‘senile’ or ‘juvenile’ pulmonary phenotype: Results from the KORA-Age study

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Background: Lung function, typically assessed by spirometry, is a strong predictor for overall morbidity and mortality. To improve our mechanistic understanding we examined whether poor spirometric lung function is associated with general respiratory limitations in elderly subjects with apparently healthy lungs.

Methods: Spirometry was performed in a random population sample from the region of Augsburg, Germany (n=935, aged 65-90y). From subjects free of lung disease (COPD, Asthma) two subgroups with either poor (‘senile’; n=87) or favourable (‘juvenile’; n=82) lung function were selected from the lower and upper 10% of the FEV1/FVC distribution. TLC, DCO, peak inspiratory pressure at RV (Pimax), the decrease in airway pressure at 0.1s (P01), and 6MWD were determined.

Results: P01 and P01/MV were not affected by age, while spirometric values, DCO/VA and Pimax showed an age dependent decline. ‘Senile’ phenotype subjects had 10% lower DCO/VA (P=0.05), while DCO/VA was not affected. P01, P01/MV and Pimax were increased by at least 45% and Pimax reduced by 13% in the ‘senile’ group (p<0.05). Multiple regression analysis in ‘senile’ and ‘juvenile’ subjects revealed that limitations in DCO and Pimax contribute to a reduced 6-MWD.

Discussion: Elderly subjects with poor spirometry, while being free from overt lung disease, also suffer from age related limitations in gas exchange capacity, reduced muscle strength, and increased workload during breathing. This limited respiratory capacity may contribute to reduced physical fitness and morbidity. Supported by German Federal Ministry of Education and Research (BMBF FKZ 01ET0713) as part of the ‘Health in old age’ program.

### P465

Poorer quality of life in asthma patients is associated with rhinosinusitis, smoking and decreased lung function – Results from the Swedish GA²LEN survey

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Introduction: We have previously reported that patients with both asthma and rhinosinusitis have impaired quality of life compared to asthma patients without rhinosinusitis.

Aim: The aim of the current study is to further analyze quality of life in asthma. The study was part of the Global Allergy and Asthma European Network (GA²LEN) survey and follow-up.

Methods: A total of 499 asthmatics (age 17-76) completed the Juniper mini- questionnaire on Lung Function (mAQLQ) in four centres in Sweden, as part of a clinical follow-up visit of the GA²LEN survey. Lung function and exhaled nitric oxide (FeNO) were measured, and the patients were interviewed. Asthma was defined as self-reported diagnosis of asthma and presence of at least one asthma symptom or use of asthma medication. Rhinosinusitis was defined as having at least two sinusitis symptoms, providing that nasal blockage or nasal discharge were reported. Multiple regression analysis was used.

Results: The overall mAQLQ score was related to having rhinosinusitis (-0.51 units, P<0.0001), current smoking (-0.42 mAQLQ units, P=0.015), lower FEV1 (-0.08 units per 10% predicted decrease, P=0.004) and high age (62-76 years compared to 17-32 years: -0.44 units, P=0.009). The analysis did not show any significant relationship between mAQLQ and BMI or FeNO. These results remain statistically significant also after adjusting for gender, centre and inhaled corticosteroid use.

Conclusion: Co-existing rhinosinusitis, current smoking, lower lung function and high age are related to poorer quality of life in asthma patients.
3.53 (1.17, 10.60) compared to women, while age, sex, BMI, waist-hip ratio and smoking. Women with postBD FEV1/FVC <0.7 had an increased risk of OSAS with an OR of 3.53 (1.17, 10.60) compared to women with an FEV1/FVC >0.7, but this relationship was not present among men; OR 0.70 (0.31-1.58).

Conclusions: Chronic airflow limitation, assessed by post bronchodilator spirometry, was associated with OSAS among women only. There was no relationship between OSAS and FEV1 or FVC.

P468
Associations between obstructive sleep apnea syndrome (OSAS) and chronic airflow limitation in a general Norwegian population
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Background: Several studies have investigated associations between OSAS and obstructive airway disease, but with inconsistent results.

Aim: To study the relationship between OSAS and pulmonary function in a general 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 study. The 3506 attendants 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. Spirometry including bronchodilator test inhaling 400 ug Salbutamol was performed by all subjects. Logistic regression analyses, including interaction analyses between sex and pulmonary function, were used to examine associations between OSAS and pre- and postbronchodilator (postBD) FEV1, FVC and FEV1/FVC.

Results: The prevalence of OSAS was 4.8% (20/422) in subjects with chronic airflow limitation as defined by postBD FEV1/FVC<0.7 and 4.4% (119/2829) in subjects with FEV1/FVC<0.7 (P=0.74). FEV1 and FVC (% of predicted) were not associated with increased risk of OSAS, after adjustment for age, sex, BMI, waist-hip ratio and smoking. Women with postBD FEV1/FVC<0.7 had an increased risk of OSAS with an OR of 3.53 (1.17, 10.60) compared to women with an FEV1/FVC>0.7, but this relationship was not present among men; OR 0.70 (0.31-1.58).

Conclusions: Chronic airflow limitation, assessed by post bronchodilator spirometry, was associated with OSAS among women only. There was no relationship between OSAS and FEV1 or FVC.

79. Gene–environment treatment and asthma

паутинная, респираторий синктивал и пикомаровirus) were examined in the Canadian Asthma Primary Prevention Study using both family-based transmission disequilibrium test and case-control methods.

Results: IL6R2 and TLR2 SNPs were associated with atopy after correction for multiple comparisons. There is significant evidence that SNPs p virus interactions with these same SNPs modifies the risk for atopic asthma and AHR in a high risk birth cohort. In addition, an NFKBIA SNP was associated with atopic asthma. All three viruses demonstrated a skew in the distribution of SNPs p viral interactions (based on QQ plot) for AHR at 7 years of age. RSV was associated with an increased number of SNP p viral interactions for atopic and atopic asthma at 7 years of age. Conclusion: We have identified novel susceptibility genes for asthma and related traits and interactions between these genes and early life viral infections.

P469
cchnic rs37972 gene’s polymorphism correlation with response to oral glucocorticosteroids treatment in severe asthmatics from the BIOAIR cohort
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A significant association of SNP rs37972 in GLCCI1 in a genomewide study was identified in children with asthma. Our goal was to evaluate biomarkers and pharmacogenetic determinants that may improve effectiveness of treatment in adults with asthma. Eighty five SA patients and 66 with mild-to-moderate asthma (MA) were included in the BIOAIR study. After optimization of treatment, they underwent a double-blind 2 week oral steroid intervention (prednisolone 0.5 mg/kg/day). DNA was extracted from whole blood and the rs37972 (C/T) polymorphism in the GLCCI1 gene was analyzed using TaqMan allelic discrimination on the ABI Prism 7500 detection system. The oral steroid intervention resulted in a significant increase in FEV1 (% predicted) in SA (6.6%, 95% CI 2.4 – 10.8, p=0.002, steroid treatment vs placebo) but not in MA (0.5%, 95% CI 3.4 – 2.4, p=0.38) or COPD (1.2%, 95% CI 1.7 – 4.0, p=0.30) (p=0.02, between group comparisons). The responsiveness to oral steroids was significantly better in patients characterized by the highest blood eosinophils (>0.44x10^9/L), the highest sputum eosinophils (>4%), the lowest sputum neutrophils (<4%) and the highest FeNO (>40ppb). A functional GLCCI1 variant was weakly associated with reduced improvement of lung function in response to glucocorticosteroids (p<0.05) and correlated significantly with the number of eosinophils in induced sputum and FeNO (<p<0.05).

In the majority of SA patients, systemic steroid treatment induces an improvement in lung function. The positive response to oral steroids may be associated with certain genotype and phenotypic markers that may improve therapeutic decisions.

P470
Two single nucleotide polymorphisms in TSLP gene promoter region are associated with asthma susceptibility in Chinese Han population
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Background: Asthma is a chronic inflammatory disease of the airway. Thymic stromal lymphopoietin (TSLP) can aggravate asthmatic lung inflammation.

Objective: To analyze the polymorphism of two single nucleotide polymorphisms (SNPs) Rs2289827 and Rs2289287 in TSLP gene promoter region to evaluate the association between the two SNPs and asthma susceptibility in Chinese Han population.

Methods: 531 asthmatic patients and 540 normal controls were collected and the genotypes of SNPs Rs2289827 and Rs2289287 were detected with polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). genotype and allele frequency were calculated and analyzed with Chi-square test.

Results: The genotype and allele frequencies of the two SNPs in asthmatic patients were significantly different from those in the healthy controls.

Table 1: Genotypic and allelic association analysis of TSLP promoter single-nucleotide polymorphisms in Chinese asthma study

<table>
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<tr>
<td>C</td>
<td>212</td>
<td>263</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Rs2289276 T allele was correlated with decreased FEV1; FVC (P<0.05).
contribute to the susceptibility to asthma, rhinitis and COPD, by candidate gene association analysis, in a large and accurately defined series of Italian subjects, even considering exposure to some environmental contexts and lifestyle.

Case-control association analysis of candidate genes in asthma, rhinitis and COPD: A preliminary report

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This study aims to determine the genetic involvement in the susceptibility to asthma, rhinitis and COPD by candidate gene association analysis, in a large and accurately defined series of Italian subjects, even considering exposure to some environmental contexts and lifestyle.

The study population included 1075 subjects (aged 20-66 years) from the general population, enrolled in the frame of the Gene Environment Interactions in Respiratory Diseases (GEIRD) study between 2007 and 2010. Cases and controls were diagnosed during a clinical examination that included a detailed interview, pre/post bronchodilator spirometry, methacholine challenge, skin prick tests. A panel of 384 Single Nucleotide Polymorphisms (Tag-SNP), representative of 63 candidate genes with a previous indication of possible association to the studied diseases, was genotyped by a customized GoldenGate Genotyping assay. Presently, genotyping of 725/1075 subjects are completed. A preliminary association study of candidate gene polymorphisms was conducted on these data, for the susceptibility to one or more of the studied phenotypes, by basic association test based on allele frequency comparison. Presence of association (unadjusted p<0.005) was observed between GSTP1 and non-atopic rhinitis, PDE4D and ever asthma with atopy, IL13 and past-asthma, TNS1 and chronic bronchitis. Moreover, a possible association (unadjusted p<0.02) was also found for IL1RL2 with ever asthma, chronic bronchitis, atopic rhinitis and non atopic rhinitis. The analysis is going on to complete the genotyping of all the enrolled subjects and to perform haplotype analysis, to confirm the involvement of these genes in the studied diseases.

P471 Association of TGFβ1 and IL-4Rα2 gene polymorphisms with asthma

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There are components of the asthma phenotype that appear to be strongly heritable. We have studied certain SNP variations in a set of genes related to the pathogenesis and evolution of asthma in patients with severe asthma and their immediate relatives, as well as in a control group of non-asthmatics patients.

Aims of this study: 1. To determine the existence of common genetic characteristics in individuals suffering from severe asthma.

2. To study whether there are common genetic patterns in relatives of patients with severe asthma.

Method: We selected patients diagnosed of severe persistent asthma according to the criteria proposed by the ATS Consensus for Definition of Severe/Refractory Asthma and their first-line relatives, symptomatic or non-symptomatic according to their responses to the European Community Respiratory Health Survey Questionnaire. A control group of non-asthmatic patients was included. We obtained saliva samples from 10 different SNPs located on different genes related to asthma (CHI3L1: rs4950928; ADRB2: rs1042713, rs1042714; DENND1B: rs1775456, ORMDL3: rs7216389, TMC06: rs2569190, ADAM33: rs2280991; IL4: rs2434250, TGFβ1: rs1800469, ILAR: rs1801275), by TaqMan SNP Genotyping Assay.

Results: We analyzed samples from 150 patients diagnosed of severe persistent asthma, 49 controls, 69 asymptomatic relatives and 83 symptomatic relatives. We found significant differences (p<0.05) between the group of patients and relatives with respect to controls in two pairs of the alleles studied: TGFβ1 rs1800469; IL-4Rα2 rs1801275.

Conclusions: We found a higher prevalence of TGFβ1 rs1800469 (AA and AG) in patients with severe asthma and their relatives; and IL-4Rα2 rs1801275 (AA) in asthmatics.

P472 Investigating the role of IREB2 genetic variants in susceptibility to COPD

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The IREB2 gene encodes the iron-binding protein 2, which is a major regulator of iron homeostasis. Several studies have shown that the IREB2 locus is a contributor to COPD susceptibility. Previously, we observed significant associations of seven IREB2 genetic variants with increased risk of COPD in a large case-control study. Subsequent in-silico analysis showed that six of these SNPs were in tight linkage disequilibrium with two variants located within the promoter (rs2565070) and the 3'UTR (rs12899351) of IREB2 gene. The promoter SNP is predicted to disrupt the binding of two transcription factors while the 3'UTR SNP is located in a region that is predicted to be target site of mir-1285 and mir-5096. The aims of this study were to evaluate the functional effect of these variants on IREB2 expression.

To test the effect of the promoter SNP, two fragments (one for each allele) of the 3'UTR region of IREB2 were inserted upstream of the luciferase gene in the pGL3 Basic vector and then transfected into the A549 cells. Our results show that there was no difference in luciferase expression from cells transfected with rs2565070 wild type construct compared with the risk allele under basal conditions. Further analysis will be undertaken to examine the effect of the rs2565070 under different stimulatory conditions. For the 3'UTR SNP, two fragments (for both alleles) spanning the potential mRNA target site was cloned downstream of the luciferase gene in pmirGLO vector and then transfected into HepG2 cells that are known to express mir-1285. Luciferase assay showed that mir-1285 did not recognize the cloned sequence. Additional investigation will consider the regulatory role of mir-5096 on IREB2 expression.
P475
Gene polymorphisms, gene expression and inflammatory markers in preschool children with and without wheeze
Ester Klaisser1, Kim van de Kant1, Qurtijn Jobbs1, John Penders2, Frederik Jan van Schooten1, Mariette Quak3, Gertjan de Hartog2, Gerard Koppelman1, Constant van Schayck4, Guillaume van Eys5, Edward Dompeling1, P. Emile Mullie1, Robert Verheij4, W,he Van Der Velden2, Wieteke Bijdendijk2, M. J. Van Stiphout2, Wieteke Van Der Velden2, M. W. Van Velsen2, The J Peeters2, J. M. Van Beek1, P. L. Shupyk5, Kiev, Ukraine; 1Department of Allergology, Medical University of Gdansk, Poland; 2Department of Pneumonology, Medical University of Gdansk, Poland; 3Unit of RFLP analysis in 222 healthy people and 207 bronchial asthma (BA) patients
Results: The AC genotype of AT2R1 gene was significantly higher among RDS cases. Impact of O.felineus to GE model and it’s modifying role on genetic component control lung function can suggests that O.felineus is important environment factor that can modify genetic risk of asthma, but clinical and mechanical factor in the development of respiratory distress syndrome (RDS).

P479
Polymorphisms in genes associated with the development of steroids-induced adverse events
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Glucocorticoids are widely used in the therapy of lung interstitial diseases or severe asthma because of their anti-inflammatory properties. Their actions are mediated through an intracellular receptor. Steroid - receptor complex translates to a nucleus and binds DNA fragments referred to as glucocorticoid-response elements (GREs). Transcription regulation is associated with both therapeutic results and unwanted effects e.g. hypertension, diabetes, osteoporosis.
Aim of the study: The aim of this study was to evaluate the frequency of polymorphisms in the selected genes (ESR2, ATP1B1, AT2R, Hind III) that may be responsible for the development of steroids-related complications in the population of Kashubia (north of Poland).

Patients and methods: Blood samples were collected from 250 participants randomly chosen from the population of Kashubia region. Presence of polymorphisms was determined by the means of PCR in the following locations: AT2R-3123 A/C, osteocalcin- rs1800247 C/T, ESR2- rs9489358 A/G, ATP1B1- rs1916264 C/T. In statistical analysis y 2 test was used to determine whether the genotypes were in Hardy-Weinberg equilibrium.

Results: For all the gene polymorphisms were found in the specified locations. The frequencies of variants were as follow: AT2R- AA 36%, AC 19%, CC 45%; HindIII (osteocalcin)- CC 9%, TC 31%, TT 60%; ESR2- AA 10%, AG 39%, GG 51%; ATP1B1- TT 1%, TC 19%, CC 80%. In ESR2, ATP 1B and osteocalcin genes variants were in Hardy-Weinberg equilibrium.

Conclusion: Polymorphisms in the genes that may be related to adverse events of steroids are frequent enough to continue to study the associations between polymorphic variants and presence of side effects of steroids.

P480

Is GLCCI1 associated with response to inhaled corticosteroids in asthma patients?

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2Medicines Discovery and Development, GlaxoSmithKline, RTP, NC, United States

Inhaled corticosteroids (ICS) are the primary anti-inflammatory therapy for the treatment of asthma. Glucocorticoid-induced protein 1, also known as GLCCI1, is expressed in the airway epithelium and has been shown to be associated with airway hyperresponsiveness (AHR) and asthma outcomes. In this study, we aimed to investigate the association between GLCCI1 genetic variants and response to ICS in asthma patients.

Methods: A total of 200 asthma patients were recruited and genotyped for two GLCCI1 polymorphisms: rs2320670 and rs2320668. Response to ICS was assessed by changes in FEV1 and symptom scores following treatment.

Results: The frequency of the rs2320670 polymorphism was significantly different between responders and non-responders (p=0.03). The minor allele (C) was associated with a better response to ICS, with a mean increase in FEV1 of 123.5 ml in the C allele carriers compared to 64.2 ml in the non-carriers (p=0.02).

Conclusion: Our findings suggest a potential role for GLCCI1 genetic variants in predicting response to ICS in asthma patients. Further studies are needed to confirm these results and to elucidate the molecular mechanisms underlying this association.

P482

The effects of eccentric and concentric exercise training on muscle strength in COPD: Preliminary results

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1Respiratory Epidemiology and Clinical Research Unit, McGill University, Montreal, Canada; 2Physiotherapy, University of Fortaleza, Brazil; 3Physiotherapy, University of Minas Gerais, Belo Horizonte, MG, Brazil; 4Department of Sport Medicine and Functional Explorations, CHU Clermont-Ferrand and INRA UMR 1019, Clermont-Ferrand, France

Since eccentric exercise greater force is produced at a reduced oxygen cost, this modality of exercise could be attractive for pulmonary rehabilitation of severe COPD patients.

Objective: To estimate the extent to which eccentric compared to concentric exercise training produces greater increases in quadriceps force, and leads to better improvements in hamstring force, exercise capacity and physical activity.

Methods: Pilot randomized clinical trial in which COPD patients were randomly assigned to either a concentric (CON) or eccentric (EC) cycling protocol, 3 sessions/week for 10 weeks. In the CON group, target training intensity was set at 80% of peak work rate (Wmax) while in the EC group the target intensity was set as 4-58% 80% of Wmax. Lung function, muscle strength (Biodex), maximal work capacity (Wmax) and physical activity (Armband) were assessed.

Results: Preliminary analysis included 11 male COPD patients (69±6 years; FEV1: 14±10%pred; BMI: 27±4 k.g.m-2). After 10 weeks of training, isometric quadriceps force was 14% (20N)(95%CI: 2-26%, p=0.03) and concentric hamstring force was 27% (14N)(95%CI: 2-50%, p=0.03) higher in the EC. A trend for greater improvements in concentric quadriceps force was observed only in the ECC group (ECC=16% of change, p=0.06 vs CON=15%,p=0.06). Both ECC and CON training yielded similar improvements in Wmax (ECC 18%,p=0.03 vs CON 16%; p=0.03). Steps/day remained unchanged (p=0.05) in both groups.

Conclusion: Preliminary results show a trend for greater improvements in quadriceps muscle force with ECC compared to CON training in severe COPD patients.

Funding: McGill Health Centre Research Institute/pilot project and Edith Strauss.

P483

Acute effect of chest wall muscle stretching on chest wall volumes distribution in chronic obstructive pulmonary disease: A randomized controlled trial

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Inspiratory muscles function is compromised in COPD due to increased loads, reduced mechanical advantage, and increased ventilatory requirements. The hyperinflation of COPD reduces the flow and pressure-generating capacity of the diaphragm.

Aims: To analyze the acute effects of chest wall muscle stretching on chest wall volumes distribution in subjects with COPD.

Methods: It was a randomized controlled trial, involving 28 COPD patients divided into two groups: 14 subjects to treatment group (TG, mean age 61.79±8.31 years) and 14 to control group (CG, 62.38±8.32 years). TG was composed for patients that received a program of chest wall muscle stretching and patients allocated in CG remained at rest in the similar conditions as in TG. Respiratory variables were measured during quiet breathing by Opto-Electronic plethysmography (OEP) before and after one intervention. Statistical analysis was performed using independent samples t-test.

Results: Tidal volume (Vt) presented a significant increase immediately after the chest wall muscle stretching in rib cage pulmonary compartment (Vtccb, p=0.02), in rib cage abdominal compartment (Vtcca, p=0.04) and their percentages regarding thoracic wall, Vtcrp (p=0.04) and Vtcca% (p=0.02). Thus, there was...
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Physiological performance of patients with COPD during activities of daily living after a physical training with and without inspiratory muscle training:

Preliminary results

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Background: Physical training (PT) improves performance of activities of daily living (ADL), decreases dyspnea and enhances the inspiratory muscle strength in patients with COPD. Less is known on the physiological benefits during the execution of ADL in patients treated with general PT (GPT) or GPT plus inspiratory muscle training (IMT).

Aim: To compare changes on ventilatory and metabolic responses, dyspnea, SpO2 and time during a set of ADL after two PT programs.

Methods: A set of 5 ADL (making bed (1), taking shower (2), brushing teeth (3), lifting and lowering containers above eye level (4) and below the pelvic waist (5)) was performed by 28 patients before and after a 16 week: 13 GPT (aero- training) and 15 GPT+IMT with PowerBreathe (FEV1<1.5L) (p<0.01). A metabolic system was used during ADL.

Results: Both groups had significant reduction in VO2, VE, Borg, SpO2 and time in ADL within them, although there are no difference between GPT and GPT+IMT throughout the performance of ADL (Table 1).

<table>
<thead>
<tr>
<th>GPT/GPT+IMT</th>
<th>ΔVE (L/min)</th>
<th>ΔVO2 (mL/kg/min)</th>
<th>ΔBorg</th>
<th>ΔSpO2 (%)</th>
<th>ΔTime (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-13.4±4.11</td>
<td>-8.7±4.3</td>
<td>2.15</td>
<td>0.09</td>
<td>96.38</td>
</tr>
<tr>
<td>2</td>
<td>-11.3±3.12</td>
<td>-8.6±4.5</td>
<td>2.02</td>
<td>0.09</td>
<td>95.46</td>
</tr>
<tr>
<td>3</td>
<td>-12.3±3.13</td>
<td>-8.5±4.6</td>
<td>2.18</td>
<td>0.09</td>
<td>96.89</td>
</tr>
<tr>
<td>4</td>
<td>-11.4±3.12</td>
<td>-7.4±5.5</td>
<td>2.18</td>
<td>0.09</td>
<td>95.87</td>
</tr>
<tr>
<td>5</td>
<td>-12.3±3.11</td>
<td>-8.5±4.5</td>
<td>2.21</td>
<td>0.09</td>
<td>96.89</td>
</tr>
</tbody>
</table>

p-value 0.0001 0.0500 0.0304 0.0001 0.0001

Conclusion: These results suggest that both groups improved their performance in the ADL. Adding IMT did not show additional benefits on physiological variables on performance of ADL.

P485

Effect of positive expiratory pressure on sternocleidomastoid and parasternal muscles in patients with COPD: A randomized clinical trial

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Introduction: Chronic obstructive pulmonary disease (COPD) leads to chronic airway obstruction and air trapping, affecting diaphragmatic action and placing it at a mechanical disadvantage, requiring the recruitment of accessory muscles.

Objective: To investigate the effect of 10 and 15 cmH2O EPAP on the activity of sternocleidomastoid (SCM) and parasternal muscles in patients with stable COPD.

Methods: A randomized clinical trial with twenty-one COPD patients. Subjects were randomly allocated to two groups: 10 cmH2O Group (n=10) and a 15 cmH2O Group (n=11). We evaluated the electromyographic (EMG) activity of SCM and parasternal muscles in spontaneous breathing (Pre-EPAP), during application of EPAP by face mask for 20 minutes, and for 10 minutes after mask removal (Post-EPAP).

Results: The application of 10 cmH2O EPAP promoted reduction EMG activity in the SCM muscle (p<0.001) and increased parasternal muscle activity (p<0.001). The group submitted to 15 cmH2O EPAP showed a tendency towards greater EMG activity in the SCM muscle and a significant decrease in activity of the parasternal muscle (p<0.005).

Conclusions: In patients with stable COPD, 10 cmH2O EPAP induced a significant decrease in activity of the inspiratory accessory muscle and increased parasternal muscle activity after the application. This may have practical benefit to reverse the extreme use of the chest wall muscles and reduce their mechanical disadvantage in patients with COPD.

P486

Does tolerance of neuro-muscular electrical stimulation (NMES) relate to gender in patients with an acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD)?

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Introduction: The maximum intensity tolerated using NMES is relatively unknown in patients with an AECOPD. Previous data suggest that healthy males are able to tolerate higher intensities than females. The aim of this study was to compare the tolerance of NMES in patients admitted with an AECOPD between males and females.

Methods: 188 patients hospitalised with an AECOPD were recruited [58 male, MRC 4 (IQR 4-5), mean (SD) age 70.7 (±9.3) years, FEV1 1.38L ±70.1, BMI 26.7 ±7.0]. NMES was applied daily to both quadriceps muscles (30 mins, frequency 50Hz, pulse duration 300usec) for the duration of hospital stay.

Results: 175 patients completed the NMES intervention. A statistically significant difference between genders was seen in the intensity tolerated at both baseline and at discharge (p ≤ 0.01) as well as change in intensity. This change remained significantly different when correcting for baseline intensity (p=0.001). There was no significant difference in the number of sessions completed during hospitalisation between genders.

Conclusion: The intensity of NMES is tolerated at significantly higher levels in males. This may have clinical implications for NMES prescription and relate to outcome measures (eg. strength).

Table 1

<table>
<thead>
<tr>
<th>No. of Inpatient Sessions</th>
<th>Male</th>
<th>Female</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (IQR 1-5)</td>
<td>2 (IQR 1-4)</td>
<td>p=0.766</td>
<td></td>
</tr>
<tr>
<td>Intensity at Baseline (mA)</td>
<td>18.97±6.9</td>
<td>15.44±7.6</td>
<td>3.53 (1.3 to 5.7)</td>
</tr>
<tr>
<td>Intensity at Discharge (mA)</td>
<td>24.3±9.3</td>
<td>18.4±7.9</td>
<td>5.93 (3.4 to 8.5)</td>
</tr>
<tr>
<td>Change in Intensity (mA)</td>
<td>5.34±7.2</td>
<td>2.94±6.5</td>
<td>2.49 (0.6 to 4.8)</td>
</tr>
</tbody>
</table>

*p ≤ 0.01. Key: mA, milliamps; IQR, interquartile range.

Conclusions: Does tolerance of neuro-muscular electrical stimulation (NMES) relate to gender in patients with an acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD)?

P487

Responsiveness of different multidimensional severity indices to pulmonary rehabilitation in patients with COPD

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Background: Multidimensional indices have been used to assess disease severity in patients with COPD. The responsiveness of these indices to pulmonary rehabilitation (PR) needs to be better investigated.

Objective: To evaluate the responsiveness of five multidimensional severity indices to PR in patients with COPD.

Methods: 35 patients with COPD (17 men, 66±8 years, FEV1 43±16%pred) participated in a PR program of high-intensity endurance and strength training during 3 months. Demographic data, lung function (spirometry), exercise capacity (six-minute walking test [6MWT] and incremental shuttle walking test [ISWT]), dyspnea (Medical Research Council [MRC] scale) and quality of life (Saint George Respiratory Questionnaire [SGRQ]) were assessed before and after the program, and the following indices were calculated: BODE, SAFE, i-BODE and i-BOA.

Results: Age, distance walked in the 6MWT and SGRQ score were the only components of the indices which changed after PR (p<0.05 for all). Table 1 summarizes the responsiveness of the indices to PR.

Table 1

<table>
<thead>
<tr>
<th>Pre-PR</th>
<th>Post-PR</th>
<th>p value</th>
<th>Standardized Response Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>BODE</td>
<td>4.29±1.84</td>
<td>4.17±1.49</td>
<td>0.66</td>
</tr>
<tr>
<td>SAFE</td>
<td>4±0.35</td>
<td>4±0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>upBODE</td>
<td>3.12±0.5</td>
<td>2.12±0.5</td>
<td>0.47</td>
</tr>
<tr>
<td>ADO</td>
<td>4.89±1.55</td>
<td>4.89±1.39</td>
<td>1.00</td>
</tr>
<tr>
<td>i-BOA</td>
<td>4.31±1.89</td>
<td>4.62±1.50</td>
<td>0.34</td>
</tr>
</tbody>
</table>

The percentage of subjects that decreased their score (i.e., improvement) in the BODE, SAFE, upBODE, ADO and i-BOA was 23%, 49%, 23%, 20% and 23% respectively (p<0.05).

Conclusions: These preliminary findings indicate that the severity indices evaluated in patients with COPD in this study present very modest responsiveness to pulmonary rehabilitation, despite the improvement in some of its components.
Differences between smokers who completed or dropped out of a program to moderate PA were observed in both groups (p < 0.05). Patients undergoing oropharyngeal exercises showed a significant decrease in neck circumference (-1.04 to -0.97 cm; p < 0.05), sleep quality (range 0–4; intensity (1–3), Epworth Daytime Sleepiness score (0–24) and Pittsburg Sleep Quality score (0–21) were determined, and full polysomnography were performed at baseline and at the end of the intervention. Results: No significant difference was found in baseline characteristics between the groups (p > 0.05). Body mass index and abdominal circumference did not change significantly over the study period (p > 0.05). Patients undergoing oropharyngeal exercises had a significant decrease in neck circumference (-1.04 to -0.97 cm; p < 0.05), sleep quality (range 0–4; intensity (1–3), Epworth Daytime Sleepiness score (0–24) and Pittsburgh Sleep Quality score (0–21) were determined, and full polysomnography were performed at baseline and at the end of the intervention. Results: No significant difference was found in baseline characteristics between the groups (p > 0.05). Body mass index and abdominal circumference did not change significantly over the study period (p > 0.05). Patients undergoing oropharyngeal exercises had a significant decrease in neck circumference (-1.04 to -0.97 cm; p < 0.05), sleep quality (range 0–4; intensity (1–3), Epworth Daytime Sleepiness score (0–24) and Pittsburgh Sleep Quality score (0–21) were determined, and full polysomnography were performed at baseline and at the end of the intervention. Results: No significant difference was found in baseline characteristics between the groups (p > 0.05).

Conclusions: Inspiratory muscle training ensures significant benefits in respiratory muscle strength, quality of life, and smoking for OSAS patients. It should be taken into consideration for the management of the patients.
Conclusions: Oropharyngeal exercises significantly reduce anthropometric measurements and symptoms in patients with OSAS. They represent a promising treatment for OSAS.

P493
Physical activity promotes pulmonary recovery after cardiac surgery
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Introduction: It is well known that physical activity has substantial impact on general health and mortality. Benefits of physical activity have been reported for patients after cardiac surgery. Patients undergoing cardiac surgery have reduced lung function postoperatively and often suffer from postoperative pulmonary complications.

Methods: In a prospective cohort study, a sample of 76 patients undergoing cardiac surgery between 2007 and 2009, was followed up two months after cardiac surgery. Physical activity level was quantified using a categorical question on physical activity at work and during leisure time. Lung function was measured by spirometry. The measurements were made preoperatively and 2 months postoperatively.

Result: Two months postoperatively the patients had increased their self-reported level of physical activity. Patients with a higher level of physical activity showed a significantly better recovery of lung function two months after cardiac surgery (VC 95% ± 11 vs 91% ± 7 (p = 0.043) and FEV1 93% ± 8 vs 89% ± 6 (p = 0.0088) compared to patients reporting low physical activity.

Conclusion: A higher level of physical activity, during the first two months after cardiac surgery is associated with a better recovery of lung function, compared to being less active or sedentary.

P494
Cardiac autonomic responses exercise-induced during inpatient cardiac rehabilitation in patients undergoing CABG and left ventricular function different
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Introduction: Patients undergoing coronary artery bypass graft (CABG) with reduced left ventricular function (LVF) are those who experience greater cardiac autonomic adaptation at rest after inpatient cardiac rehabilitation (CR). However, the acute cardiac autonomic response (CAR) during exercise remains to be investigated.

Aim: To assess whether physical exercises can evoke beneficial CAR in post-CABG patients with different LVF.

Method: Forty-four patients, divided into LVF normal (LVFN, n=23) composed of patients with left ventricular ejection fraction (LVEF) ≥ 55% and LVF reduced group (LVRF, n=21) with LVEF<55% were evaluated. CAR was assessed by heart rate variability (HRV) during extremity ROM exercises and ambulation on the first postoperative day (PO1) and before discharge, respectively.

Result: PO1 were observed significant intragroup differences for mean heartbeats per minute (HR) at rest and exercise, respectively. PO1 were observed significant intergroup differences for mean heartbeats per minute (HR) at rest and exercise, respectively.

Conclusion: In patients with normal LVF, physical exercise triggered more attenuated CAR compared with patients with reduced LVF post-CABG. Thus, prescribed intensities of physical exercises at this time should be reviewed considering the differences of ventricular function of patients involved.

P497
Respiratory muscle training is safe and effective in malnourished patients
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Malnutrition is prevalent in 50% of hospitalized patients worldwide and causes systemic damage, including the respiratory system and muscles and leading to increased predisposition to infections and respiratory muscle weakness. The safety and effectiveness of respiratory muscle training in this population are poorly studied.

Objective: To assess the effect of specific respiratory muscle training in malnourished patients.

Methods: This prospective, randomized and controlled study enrolled 29 malnourished patients with no previous pulmonary disease (BMI<20kg/m² and serum albumin<3.5g/dL). Patients were randomly divided into 3 groups: sham training (CG, n=10), inspiratory (ITG, n=10) and expiratory (ETG, n=9) training. The intensity of ITG and ETG training was at 30% of maximal inspiratory or expiratory pressure (respectively, MIP and MEP). Training sessions were conducted daily in the afternoon for 30 minutes (3 sessions of 10 min, during 7 days) using the threshold DTM® or PEP®. All patients received the same nutritional support. Maximal respiratory pressures and lung function was evaluated before and after the protocols. The evaluator was blinded to patient’s group. Two way repeated measures ANOVA and post hoc Newman-Keuls test were performed and significance level was set at 5%.

Results: All groups were similar in gender, age, BMI and serum albumin. No patient demonstrated any signs of respiratory distress. After training period, there was increase in MIP in the ITG (59.9±25.8 x 107.9±52.6cmH2O; p=0.02) and MEP in the ETG (46.5±12.9 x 81.1±23.2cmH2O; p=0.01) compared to CG.

Conclusion: The respiratory muscle training is safe in malnourished patients and promotes a specific increase in the trained muscle.
Feasibility of neuromuscular electrical stimulation (NMES) on the intensive care unit (ICU): Preliminary results
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General Internal Medicine - Medical ICU, UZ Leuven, Belgium;
Physical Medicine and Rehabilitation, UZ Leuven, Belgium;
Intensive Care Medicine, UZ Leuven, Belgium

Background: Survivors of critical illness often have a prolonged ICU stay. To attenuate their reduction in muscle mass and muscle strength, NMES might be useful. Aim was to study feasibility and safety of NMES in ICU.

Methods: Patients with expected prolonged stay in ICU of 5 additional days (judged on day 3) without neurological disease were included. They received daily bilateral quadriceps NMES sessions of 25 minutes. Main outcome was to produce contraction of quadriceps. Patients with contraction in 75%-100% of sessions were considered responders. Patient characteristics and stimulation parameters were compared between responders and non-responders. Safety was judged by cardiovascular and respiratory responses.

Results:

Table 1. Feasibility of NMES

<table>
<thead>
<tr>
<th>Responders, N=17 (50%)</th>
<th>Non-responders, N=17 (50%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.6 (±10.8)</td>
<td>63.2 (±11.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.3 (±4.2)</td>
<td>25.1 (±6.1)</td>
</tr>
<tr>
<td>Barthel-index (0/20; premorbid)</td>
<td>17.1 (±3.5)</td>
<td>18.3 (±2.3)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>22.5 (±8.1)</td>
<td>27.5 (±6.9)</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>7.0 (±3.2)</td>
<td>8.4 (±3.4)</td>
</tr>
<tr>
<td>5 questions for adequacy</td>
<td>1.5 (±1.5)</td>
<td>2.3 (±1.6)</td>
</tr>
<tr>
<td>Oedema</td>
<td>4 (±0.7)</td>
<td>11 (±0.8)</td>
</tr>
<tr>
<td>Placing of electrodes*</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Intensity (mA)</td>
<td>64.9 (±8.9)</td>
<td>66.1 (±13.7)</td>
</tr>
<tr>
<td>*Different from standardised position due to catheters.</td>
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</tr>
</tbody>
</table>

Conclusion: In this small sample a trend is observed for age, APACHE II and Barthel-index.</p>

Physiotherapy led weaning plans reduce the number of days patients require non-invasive ventilation (NIV)
Stephanie Harlan, Amber Lane, Paul Murray, Physiotherapy Department, Ashford and St Peter’s Hospitals NHS Foundation Trust (ASPH), Chertsey, Surrey, United Kingdom; Rehabilitation Department, Ashford and St Peter’s Hospitals NHS Foundation Trust, Chertsey, Surrey, United Kingdom

Background: Respiratory physiotherapists at ASPH assess, monitor and wean patients requiring NIV. In May 2009, as a result of previous NIV audit data, a physiotherapy led weaning proforma was implemented to improve successful weaning rates.

Aims and objectives: The aim of the investigation was to establish if physiotherapy led weaning plans reduced the number of days patients spent on NIV.

Methods: Data were collected prospectively from 255 consecutive patients requiring NIV over a two year period from May 2009 to April 2011 using a locally adapted version of the BTS NIV data collection tool. Number of days on NIV were collected from patients nursing notes. 84 patients had physiotherapy led weaning plans and were included in the analysis (T-test).

Results: 33% (n=84) of patients had a physiotherapy led weaning plan. The impact of physiotherapy led weaning plans is summarised.

Table 1. Impact of physiotherapy weaning plans on time on NIV

<table>
<thead>
<tr>
<th>Patients with a physiotherapy weaning plan (n=84)</th>
<th>Patients without a physiotherapy weaning plan (n=171)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of days on NIV (range)</td>
<td>3.0 (1-8)</td>
<td>8.1 (1-17)</td>
</tr>
</tbody>
</table>

8% (n=21) patients required referral for domiciliary NIV and therefore could not be weaned and were excluded from the analysis.

Conclusion: Physiotherapy led weaning plans reduce the length of time patients remain on NIV. A possible explanation could be faster optimisation in the first 24 hours facilitating a shortened weaning time. Further investigation is required to establish if earlier physiotherapy input can impact on NIV outcome.

Thanks to Tina Thomas for data entry.
P502

Asthma control test administered by web-based text messaging (short message service-SMS): Is it comparable with paper form?

Method: Asthma control test (ACT) and Asthma Control Questionnaire (ACQ) were administered as paper and web-based. Each questionnaire was written at a 5.7 grade level and completed by 210 adults (88% asthma control test (ACT) and Asthma Control Questionnaire (ACQ) has been used in clinical practice. The ACT uses a standardized guide for recording difficulty encountered by subjects during self-administration was used to evaluate comprehension and ease of reading.

Results: The 39-item Conventional and Alternative Management for Asthma questionnaire was written at a 5.7 grade level and completed by 210 adults (88% female; mean age 48.76% Black; 20% White; 62% with < high school education). On average, subjects completed the questionnaire in < 5 minutes. Three subjects required assistance to complete the questionnaire; one was legally blind. Eight (4%) had difficulty with the Likert scale. As many as 31 (15%) asked for clarification on the wording of 15 distinct items. Four (2%) requested help in reading one or two unfamiliar words. Only 1 item elicited no comments.

Conclusions: The use of a standardized debriefing guide allowed for the identification of problematic words, unclear meanings and confusion over scaling despite a deliberate attempt to develop a low literacy text. Data suggest that a lower reading level is not sufficient to remove the potential for misreporting.

P503

Creating and testing a low literacy asthma questionnaire

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Background: Nearly half of the US population reads at or below the 8th grade level. Recognition of low literacy has resulted in greater attention to developing low literacy questionnaires. A standardized guide for recording difficulty in understanding wordings was developed and evaluated in a clinical setting.

Objective: To systematically develop a research questionnaire that accurately captures subjects’ responses when self-administered.

Methods: Following traditional instrument development steps (comprehensive review of the literature and selection of items using content experts), researchers created a low literacy questionnaire. A standardized guide for recording difficulties encountered by subjects during self-administration was used to evaluate comprehension and ease of reading.

Results: The 39-item Conventional and Alternative Management for Asthma questionnaire was written at a 5.7 grade level and completed by 210 adults (88% female; mean age 48.76% Black; 20% White; 62% with < high school education). On average, subjects completed the questionnaire in < 5 minutes. Three subjects required assistance to complete the questionnaire; one was legally blind. Eight (4%) had difficulty with the Likert scale. As many as 31 (15%) asked for clarification on the wording of 15 distinct items. Four (2%) requested help in reading one or two unfamiliar words. Only 1 item elicited no comments.

Conclusions: The use of a standardized debriefing guide allowed for the identification of problematic words, unclear meanings and confusion over scaling despite a deliberate attempt to develop a low literacy text. Data suggest that a lower reading level is not sufficient to remove the potential for misreporting.

P504

Asthma control test/Questionnaire for assessing asthma control: Systematic review and meta-analysis

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Background: Currently the cornerstone of asthma management is to achieve and maintain asthma optimal control, but the diagnostic performance of Asthma control test (ACT) and Asthma Control Questionnaire (ACQ) has not systematically been evaluated.

Objective: We explored the diagnostic performance and its comparison between ACT and ACQ.

Methods: Studies concerned with the accuracy of ACT and/or ACQ for assessing asthma control were searched from Pubmed, CENTRAL, Web of Science, Ovid and Embase. The summary estimates of sensitivity, specificity, and diagnostic odds ratios (DORs) at different levels of asthma control were performed using bivariate random effects model and hierarchical summary receiver operating characteristic (HSROC) model.

Results: Twenty-two studies with 12909 subjects in ACT and 4447 in ACQ were identified. The summary estimates in ACT for assessing controlled, not-well controlled, and uncontrolled asthma were sensitivity (0.81, 0.77 and 0.79), specificity (0.79, 0.78 and 0.73), and DORs (15.56, 12.42 and 10.46), respectively, and those in ACQ were sensitivity (0.93, 0.72 and 0.87), specificity (0.65, 0.83 and 0.66), and DOR (24.92, 11.98 and 12.72), respectively. There were no statistical differences in diagnostic accuracy between ACT and ACQ by using HSROC areas under the curve (all P > 0.05). Subgroup and meta-regression implied that age, setting, asthma severity, and the race could influence the diagnostic accuracy.

Conclusion: The diagnostic performance between ACT and ACQ is not different, but clinicians need to consider the impact of the potential factors when establishing asthma control levels to promote therapies in a real-world setting.

P505

Air-trapping and decreased diffusion capacity in patients with severe asthma

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Introduction: Patients with severe asthma tend to have impaired lung function despite the high-intensity treatment. Aim: The aim of the study was to assess the lung function parameters in patients with severe asthma compared with nonsevere disease.

Methods: In the recent research we have studied data of pulmonary function tests (spirometry, body plethysmography, diffusion capacity) in 31 patients with severe and in 23 patients with nonsevere asthma. To compare two groups of patients we used the Mann-Whitney U-test and Chi-squared test. Data are presented as median (interquartile range).

Results: Patients with severe asthma compared with those with nonsevere disease had lower VC, pre- and postbronchodilator FVC and FEV1, FEV1/FVC, FEF25-75 %, and FEF50-75 % values. FEV1 was not different between the two groups of patients. The prevalence of nonreversible airway obstruction was revealed in 77% patients with severe asthma and in 43% with nonsevere asthma (p=0.011). TLC was similar in patients with severe and nonsevere asthma, but RV and RV/TLC was significantly higher in severe asthma group (RV: 192.6 (160.2-249.5) vs 163.8 (143.9-174.7) % pred, p=0.018; RV/TLC: 145.0 (132.1-161.6) vs 119.1 (112.5-135.4) % pred, p<0.001).

Conclusion: The presence of persistent airflow limitation, air trapping and decreased diffusion capacity are important features of lung function impairment in patients with severe asthma, suggesting that these patients have more considerable airway remodelling and structural changes of lung parenchyma.

P506

Influence of anxiety on the quality of life of people with bronchial asthma (BA)

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Aim: To study the influence of anxiety on the QL of BA patients in the cold season.

Methods: Twenty-two patients with severe asthma were studied in the cold season.

Results: The presence of persistent airflow limitation, air trapping and decreased diffusion capacity are important features of lung function impairment in patients with severe asthma, suggesting that these patients have more considerable airway remodelling and structural changes of lung parenchyma.

Conclusion: The diagnostic performance between ACT and ACQ is not different, but clinicians need to consider the impact of the potential factors when establishing asthma control levels to promote therapies in a real-world setting.
Methods: 111 BA patients were studied in winter. They were divided into two groups: with anxiety (68) and without it (43). To estimate QL a questionnaires SF-36 and AQLQ were used. “Hospital Anxiety and Depression Scale” was applied to find out anxiety. CAHR was estimated by the results of 3-minute isocapnic hyperventilation with cold air.

Results: In the group of patients with anxiety in comparison with the patients without anxiety a decreased decrease of QL in domains PF (52.7±3.1 and 65.0±4.4, p<0.05), VT (45.3±2.3 and 59.2±2.8, p<0.001), SF (48.3±3.0 and 64.6±3.5, p<0.001) and MH (56.6±2.3 and 71.2±2.7, p<0.001) by SF-36, and in domains “Emotion” (3.4±0.2 and 4.5±0.2, p<0.001) and “General QoL” (3.3±0.2 and 3.9±0.1, p<0.01) by AQLQ. The direct correlation was found out between FEV1 and “Environment” in the group without anxiety (r=0.41, p<0.01), whereas patients with anxiety did not have it. Hence, anxiety but not lung dysfunction is a dominating factor of QL decline in the latter case. The QL of patients with CAHR and anxiety gets considerably worse. The decline of QL of these patients in all domains except “Emotion” was revealed by AQLQ. The most significant worsening was obtained in domain “Environment”.

Conclusion: Anxiety in BA patients has a negative influence on QL mainly on the psychosocial status. CAHR in winter also affects physical aspects of QL.

P507 Prediction of deterioration of bronchial asthma (BA) control after six months of basic anti-inflammatory therapy

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Background: Now it is accepted that the assessment of asthma control should include not only clinical manifestations, but also control of the expected future risk to the patients. Aim: To develop the way of prediction of uncontrolled BA after 6 months of basic anti-inflammatory therapy.

Methods: 84 patients with uncontrolled BA were examined. At the first examination the test of isocapnic hyperventilation with cold air (IHCVA) was conducted; the level of LTD4 and LTE4 in the exhaled breath condensate before and after the IHCVA with the identification of hydrogen peroxide (H2O2) was done. In 24 weeks of basic therapy there was the second clinical examination where the control level over BA symptoms was determined. Depending on the obtained data the patients retrospectively were divided into two groups: the 1st group included 48 patients with the partial or total BA control, the 2nd group consisted of 36 patients with uncontrolled BA.

Results: It was established that high airway hyperresponsiveness and the degree of bronchial inflammation being independent factors of BA control. On this basis and with the help of discriminant analysis we made a discriminant equation that allows to predict an uncontrolled course of the disease: D=0.502*FEV1 (after IHCVA)+0.062*H2O2 (after IHCVA). The boundary value of the discriminant function is 23.07. If D>23.07, an uncontrolled course of the disease after 6 months of basic therapy can be predicted with 91% probability.

Conclusion: The application of the developed method gives a possibility of a differentiated approach to the choice of BA basic therapy taking into account the risk of uncontrolled course of the disease.

P508 Interrelations of rhinitis, rhinosinusitis and bronchial asthma, associated with stressful life events

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One of the causes of ineffective treatment of bronchial asthma (BA) is comorbid pathology, which is a combination of BA with rhinitis. Aim: To study the characteristics and order of nasal pathology development in patients with BA associated with psychological stresses.

173 patients with BA allocated to 2 groups were studied. The first group included 56 patients in whom the first episode of the disease were associated with stressful life events. The second group included 117 patients in whom the disease was not linked to psychological factors.

Results: Nasal pathology was diagnosed only in 25 of 56 (44.6%) patients in the first group and in 106 of 117 (90.6%) in the second one, p = 0.0000. Allergic rhinitis was observed in only 6 (10.7%) patients in the first group and in the majority of cases (93 (70.9%)) in the second group, p = 0.0000, while rhinosinusitis was most frequent in the first group (19 of 56 (33.9%) versus the second one (12 of 117 (10.3%)), p = 0.0000. The order nasal pathology formation differed markedly between the two groups. So, nasal symptoms preceded the onset of asthma symptoms in the first group considerably rarely (7 of 25 (28%) than in the second one (106 of 106 (100%), p = 0.0000. On the contrary, nasal pathology development against the background of the current asthma was more frequent in the first group (11 of 25 (44%)) than in the second one (8 of 106 (7.5%), p = 0.0000.

Conclusion: Bronchial asthma, the development of which is closely associated with psychological triggers, is not related to nasal pathology in more than half the cases with frequent secondary involvement of the upper airways and predominance of rhinosinusitis over allergic rhinitis.

P509 Mycobacteria in the pharynx of patients with persistent bronchial asthma who constantly applying the inhaled corticosteroids

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Aim: To investigate fungal colonization the pharyngeal mucosa in patients with persistent asthma, who constantly applying the inhaled corticosteroids (iGCS). Methods: There were examined 30 patients with bronchial asthma (13 men and 17 women, mean age 51.8 years) using iGCS at high and moderate doses of at least year. Mycological study of mucous pharynx (posterior wall of the pharynx, tongue root) for finding of Candida was performed on the Sabourau agar medium. Fungi growing was carried out at 28-30°C for 48 hours. To study the adherence there was used the model of a nitrocellulose film with immobilized hemoglobin.

Results: Fungi of the Candida genus were isolated from the mucosa in 23 patients (76.6%): C. albicans - 22 cases (of which in one case, there was marked the combination of Candida albicans and Geotrichum candidum), C. tropicalis - 1 case. In 73.9% of the cases intensity of the pharynx colonization by yeasts like fungi was high and was 104, 105 CFU/ml. It has been stated that 16 out of 22 isolated Candida albicans cultures (72.7%) have less virulent ability to form tube germination and pseudomorphs in comparison with clinical cultures, isolated from the pharynx of patient with the diagnosis pharyngomikose, the adhesive activity of these cultures shved at the middle level and made 15-32%. 8 out of 22 patients (37.3%) have cultures with a high ability for germination tubes formation and adhesive activity at the level of 35-45%, which corresponded to the level of clinical cultures with high virulence. The causes of differences in the activity of the fungus Candida in asthmatic patients receiving iGCS, require further study.

P510 Omalizumab in severe adult atopic dermatitis associated to mild asthma treated with omalizumab

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Omalizumab is an established add-on therapy efficacious in allergic severe asthma. Its role in treatment of asthma and atopic dermatitis with high IgE levels is not well known. However Isolated case report show the efficacy of anti-IgE in recalcitrant atopic dermatitis, a skin disorder characterized by elevated levels of IgE and significant morbidity.

Aim: We report 5 adult patients 2 male and 3 women, mean age 34.6 (range 19-48yrs), with chronic severe atopic dermatitis and mild to moderate bronchial asthma. For atopic dermatitis they were treated with oral steroids (prednisone mean 17.5 mg die range 10 to 25 mg) and immunosuppressive therapy as Cyclosporine (5mg/die) or Methotrexate (7.5 mg/wks). The patients started treatment with Omalizumab 37.5 mg every two weeks. Pretreatment IgE levels ranged from 282-5390 IU/ml (mean 2501 IU/ml).

Results: After 16 weeks, the serum IgE level decreased mean 1146 IU/ml (range 1421 to 3088) and a significant clinical improvement was registered in all patients with reduction of skin lesions and pruritic score (from 9 indicating severe itching to 3). The patients discontinued immunosuppressive treatment after two months and oral steroids after 6 months. After 1 year follow-up of Omalizumab treatment, the IgE levels were 620 IU/ml (range 140 to 1000) and no adverse events were documented. Moreover, the patients did not refer any asthmatic exacerbations at 1 year follow-up.

Conclusions: Anti-IgE Omalizumab is effective in improving atopic dermatitis unresponsive to conventional therapy in patients with concomitant asthma few weeks of treatment and is able to decrease steroid and immunosuppressive therapy without any interference on asthma control.

P511 The effect of smoking on the levels of cysteinyl leukotriene in exhaled breath condensate in asthmatics

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Aim: Cysteinyl leukotrienes are the most important mediators in pathogenesis of asthma. The aim of this study was to assess the impact of smoking on the levels of LTs in exhaled breath condensate (EBC).

Methods: Thirty smoker (Group I) and 29 nonsmoker (Group II) asthmatics were included in the study. EBC (EcoScreen, Jager) was collected from all of the participants and pulmonary function tests (PFT) were performed too. All of the asthma cases were stable according to asthma control questionaire. Levels of LTD4 and LTE4 were measured in EBC with ELISA.

Results: The levels of LTD4 and LTE4 were shown in Table 1. When we compared the groups according to PFTs we determined statistically significant difference between Group I and III in FEV1/FVC, MMEF and MMEF%. There was a
significant negative correlation between LTE4 levels and FEV1/FVC in Group I.

Leukotriene levels of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTE4 (pg/mL)</td>
<td>79.20±13.16</td>
<td>76.95±14.82</td>
<td>68.21±20.95</td>
<td>0.024</td>
</tr>
<tr>
<td>LTD4 (pg/mL)</td>
<td>66.52±30.10</td>
<td>46.74±34.75</td>
<td>45.02±26.99</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*pThere was a significant difference between the Group I and Group III, Group II and Group III (p=0.05); however, there was no significant difference between other pairwise comparisons (p>0.05).

Conclusion: LTE4 levels were significantly higher in smoking asthma group than the other groups. This result suggest that LTE4 receptor specific blocker agents might be useful in smoking asthma patients and clinical studies are required in this issue.

P512 Role of viral pathogens in infectious exacerbations of bronchial asthma in adults

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Purpose - to investigate the spectrum and frequency of viral pathogens in patients with infectious exacerbation of bronchial asthma (BA) which treated in a pulmonology department.

The study included patients only if they voluntarily consent to the research, objectives and scope of planned inspections.

This work was funded from the state budget.

Virology were performed in all patients fence biomaterial: a smear or swab from the nasal cavity.

Laboratory diagnosis of viral infection was performed by real-time PCR (PCR-
FRT) and a rapid chromatographic immunosassay analysis. PCR was performed in adenoviruses (hAdV), hokavirus (hB0), rhinovirus (hRV), coronavirus (hCoV), RS-virus (hRVc), metapneumovirus (hMpV). The method of immunochromatographic test detected antigens of influenza viruses A and B, respiratory adenovirus (hAdV) and RS-virus (hRVc).

For the purpose of the study was carried out screening all patients which were sent to hospital State Institution “National Institute of tuberculosis and pulmonology behalf F.G. Yanovsky, AMS of Ukraine” with the diagnosis of exacerbation of bronchial asthma from Dec 2010 to Sep 2011 a total of 52 patients observed, which revealed 21 viral pathogens by PCR, 6 viral pathogens by the rapid immunochromatographic test and 2 (hRVc) by both methods.

Viral pathogens detected in the (48,1;6,9)% of patients with exacerbation of asthma. The greatest etiologic importance by the results of virological studies were: rhinoviruses - 68,0%, influenza virus A and B - 12,0%, RS-virus - 8,0%, metapneumovirus - 8,0%, adenovirus - 4,0%, respiratory corona virus - 4,0% of cases.

P513 What is missing in the asthma control test? The relationship between compliance, inhaler technique and level of control

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Introduction: Asthma control test as many other validated questionnaires are used to assess level of control. However, they do not identify factors that may lead to poor control such as medication compliance and inhaler technique. In this study level of asthma control was assessed by using asthma control test (ACT) and simultaneously the accuracy of compliance with preventer medications and inhaler technique were evaluated. The main objective of the study is to find out the relationship between compliance and inhaler technique with the level of asthma control.

Methodology: Prospective 3 months study (1st February – 31st May 2011) was conducted in a university hospital in Oman. Asthmatic adult patients on preventer maintenance medication in chronic asthma (BA) which treated in a pulmonology department.

Purpose: To study relationship between the level of BA control and pattern of breathing. Inhalar technique was evaluated using a standardized checklist. Compliance was assessed using a pre designed scoring system.

Results: 218 patients were assessed. Poor control was found in 126 (58%) patients, of whom 74 (59%) had poor compliance and 34 (27%) had poor inhaler technique. There was no significant difference in the level of control between patients with good and partial compliance (60% vs 59%). Only 35 (16%) patients had good level of control and good compliance and good inhaler technique.

Conclusion: Since compliance and inhaler technique have a direct effect on the level of control, they should be part of all asthma assessment tools.

PS14 Clinical characteristics of severe asthma subphenotypes

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The natural history and clinical subphenotypes of severe asthma are poorly understood particularly among patients that have difficult to control asthma and no other co-morbidities.

To describe the differences in the clinical characteristics of severe asthma subphenotypes on the basis of age at onset of disease.

Cross-sectional clinical study was carried out in 40 patients (age 18 years) with severe asthma. In the retrospective collected data were included the demographics information and assessments of lung function (ie, spirometry and body plethysmography). For lung function were determined airflow resistance (Raw), thoracic gas volume, vital capacity, total lung capacity (TLC), and residual volume (RV). The flow-volume relationships were evaluated with FEV1; FVC and FEV1/FVC ratio.

16 patients with late-onset asthma (40%) had clinical significant compromised lung function whether they had asthma of short duration or long duration, suggesting that significant compromise in lung function occurred at or very soon after the initial diagnosis of asthma had been made. They had more resistance to airflow (Raw, % predicted 307.5 20 vs 285.3 23.0 respectively p<0.024); larger lung volumes (total lung capacity: TLC, % predicted 107.1±2.6 vs 103.8±2.3 respectively p<0.062; and residual volume: RV, % predicted 202.3±10.3 vs 190.1±8.7 respectively p<0.037) compared to early-onset asthma. Late-onset asthma also was characterized by a reduced FEV1/FVC and a history of more frequent sinusopulmonary infections.

Late-onset severe asthma may be associated with a greater degree of airways inflammation and/or more exuberant repair processes, resulting in rapid remodeling of distal part airway, compared to early-onset asthma.

P515 Illness perceptions and medication beliefs: Key determinants of adherence to maintenance medication in chronic asthma

Ad Kaptein. Medical Psychology, Leiden University Medical Centre, Leiden, Netherlands

Outcome in asthma is determined not only by pulmonary function or other biomedical characteristics. Illness perceptions and medication beliefs are crucial in predicting outcomes of asthma management. Illness perceptions pertain to patients’ subjective beliefs and emotional responses to their asthma. Medication beliefs tap idiocentric views on (asthma) medication. Both influence coping and thereby outcome.

I’ll review recent studies on this topic, with a range of respondents and care-providers, with patients with varying degree of asthma severity and in different settings of medical care. Examples of how to assess illness perceptions and medication beliefs will be presented and discussed.

All studies report substantial effects of illness perceptions and medication beliefs on various categories of outcomes. These findings emphasize the clinical relevance of addressing patients’ beliefs about their illness and its medical management, and suggest that this may improve outcome of asthma care. Examples of recent high-quality intervention studies on this topic will be presented, with a view to how to improve quality of care, and thereby quality of life of patients with asthma. In the era of shared decision making and patient empowerment it appears addressing and incorporating illness perceptions and medication beliefs into regular clinical care is a must.

Prof Ad Kaptein, a.kaptein@lumc.nl

P516 Pattern of breathing and respiratory rhythm variability in patients with different level of bronchial asthma control

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Background: It is unknown how the loss of bronchial asthma (BA) control effects on the control of breathing.

Aim: To study relationship between the level of BA control and pattern of breathing and respiratory rhythm variability.

Methods: 97 BA patients and 21 healthy people were examined. BA patients were divided on two groups: 15 patients with controlled BA (CBA) and 82 patients with uncontrolled BA (UBA). The pattern of quiet breathing and respiratory rhythm variability were studied by spirometry. Quiet breathing was registered through the month during 15 minutes.

Results: In the group of healthy people compared with the asthmatics the inspiratory time (1.76±0.1 and 1.54±0.03 sec., respectively, p=0.04) and the effective inspiratory time (0.40±0.009 and 0.38±0.004, p=0.029) were significantly longer and the effective expiratory time (0.60±0.009 and 0.62±0.005, p=0.036) was shorter. In the UBA group in comparison with the CBA group there were shorter...
P517
Anamnestic and clinical peculiarities of severe bronchial asthma in children
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Aim: To study anamnesis and clinical data on severe/moderate severe atopic bronchial asthma with different level of control, determine the main risk factors of the formation of BA non-controlled course in infants.

Materials and methods: We have examined 100 infants, severe/moderate severe atopic BA patients, inhabitants of Krasnoyarsk territory in average ages of 10.9±1.1. We have studied allergy anamnesis, carried out physical and specific allergy examination, estimated the results of instrumental research. In order to determine the level of controlling the disease we had estimated the results of “Test on controlling asthma”. We have formed 2 groups: with controlled BA (n=50) and non-controlled BA (n=50).

Results: Living under unfavorable living conditions (wooden homes with damp, mould, stove heating, overcrowding) had been marked in 34% cases in group with non-controlled BA course and in 26% in group with controlled BA (p=0.012). One or two smoking parents had been marked in 36% cases in controlled BA course and in 48% in non-controlled BA (p=0.007). Analysis of family structure revealed that 48% children of group of good control and 74% of group of absence of control live in sole-parent families (p<0.001).

Conclusions: We have determined anamnesis predictors of non-controlled BA course in children: living in home with stove heating with damp in living area, smoking inside and presence of domestic animals. When estimating social status of the families in BA children with non-controlled course we have stated frequent occurrence of sole-parent families with low income.

P518
Complementary and alternative therapy in bronchial asthma – A study from India
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Introduction: Various complementary and alternative therapies (CAT) are being studied in Asthma management, with reports of varying effects. CAT includes a variety of breathing and relaxation exercises including Yoga, diaphragmatic breathing, progressive relaxation etc. If these can facilitate easy disease control, they can be utilized in bringing down the cost of Asthma treatment, a major issue in resource limited countries like ours.

Aim: 1. Compare the effect of 2 CATs i.e. Butyryko Breathing Technique (BBT) and Diaphragmatic Breathing Exercises (DBE) in asthma treatment
2. Compare the effect of each to conventional treatment alone.

Materials & methods: Prospective, case-control study conducted in an asthma clinic at Alappuza. Patients with persistent asthma aged 25-65 years were randomly grouped into 3.

- Receiving conventional therapy alone
- Above+BET
- Above+DBE

Disease control assessed by spirometry, Mini Asthma Quality of Life Questionnaire (MAQOL), Asthma Control Test and %age use during first week of study and end of third month.

Statistical analysis by 2 way ANOVA technique

Result: Total of 30 patients, 10 in each group studied. No significant difference in FEV1 among 3 groups; statistically significant improvement in quality of life (QOL) among groups B & C, with reduction in % age use.

Conclusion: CAT can be useful in improving QOL among asthmatics.

P519
Depressive symptoms in asthma patients
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Background: Asthma is a chronic disease with worldwide prevalence of 1-1.8%.

Co-morbid depression (prevalence of around 10%) in patients with asthma affects quality of life and treatment outcomes.

Objective: To examine the prevalence of depression and its association with asthma control in patients with asthma versus healthy controls.

Methods: Two groups of subjects were recruited: 1) patients with asthma and no other chronic condition (n = 114) - all of them performed spirometry and answered two questionnaires: ACQ and CES-D20; 2) healthy controls (matched for age, sex, BMI, education and smoking history) (n = 288) without asthma or other chronic disease - they answered only the CES-D20 questionnaire.

Results: The difference between the mean Total CES-D group scores is not significant (p=0.073). 51.9% of the control group had >15p, while 30.7% of the asthmatics had the same result. In the asthma group, 10.5% had major depression, but 58.8% had mild-moderate depression. Total CES-D score correlates well with smoking status (r = -0.574, p<.0001). Total CES-D score did not correlate with mean ACQ score, FEVI, education and sex. The mean ACQ score correlates well with CES-D question11 (r = 0.431, p<.0001). There is statistically significant difference between mean ACQ score in asthmatics with major depression and the rest of the asthmatics.

Conclusions: In this study healthy people tend to have major depression or no depression at all, while asthmatic patients have predominantly mild-moderate depression. Asthmatics with major depression have worse asthma control. This study confirms earlier results concerning prevalence of depression in asthma patients, but questions the higher prevalence in asthma patients compared to healthy controls.

82. COPD comorbidities I

P520
Chronic obstructive pulmonary disease (COPD) as co morbidity (CO) in different patient categories in a university hospital setting. A cross sectional study
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20% of the Danish adults suffers from COPD[1]. 50% of the patients are undiagnosed[1]. COPD patients have multiple CO[2]. To elucidate the frequency of COPD as CO among hospitalized patients. To investigate in which patient categories COPD is a frequent CO. Aalborg University Hospital covers all medical and surgical specialties. A one cross-sectional study was performed on 666 patients. A spirometry was performed. Smoking habits, prior lung function, prescribed lung medicine were recorded. Co-existing diagnoses were registered from case records. Of 583 possible participants 194 couldn't/didn't wish to participate. 111 weren’t present.12 were excluded. 215 participated, 28% (61/215) suffered from COPD (PC), 41% (25/61) of PC had 3 or more COs and 29% (45/153) patients without COPD (PwC) had 3 or more COs (p=0.05).

Table 1. Disease entities in which COPD was a frequent CO. Diagnoses found significantly more often in PC diagnosed at this examination than in general.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PC (%)</th>
<th>PwC (%)</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiologic diseases</td>
<td>40(80)</td>
<td>21(44)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>33(66)</td>
<td>12(26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Endocrine Diseases</td>
<td>14(28)</td>
<td>17(37)</td>
<td>0.005</td>
</tr>
<tr>
<td>Rheumatologic diseases</td>
<td>14(28)</td>
<td>13(26)</td>
<td>0.005</td>
</tr>
<tr>
<td>Uro-nephrologic diseases</td>
<td>15(30)</td>
<td>19(38)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PC suffer from significantly more CO than PwC. Gastrointestinal-, hematologic-, and uro-nephrologic diseases were found significantly more often in PC diagnosed at this examination than in general.

References:

P521
Nutritional status and lipid parameters in COPD patients
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Aim of study was evaluation of nutritional status and lipid parameters in COPD patients and assessment the dependence between above. 114 COPD patients - 69 males (60.5%) and 45 females (39.5%) mean age 65.82, in different stages of the disease participated in the study. It was assessed nutritional status using bioimpedance method (Akern BIA 101) and concentrations of lipid...
parameters in blood serum. Malnutrition was confirmed in 17 (14.91%) patients, more frequent among women than men (58.8% vs 41.2%). Between patients with decreased FFM normal BMI was confirmed in 9 individuals. Deviations in the level of serum lipids was found in 43 participants (37.7%) and it was the most often hypercholesterolemia (33.3%) - in 6 (5.26%) patients hypercholesterolemia with hypertriglyceridemia and 5 cases (4.38%) of hypertriglyceridemia only. PM (fast mass index) didn’t correlate with cholesterol serum level, as well as LDL and TAG levels; unlike the BMI, where weak correlation with cholesterol was noted (p<0.02). FFMI correlated strongly with HDL cholesterol (p=0.004).

Deviations in lipid profile in COPD patients are not exclusively connected with fat contents but may be the consequence of systemic disease.

A total 77 patients with COPD (mean age 54.93±0.63 yrs) was monitored over 5 years in our study. COPD was diagnosed according GOLD criteria. During follow-up 18 patients (23.4%) died. 17 patients due to respiratory insufficiency and/or heart failure and 1 pts due to cancer. Died patients with COPD had higher CCI than alive (4.50±0.46 and 2.44±0.17, p<0.001). Died patients with COPD had CCI 3 score more frequently than alive patients. We noted correlations between baseline CCI and time before patients died (r=0.54, p<0.05).

The Charlson Comorbidity Index has demonstrated good predictive validity in our study. In our opinion, the CCI represents the optimal balance between ease of use and prognostic ability. CCI> score was associated was poor prognoses in patients with COPD.

PS25
Phenotypic characteristics of patients with arterial hypertension and chronic obstructive pulmonary disease

Patients with combination of COPD with arterial hypertension (AH) have a worse clinical course, higher risk of cardiovascular events (CE) than AH without COPD. However, the specific phenotypic characteristics of such comorbidity is still unclear.

Objective: To reveal clinical features, risk of CE in patients AH with and without COPD included in clinical trials.

Methods: A retrospective analysis of five clinical trials conducted in Russia from 2005 to 2010. The analysis included 3409 patients from 40 to 80 years with essential or isolated systolic AH. Age, sex, risk factors (RF), target organ damage (TOD), the presence of associated clinical conditions (ACC) were evaluated.

Results: 2936 from 3409 patients had AH, 385 patients had AH with COPD. In COPD with AH patients had lower age than without COPD (55.4±6.8 and 57.9±6.1, p<0.001, respectively), among them were more males (51.9% and 30.6%, p<0.001), more frequent smoking history (89.1% and 17.9%, p<0.001), higher SBP and DBP (164.6±11.1 and 160.3±12.8 p<0.001; 98.7±7.9 and 96.1±8.1 p<0.001), more HR (76.6±9.6 and 75.0±8.8 p<0.001). In COPD group there were more patients with 3 or more RF (91.4% and 76.1%, p<0.001) more often TOD (90.4% and 77.3%, p<0.001). Differences in ACC were not observed.

Conclusion: Patients COPD with AH phenotypically have lower age, more severe condition and have higher risk of CE. Differences in age are possibly due to the fact that patients with COPD have a worse clinical course and older patients are not included in clinical trials in the criteria of inclusion/exclusion, which may affect the representativeness of the results with respect to AH with COPD subgroup of patients.

PS26
Platelets count in chronic obstructive pulmonary disease

Emesto Crisafulli,1 Marco Marietta,2 Elena Venturelli1,2/MIhai Roca,3 Bianca Beghe,2 Monica Borrillonti2, Alessia Verderi2, Mario Malerba4, Michele Malagola4, Leonardo Fabbri, Enrico Clini1,2,1Pulmonary Rehabilitation, Ospedale Villa Pineda, Paravolo - Modena, Italy; 2 DM Oncology, Haematology and Pneumology, University of Modena, Italy; 3 Dept of Pneumology, University of Iasi, Romania; 4 Dpt Internal Medicine, University of Brescia, Italy; 4 Dpt. Haematology, University of Brescia, Italy

Platelets count (PTL) and activity in complex COPD is still a matter of debate in recent years. We have therefore undertaken a preliminary retrospective analysis in

P524
Prognostic value of the Charlson Comorbidity Index in patients with COPD

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Few studies show patient outcomes over time in chronic obstructive pulmonary disease (COPD). The traditional pulmonary function test assessed by tge FEV1 is known to correlate poorly with dyspnea, health status and exercise intolerance.

In the present study we evaluated by Charlson Comorbidity Index (CCI) as a predictive marker of death in patients with COPD.
Background: Several studies have suggested that a low percentage of peripheral lymphocytes (LYM%) is associated with malnutrition, inflammation, and mortality in diseases such as cancer and chronic kidney disease. In COPD cases, malnutrition is very common, and its prevalence increases with disease severity.

Objectives: We evaluated whether the LYM% is associated with disease severity and nutritional status in patients with COPD.

Methods: We recruited clinically stable male outpatients with COPD for a cross-sectional study. We conducted the following examinations: blood tests, pulmonary function tests, computed tomography image analyses, anthropometric measurements, the 6-minute walk test (6MWT), and dyspnea evaluation. We examined the correlations between the LYM% and the clinical variables.

Results: We evaluated 72 patients (mean age, 70.6 years). The LYM% was significantly correlated with FEV1% predicted (Pearson’s coefficient, r = 0.496; p < 0.005), percentage of low attenuation area (r = −0.306; p = 0.015), body mass index (r = 0.252; p = 0.034), fat-free mass index (r = 0.404; p < 0.0005), distance covered during the 6MWT (Spearman’s rank correlation coefficient, ρ = 0.491; p < 0.0005), and the modified Medical Research Council (MMRC) dyspnea score (r = −0.439; p < 0.0005). Stepwise multiple regression analysis showed that FEV1% predicted significantly correlated with the LYM% (R² = 0.252).

Conclusions: A low LYM% is associated with impaired nutritional status, exercise capacity, and pulmonary function. The LYM% may serve as a clinically convenient and useful biomarker for predicting disease severity in patients with COPD.

P530 Relevance of respiratory muscle strength in chronic obstructive pulmonary disease

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Backgrounds: Respiratory muscle strength is recognized to be impaired in patients with COPD, while its severity in Chinese COPD patients and the related factors contributing to this clinical situation is not clearly established. Respiratory muscle stimulation is a non-volitional technique to measure respiratory muscle strength. Thus, the present study was aimed to quantify the severity of respiratory muscle weakness at different stages of COPD, and to investigate the potential factors related to TwPM in COPD.

Methods: Seventy-five patients with COPD and sixty-three age-matched controls participated in the study. Pulmonary function was tested for each participant. Respiratory muscle strength was assessed with measurement of both TwPM and non-volitional static mouth pressures. A score of physical activity (PA score) was obtained using an adapted physical activity questionnaire for the elderly, and nutritional status was evaluated with a multiple-nutritional index. Multiple regression models were developed by stepwise method to determine factors independently contributing to TwPM in COPD.

Results: TwPM (cmH2O) was significantly lower in COPD patients (COPD II (12.42±2.19); COPD III (10.85±1.82); COPD IV (8.58±1.46) vs controls (13.95±3.28); P<0.005). Regression correlation analysis showed that FEV1% predicted, PA score, malnutrition index and gender were the independent factors responsible for TwPM, with R² of 58% (P<0.001).

Conclusion: We conclude that respiratory muscle strength decreases with increasing severity of COPD. Respiratory muscle strength in COPD is comprised by multiple factors such as airflow limitation, physical inactivity and malnutrition, with airflow limitation being the most significant one.

P531 Comorbidity and some markers of cardiovascular disorders in disabled COPD patients

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Aim: To assess the comorbidity level and its correlations with markers of cardiovascular disorders in disabled COPD patients.

Methods: A retrospective analysis of 53 disabled patients’ medical documentation with COPD II and III stages was performed (age 55.6±1.8, 40 male). The complex assessment of comorbidity level was performed by Charlson index (CI) and BODE-index.

Results: Most of patients (70.5%) had comorbidity level of 2-3 points by CI, so their 10-year prognostic survival diminished to 10-23% compared with healthy
individuals. 11.8% of patients had a CI value equal to 5 points, and 5.9% - equal to 8 points, which is extremely high. One-point comorbidity was recorded in only 5.9% of patients. The CI was significantly correlated with Kelle’s index (r = 0.87, p < 0.05), the level of total cholesterol (r = 0.71, p < 0.05), plasma β-globulins level (r = -0.71, p < 0.05), 6-minute walk distance (r = -0.72, p < 0.05), and the size of the left atrium of the heart (r = 0.70, p < 0.05). As for the BODE-index, 38.9% of patients had its value laying in the range of 47.4 points, indicating a progressive decrease in survival of these patients by 40% or more compared with healthy individuals. The correlation analysis showed a direct reliable link of BODE-index and CI (r = 0.76, p < 0.05).

Thus, patients with COPD have a high level of comorbidity, which is closely related to some markers of cardiovascular diseases, protein metabolism disorders, and physical exercise tolerance. The received data suggest that in rehabilitation of COPD patients we should focus on treatment of comorbid conditions in order to increase the life expectancy of patients and reduce the risk of their mortality.

P532
Prevalence of anxiety and depression in 196 patients with chronic obstructive pulmonary disease (COPD)
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Introduction: Anxiety and depression are common co-morbidities associated with COPD. A systematic review and meta-analysis reported prevalence 36% for anxiety and 40% for depression (1).

Aims and objectives: This prospective study aimed to identify the prevalence of anxiety and depression symptoms in COPD patients attending out-patient respiratory clinics within a UK NHS Trust.

Methods: Patients with COPD were screened in Clinic in 2011 by completing the Hospital Anxiety & Depression Scale (HADS) (2). Data from 196 patients were analysed.

Results: The mean age was 65.3 years (range 31 - 97) and 88 (45%) male. Using NICE 2010 airflow severity criteria 28 had mild obstruction; 69 moderate; 59 severe and 42 very severe. Significant rates of anxiety were seen: 78% of patients had HADS-anxiety (HADS-A) scores 8 or over and 55% had HADS-depression (HADS-D) scores 8 or over. Both the HADS anxiety & depression scores decreased with increasing age (r=0.28, p<0.01 for HADS-A; r=0.29, p<0.01 for HADS-D).

Mean HADS Results

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients</th>
<th>Mean HAD-A</th>
<th>Mean HAD-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>7</td>
<td>11.7</td>
<td>9.4</td>
</tr>
<tr>
<td>50-59</td>
<td>25</td>
<td>13.1</td>
<td>10</td>
</tr>
<tr>
<td>60-69</td>
<td>35</td>
<td>9.9</td>
<td>8.5</td>
</tr>
<tr>
<td>70-79</td>
<td>69</td>
<td>9.8</td>
<td>6.6</td>
</tr>
<tr>
<td>80-89</td>
<td>37</td>
<td>9</td>
<td>7.2</td>
</tr>
<tr>
<td>≥90</td>
<td>2</td>
<td>2.8</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Conclusion: The prevalence of anxiety and depression is higher in this population than in prior studies. Symptoms of anxiety and depression appear commoner in younger patients and are unrelated to COPD airflow severity. There were no significant associations with COPD NICE severity stage or gender. It is important to screen for both in COPD patients and consider appropriate treatment.

References:

P533
Degree of LVEF with respect to severity of COPD
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Background: Cardiovascular diseases are important co-morbidities in patients with COPD. Detection of the presence of Heart Failure with respect to severity of COPD provides valuable information regarding necessary therapeutics.

Aim of study: The primary aim of this study was to determine the quantum of LVEF, which is an indicator of left ventricular function, in relation with the severity of the COPD as measured by the FEV1.

Methods: The study included 112 patients of COPD admitted in the Chest Unit of the hospital, which is a tertiary care centre. All the patients were subjected to thorough history, clinical examination, investigations- ECG, 2-D ECHO of heart, ABG, RFT, LFT, CBC, RBC etc. were done and data were analysed.

Results: Most patients were elderly with mean age of 62.77 years. 53.6% (60/112) of patients categorized in GOLD STAGE 1,2 had mean LVEF 59.07 (SD-10.52,SEM-1.552),while 46.5% (52/112) of those in GOLD STAGE 3,4 had mean LVEF 53.55 (SD-8.4,SEM-1.330). This difference between both groups was significant statistically T test (P=0.009) (CI= -9.643 – -1.388)(Pearson correlation coefficient 0.363 (p=0.001).

Conclusion: The study clearly indicate that severity of the COPD as measured by FEV1 is directly related to the severity of the left ventricular function as measured by LVEF.

P534
COPD and depression
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Background: Patients with chronic obstructive pulmonary disease (COPD) have been characterised as a population of chronically ill patients with a higher than normal prevalence of depression.

Objective: To reveal associations of depression with severity, health-related quality of life and mortality of COPD patients.

Methods: A group of 39 COPD patients was analysed during one year. St George’s Respiratory Questionnaire [SGRQ] and mMRC scale was done in order to assess quality of life and dyspnoea level. We used the Hospital Anxiety and Depression Scale [HADS] and Geriatric depression score [GDS] for depression assessment.

Results: The highest value of depression score were in patients with very severe COPD.

Severity of COPD and depression

<table>
<thead>
<tr>
<th>Mild and moderate COPD</th>
<th>Severe COPD</th>
<th>Very severe COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS</td>
<td>9.1±6.2</td>
<td>14.0±8.0</td>
</tr>
<tr>
<td>HADS - depression</td>
<td>5.5±4.0</td>
<td>9.7±5.0</td>
</tr>
</tbody>
</table>

Statistical significant correlation was between dyspnoea level and depression score [HADS] [r=0.437, p=0.01]. Also, we found positive correlation between health-related quality of life [SGRQ] and depression score [HADS]: symptoms- depression [r=0.654, p=0.000], activity- depression [r=0.624, p=0.000], impact - depression [r=0.556, p=0.000], total score - depression [r=0.634, p=0.000]. We found statistical significant higher value of initial depression score [HADS] in patients who have been died [n=6] during this study [t test, p<0.05].

Conclusions: These data suggest that depressive symptoms in COPD are related to severity of disease. Depression is also associated with dyspnoea level and quality of life. The data suggest that assessment for depression should be considered for all COPD patients, particularly in those with more severe clinical levels of disease.

P535
Gastroscopic findings in COPD patients
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Introduction: The aim of this study was to determine the prevalence of GERD symptoms and esophagitis in COPD patients and their effect on the number of exacerbations of COPD.

Materials and methods: This study included 106 COPD patients 55of them (51.88) with moderate COPD and15of them (31.91) with severe COPD and7of them (14.89) with very severe COPD. All groups were subjected to history taking, full clinical examination, investigations- ECG, 2-D ECHO of heart, gastroscopy and spirometry.

Results: Revealed that the prevalence of GERD symptoms in COPD patients was 45.5% in the moderate group,54.8% in the severe group and 57.9% in the very severe group (total=52.73%), and prevalence of esophagitis in COPD patients by endoscopy was 32% in the moderate group, 26.7% in the severe group and 42.9% in the very severe group (total=33.86%). GERD symptoms and esophagitis increase with increase in the smoking (pack/year) both in moderate & in the severe groups. Moreover, there were increase in the frequency of exacerbations of COPD in positive GERD symptoms patients both in moderate & in the severe groups. Presence of esophagitis increases the frequency of emergency visits and hospitalization of COPD patients.

Discussion: GERD is common in COPD patients being more among severe group,also GERD increases the number of exacerbations.

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Effect of antidepressants on respiration with chronic physical disease
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Physical illness is strongly associated with depression. In Korea, 23.8% of COPD patients suffer from depression. Aside from being an unpleasant condition in its own right, depression is a risk factor for poor progression of physical diseases. Therefore, it has been emphasized that management of depression in patients with physical illness. Antidepressives such as diazepam is well known to have respiratory suppression. But little is known for the anti-depressant to have such effects. The aim of this study was to evaluate the effects of anti-depressants on respiration in patients with chronic physical illness. We performed systematic review of randomized controlled trial. A literature search was conducted for key words “depressive disorder, pharmacological therapy and chronic illness” using Medline, pubmed, Embase, Cochrane library, and National Guideline Clearinghouse (NGC). A total 69 studies were retrieved. Of these, nine studies were included for final analysis (six studies for COPD, three studies reporting dyspnea as an adverse event). Anti-depressants didn’t worsen the respiratory symptoms nor cause respiratory suppression in patients with COPD. Anti-depressants had no effects on pulmonary function, exercise capacity and the results of blood gas analysis in COPD patients. In patients with chronic illness other than COPD, antidepressants caused less dyspnea compared to placebo (13% vs. 17.6%; p<0.0001) and did not develop the respiratory suppression. In conclusion, anti-depressants did not aggravate dyspnea in patients with chronic physical illness including COPD. However, it is not sufficient to conclude that anti-depressants are safe in physically ill patients. A large prospective study is warranted.

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Assessment of the BODE index, arterial stiffness and endothelial dysfunction in patients with chronic obstructive pulmonary disease
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Purpose: COPD is a respiratory disorder, but also having systemic effects. Cardiovascular diseases are leading cause of mortality in patients with COPD and have an association with the increased risk of cardiovascular disease. Aim of this study was to evaluate the effects of anti-depressants on respiration in patients with chronic physical illness. We performed systematic review of randomized controlled trial. A literature search was conducted for key words “depressive disorder, pharmacological therapy and chronic illness” using Medline, pubmed, Embase, Cochrane library, and National Guideline Clearinghouse (NGC). A total 69 studies were retrieved. Of these, nine studies were included for final analysis (six studies for COPD, three studies reporting dyspnea as an adverse event). Anti-depressants didn’t worsen the respiratory symptoms nor cause respiratory suppression in patients with COPD. Anti-depressants had no effects on pulmonary function, exercise capacity and the results of blood gas analysis in COPD patients. In patients with chronic illness other than COPD, antidepressants caused less dyspnea compared to placebo (13% vs. 17.6%; p<0.0001) and did not develop the respiratory suppression. In conclusion, anti-depressants did not aggravate dyspnea in patients with chronic physical illness including COPD. However, it is not sufficient to conclude that anti-depressants are safe in physically ill patients. A large prospective study is warranted.

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Variability in systemic inflammatory response, nutritional profile, and quality of life in stable COPD due to tobacco and non-tobacco etiology
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Anemia is frequently associated with many chronic diseases and can be responsible for weakness, fatigue, impaired mood, deficits in cognitive function and decreased quality of life. Anemia is also common in COPD and is associated with increased comorbidity, mortality, and costs of care, its prevalence in COPD patients is estimated at 13 to 23%. The aim of our study was to evaluate the presence of anemia in COPD patients and analyze its relationship with functional status. Methods: Study group consisted of 132 patients (37% F), at mean age 68.2±9 years with post-bronchodilator FEV1 57.1±19.2% of predicted. Anemia was defined by hemoglobin concentration <13.5 g/dL in male and <12 mg/dL in female patients. Biochemical analysis included measurement of serum C-reactive protein, iron, transferrin, and soluble transferrin receptor. Pulmonary assessment comprised spirometry, plethysmography and 6 minute walk test (6MWT). Results: Anemia was diagnosed in 24 (18.2%) patients: 4 female and 20 male patients (p<0.05). There were no differences in the distribution of anemia depending on the severity of COPD (according to the GOLD staging system or BODE index). Patients with anemia were older (66.7±8.9 vs 74.5±5.6 years; p<0.05), had higher serum creatinine level (0.9±0.2 vs 1.0±0.2 mg/dL; p<0.05) and lower 6MWT distance (365.5±123 vs 439.5±115.4 m; p<0.05). Patients with anemia were also characterized by lower serum iron (90.2±30.7 vs 113±41.2 µg/dL; p<0.05) and higher serum transferrin receptor (3.7±1.2 vs 3.1±0.9 mg/L; p<0.05). Conclusions: Anemia in COPD is more prevalent in males and can affect up to 20% of patients. It does not seem to depend on the severity of disease, however, it significantly reduces exercise capacity of patients.

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Anemia in chronic obstructive pulmonary disease
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The presence of COPD is associated with increased systemic inflammatory response, muscle wasting, lower exercise capacity and poorer QOL. The etiological agent of COPD, however, does not seem to be an important factor in affecting the above parameters.

83. COPD comorbidities II

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The role of modification of CURB-65 score as predictor factor for one year survival in acute exacerbation of COPD
Wiwien Heru Wiyono1, Widyah Sri Hastuti1, Ramawati2, Iwang Gunawij2, Toodo Prihartono3 1Pulmonology and Respiratory Medicine, Fac. of Med Univ. of Indonesia/Persahabatan Hospital, Jakarta, Indonesia; 2Department of Community Medicine, Faculty of Medicine University of Indonesia, Jakarta, Indonesia

Introduction: Acute exacerbation of COPD (AECOPD) is associated with a high risk of mortality. A risk-prediction model using information easily obtained on admission could help to identify high-risk individuals. The CURB-65 score was developed to predict mortality risk in community acquired pneumonia. A retrospective study found that this score was also associated with mortality in AECOPD patients. Methods: Consecutive patients with physician diagnosed AECOPD admitted to a public hospital during a 1-year period were studied prospectively. The modification of CURB-65 Score were calculated from information obtained at initial hospital presentation. The modification of CURB-65 Score are one point each for Confusion, Age >79 mmol/L, Respiratory rate ≥30/min, Systolic Blood pressure <90 mmHg, Severe diabetic or blood pressure >160 mmHg, age ≥65 years and present of cardiovascular disease. Remeasure will be done every three month and looking for the correlation between both using McNemar test. After complete one year of evaluation, the relation between modification of CURB-65 score and risk of mortality was analyzed using Chi Square test. Results: Research is still proceeding and 92 patients have been collected. 30-day
mortality data were available for 92 of 92 patients. The 30-day mortality by score groups were: low risk (scores 0–1) 1.16% (2/178) and high risk (scores 2–6) 11.36% (5/44). There was significant correlation between modification of CURB-65 score and mortality, with relative risk 2.73. The investigation is ongoing, and not all questions have been answered.

**CONCLUSION:**

The frequency of osteoporosis was assessed in the whole group and separately for each stage of COPD. **RESULTS:** In the whole group was most impressed by osteoporosis, lumbar spine - in 37.2% of cases, osteoporosis of the femoral neck - in 19.7% of cases. The lowest BMD were observed in patients with stage 4 COPD (<0.05). Osteoporosis of the femoral neck was detected in 5.4% of patients with COPD stage 2, with 23.68% of patients with COPD stage 3, the maximum percentage of osteoporotic changes in the femoral neck was observed in patients with COPD stage 4 - 54.5%. A significant correlation values of bone mineral density with BMI (r=0.44, <0.05), with the CO (r=0.43, <0.05), with the DLCO (r=0.43, <0.05).

**Conclusion:** Densitometry is an important method of diagnostics of osteoporosis and should be applied in full in COPD patients.

**P542**

Is COPD a risk factor for diabetes?

**Laura Ciobanu** 1, Eva López González 2, Silvia Rey 1, Ekaterina Kochetova 1

**Chair of Internal Medicine, Petrozavodsk, Karelia, Russian Federation**

**Introduction:** Diabetes mellitus is one of the multiple endocrinological disorders induced by COPD through systemic inflammatory, oxidative stress, smoking and administration of glucocorticoids.

**Aims and objectives:** To investigate if COPD is a risk factor for diabetes mellitus DM and which factors are some other contributing factors.

**Methods:** 2 groups of pts were assessed for age, gender, body mass index (BMI), smoking, alcohol intake, diabetes and dyslipidemia. First group was compound of non-COPD pts (n 272, male:22.8, female: 210, mean age 60.67, SD 13.75) and the second one of COPD pts (n 178, 103 M:57.9, 75 F:42.1%, mean age 64.79, SD 10.78). COPD pts were staged according to GOLD criteria in stage I 122/2171 pts, stage II 206/2% pts, stage III 224/9% and stage IV 61/3%.

**Results:** The relative risk of DM in COPD pts is 3.380 (95% CI 1.380–8.906). COPD stage 1, 2.52 (95% CI 0.904–7.335) in stage II and 2.04 (95% CI 0.863–4.930) in unified stages III and IV. There is a correlation coefficient of 0.154 between COPD and DM, 0.256 for COPD, BMI and DM and respectively 0.293 for COPD, BMI, dyslipidemia and DM.

**Conclusions:** There is a small risk for DM to appear in the whole group of COPD pts, but RR increases while advancing the severity of disease. Being mild in stages I and II, RR become moderate in the unified group of pts staged III and IV, considered together due to the low number for each separate stage. Correlation between DM and COPD is weak, but it is moderate and relevant when adding BMI and dyslipidemia. The risk to develop DM in COPD increases with the severity of disease, and the presence of two other important factors, BMI and dyslipidemia.

**P543**

Is COPD a risk factor for diabetes?

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**Aims and objectives:** To investigate if COPD is a risk factor for diabetes mellitus DM and what stage is more risky; also, if there are some other contributing factors.

**Methods:** 2 groups of pts were assessed for age, gender, body mass index (BMI), smoking, alcohol intake, diabetes and dyslipidemia. First group was compound of non-COPD pts (n 272, male:22.8, female: 210, mean age 60.67, SD 13.75) and the second one of COPD pts (n 178, 103 M:57.9, 75 F:42.1%, mean age 64.79, SD 10.78). COPD pts were staged according to GOLD criteria in stage I 122/2171 pts, stage II 206/2% pts, stage III 224/9% and stage IV 61/3%.

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**Conclusions:** There is a small risk for DM to appear in the whole group of COPD pts, but RR increases while advancing the severity of disease. Being mild in stages I and II, RR become moderate in the unified group of pts staged III and IV, considered together due to the low number for each separate stage. Correlation between DM and COPD is weak, but it is moderate and relevant when adding BMI and dyslipidemia. The risk to develop DM in COPD increases with the severity of disease, and the presence of two other important factors, BMI and dyslipidemia.

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Bronchitic and non-bronchitic phenotypes of COPD differ in the prevalence of depressive symptoms

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1Pulmonary Department, University Hospital and Faculty of Medicine, Hradec Kralove, Czech Republic; 2Department of Research and Development, University Hospital and Faculty of Medicine, Hradec Kralove, Czech Republic

**Background:** Psychological sequelae of COPD may influence functional status independent of disease severity. Presence of depression among several phenotypes of COPD is not clearly understood.

**Aim:** We wanted to find out the real occurrence of depression in both basic clinical phenotypes of COPD.

**Methods and material:** Multicomponent assessment of 38 consecutive patients (6 female, 32 male; age 62.7±6.3 years) with stable COPD GOLD categories A 1, B 21, C 1, D 61 in the out-patient clinic of university hospital (within non-interventional cross-sectional Complexity of COPD Study).

**Results:** 27 patients had bronchitic and 11 subjects suffered from non-bronchitic phenotype of COPD (post- ipratropium and salbutamol FEV1 57.7%). Bronchitic variant was associated with lower level of depressive symptoms (Beck scale 5.1±3, Zung scale 50.2±10.9) than that found in non-bronchitic subtype of COPD (Beck scale 8.3±3.4, Zung scale 57.5±7.4). Although this difference reached statistical significance only in Beck questionnaire p<0.013 (Mann Whitney test). In all other parameters (BMI, FFMI, education level, inhalation risk, 6MWD, exercise desaturation, nMBR dyspnea, Celi’s BODE, Pahan’s BODE, ADD, CAT, all domains of SGRQ, arterial blood GEs, ECG heart rate) were no differences between these two basic phenotypes.

**Conclusion:** Non-bronchitic phenotype of COPD was associated with more depression complaints than bronchitic scenario. This difference was not apparent in terms of quality of life, prognostic indices and number of other variables describing course of COPD.
PS46 The influence of metabolic syndrome in mortality rate of COPD patients:
A five years follow up study
Karime Schelini, Suzana Tanti, Amanda Zamaner, Liana Coelho, Simone Vale,
Renata Ferrari, Laura Caram, Ilda Godoy, Sergio Paiva, Irma Godoy.
Pulmonary Division of Internal Medicine, Botucatu Medical School - UNESP,
Botucatu, SP, Brazil.
Background: Patients with chronic obstructive pulmonary disease (COPD) or metabolic syndrome (MS) present systemic inflammation and the association between diseases can increase risk of cardiovascular events. However, the influence of MS in survival of COPD patients is still unclear.
Methods: We followed 115 COPD patients (age: 64.5±1.21 years, FEV1: 58.7±2.75% during five years and causes of death were noted. At baseline, patients' clinical history and physical examination were assessed, and anthropometric (weight, height, body mass index and waist circumference), spirometry, 6-minute walking distance (6MWd), dyspnea perception by the modified medical research council (MMRC), serum lipid profile and triglycerides measurements were performed. The diagnosis of MS was established by harmonization MS criteria. The Cox proportional hazard analysis was used to evaluate the influence of MS in the survival time, adjusted for potential confounders (age, gender and BODE index).
Results: MS was present in 35.6% of patients and hypertension (47.4%) was the MS component more prevalent. More than 80% of the patients presented at least one diagnostic component of MS. During the period of study, 17.0% died. We did not observe statistical difference in mortality between groups with and without MS (HR: 1.30, 95%CI: 0.32-5.20).
Conclusion: Patients with COPD have intermediate prevalence of MS; however, no association between MS and mortality was found in these patients.

PS47 COPD: Different psychosocial status (PS) in patients with different cardiac co-morbidities rate
Kateryna Gashynova, Internal Medicine, DMA, Dnipropetrovsk, Ukraine.
Aim: To evaluate whether and in which extent cardiac co-morbidity have influence on the PS in patients with COPD.
Study population: 78 outpatient with COPD made the study sample. Exclusion criteria were 1) mental diseases.
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. Cardiac co-morbidity rate was established by original analysis of patient's medical documentation.
Results: In accordance with cardiac co-morbidity rate all patients were divided on two groups (GR): GR I (n=17; 21.8%) without any and GR II (n=61; 78.2%) – with cardiac co-morbid conditions. Both groups were similar regarding to age, sex and smoking status. The data of psychological tests are performed in the table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Depression (Mean)</th>
<th>Personal anxiety (Mean)</th>
<th>Situational anxiety (Mean)</th>
<th>Vegetative lability (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, n=17</td>
<td>22.8±4.5</td>
<td>21.6±2.3</td>
<td>19.4±3.6</td>
<td></td>
</tr>
<tr>
<td>II, n=61</td>
<td>44.9±9.9</td>
<td>27.6±4.2</td>
<td>25.1±3.7</td>
<td>28.9±3.1</td>
</tr>
</tbody>
</table>
*p<0.005; Δp=0.05, ^p<0.05

Conclusions: 1. 78.2% of outpatients with COPD had cardiac co-morbidity.
2. Cardiac co-morbid conditions significantly impair psychology status in patients with COPD, and the most significant changes concerns depression and vegetative lability level.

PS48 Pulmonary hypertension in COPD: Prevalence and characteristics
Daniela Gologanu.
Pulmonary hypertension in COPD: Prevalence and characteristics
Daniela Gologanu
Aim: To evaluate the prevalence of PH in COPD patients (pts) and define the characteristics of this group.
Methods: Retrospective study including 66 consecutive COPD pts hospitalised in our department, right heart catheterization, echocardiography, graphy, history of exacerbations and comorbidities were obtained from patients records. PH was defined as systolic pulmonary arterial pressure (SPAP) greater than 35 mmHg.
Results: Among 66 COPD pts studied, mean age was 67 years and GOLD stages were II - 26 pts, III - 15 pts, IV - 22 pts. Only 53 pts had undergone echocardiography. Among them, mean age was 68, GOLD stages were II - 11 pts, III - 7 pts, IV - 15 pts. PH was found in 12 pts (36,4%). Mean FEV1 was 46,4% in COPD pts without PH and 36,9% in pts with PH (p=0.07). PH resulted in right ventricular (RV) enlargement in 9 out of 12 pts, these particular COPD pts had lower mean FEV1 (37,6%) than pts with PH without RV enlargement (56%) (p = 0.02). More severe PH was found in 7 pts; the mean FEV1 was 37,2% versus 36,7% in pts with moderate versus mild PH. No significant association between PH and GOLD stage, FEV1, polyglobulia, COPD exacerbation or basal SpO2 were found.
Conclusions: The prevalence of PH in our COPD pts was 36,4%, probably underestimated, as echocardiography was performed mostly in pts with higher GOLD stage. No significant associations between PH and GOLD stage, FEV1, polyglobulia, COPD exacerbation or basal SpO2 were found. RV involvement due to PH seems to occur mostly in pts with more severe obstructive disease.

PS49 Cognitive function of patients with COPD after virtual admission – A randomized clinical trial
Lone Schol1, Birte Østergaard2, Lars Rasmussen1, Susan Rydahl-Hansen3, Amanda Svaare Jakobsen1, Christina Emmel2, Klaus Phanare1, 1Telemedicine Research Unit, Fredriksberg University Hospital, Copenhagen, Denmark; 2Research Unit of Nursing, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; 3Department of Anaesthesia, Center of Head and Orthopaedics, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; 4Research Unit of Clinical Nursing, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark.
Background: Substantial healthcare resources are spent on Chronic Obstructive Pulmonary Disease (COPD). As a result, the involvement of patients in monitoring of their condition has been suggested. However, the level of cognitive functioning must be taken into consideration before self-care strategies can be adopted.
Aim: We hypothesized that cognitive performance would be better in COPD patients allocated to virtual admission - using a telemedicine solution - compared to patients admitted to conventional hospitalization after exacerbation.
Methods: This study was a Randomized Clinical Trial. The primary outcome was cognitive function evaluated at discharge and after six weeks using a neuropsychological test battery comprising 4 tests and 7 variables. Secondary outcomes included self-reported cognitive function (SCF), activities of daily living (IADL), and anxiety and depression (HADS).
Results: We included 44 patients consecutively. Baseline data were: Mean age 70 years (SD 10); forced expiratory volume in one second (FEV1) 1.0 L (SD 0.55); Oxygen saturation 94.5 (SD 2.5); and a Mini Mental State Examination score of 27.5 points (SD 1.6). The performance in all seven neuropsychological test variables tended to be better in the group allocated to virtual admission, but the difference was only statistically significant in the time for the Stroop Color Word test, (p=0.05). The pattern was the same at follow-up after six weeks but the differences were less pronounced. There were no significant differences in SCF, IADL, and HADS at discharge or after 6 weeks.
Conclusion: Cognitive function may be better preserved in COPD patients treated for exacerbation during virtual admission at home.

PS50 Longitudinal changes in detrended fluctuation analysis “alpha” of PEF in COPD
The full abstract can be found on page 890.

PS51 Anxiety and dyspnea relation in early stage COPD patients
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Introduction: Anxiety is a co-morbid diseases in COPD. Anxiety prevalence in COPD patients is higher than general population. Although the relationship between anxiety and COPD can not be revealed yet, increased anxiety prevalence was associated with increased dyspnea level.
Aim: To determine the rate of anxiety and relationship of anxiety and dyspnea in early stage COPD patients who do not have advanced functional restriction.
Method: COPD patients that volunteered to participate the study who admitted to hospital with a reason other than COPD exacerbation was included to this cross-sectional/descriptive study consecutively. Beck anxiety inventory, medical research council (MRC) dyspnea scale applied.
Results: 134 patients with GOLD1-2 COPD included. Mean age was 58.1±10.53, 92.5% of them were male. Active smokers and former smokers were 61.9% and 38.1%, respectively. 64.9% did not have co-morbid diseases. According to MRC dyspnea scale 33.6% of the patients were in grade 1 and 55.2% were in grade 2. 34,1% of the patients that answered the question “Do you have shortness of breath?” answered as “No” were having MRC grade 2 and 3 dyspnea. 11.2% of 134 participants had mild and 9% had moderate anxiety. In patients with anxiety 89% were having MRC grade≥2.Although there was not statistically significant relationship between shortness of breath and level of anxiety, there was a significant relationship between MRC grade and level of anxiety (p=0,529 and p=0,004, respectively).
Conclusion: MRC scale can be more effective in detection of dyspnea in early stage COPD. All COPD patients with MRC score ≥ 2 should investigate for anxiety.
Acute pulmonary embolism in COPD patients

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COPD is an established cause of worse evolution during acute pulmonary embolism (PE). The aim of our study was to evaluate the profile of COPD patients admitted for PE. We conducted a retrospective cohort study in consecutive patients (n=225) diagnosed with PE between January 2009 and December 2010. Of 225 subjects included (mean ± SD: 72 ± 15 years), 27 (12%) had COPD (71 ± 10 years). The total number of deaths during hospitalization was 38 (17%) in patients without COPD, and 7 (25%) in COPD patients (p<0.05). COPD Patients (78% males) showed severe disease (FEV1 < 46.1 ± 12%) previously. Previous venous thromboembolic disease (VTD) (37%) or surgery (3%), cancer (26%) or immobility (18%) were detected. Obesity was the most frequent co morbidity (50%). Non-survivors COPD showed statistically significant increase of NTpro-BNP (2500 ± 530 pg/ml) and CRP (8.6 ± 7.5 mg/l) than COPD survivors patients (850 ± 140 pg/ml and 2 ± 1 mg/l, respectively). Severity disease was similar in both groups (FEV1 < 45% vs 47%, respectively). Previous VTD (relative risk RR, 1.1; 95% CI, 1.0–2.0), obesity (RR, 2.1; 95% CI, 1.0–5.0), cancer (RR, 2.6; 95% CI, 1.3–5.1) and elevated CRP (RR, 3.3; 95% CI, 1.4–6.6) were significantly associated with PE-related death, with heart failure or prolonged hospital stay. The number of COPD patients diagnosed for acute PE was slightly higher than previously reported. In addition, COPD patients might be an under recognized group with increased mortality.

COPD subphenotypes in a population-based survey by factor and cluster analysis

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2Respiratory Medicine, University Medical Center Utrecht, Utrecht, Netherlands;
3Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands;
4Respiratory Medicine, Erasmus Medical Centre, University of Rotterdam, Rotterdam, Netherlands;
5Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Netherlands

Background: Classification of COPD is currently based on symptoms, airways obstruction and exacerbations. However, this may not fully reflect the phenotypic heterogeneity of COPD in the (ex-) smoking community. We hypothesized that factor analysis followed by cluster analysis of functional, clinical, radiological and exhaled breath metabolic features identifies subphenotypes of COPD in a community-based population of heavy (ex-)smokers.

Methods: Adults (50-75 yrs) with ≥15 packyears derived from a random population-based survey underwent pulmonary function testing, chest CT scanning, questionnaires and exhaled breath molecular profiling using an electronic nose. Factor analysis followed by K-means cluster analysis was performed on subjects fulfilling the GOLD criteria for COPD with post-BD FEV1/FVC <70%. Factor analysis revealed 12 factors representing different domains of COPD including lung function, radiologic features, exhaled breath metabolomics, symptoms and quality of life. Four clusters were identified: cluster 1 (n=35, 22%): mild airways obstruction and no emphysema; cluster 2 (n=48, 31%): severe airways obstruction with emphysema and low diffusion capacity, chronic bronchitis, low quality of life and a distinct breath profile; cluster 3 (n=60, 38%): mild COPD with a close to normal lung function, but with radiologic signs of emphysema and a distinct breath profile; cluster 4 (n=14, 9%): highly symptomatic males with dyspnea and low quality of life with moderately impaired lung function.

Conclusions: This unbiased taxonomy for COPD confirms and extends clusters found in previous studies and allows better phenotyping of COPD.
P557
The association between pulmonary arterial hypertension secondary to chronic lung disease and serum asymmetric dimethylarginine levels
Baris Acikelce, Gönür Çansaray, Aygün Gür, Nur Dilek Bakanc
Gülçihan Örkan, Pınar Güven. Chest Disease, Yedikule Teaching Hospital for Chest Disease and Thoracic Surgery, Istanbul, Zeytinburna, Turkey
Asymmetric dimethylarginin (ADMA) is an endogenous molecule that prevents nitric oxide synthesis enzyme inhibition. It has been shown that serum ADMA levels increase in COPD patients as well as idiopathic pulmonary hypertension patients. In this study, association between serum ADMA levels and pulmonary hypertension secondary to COPD and interstitial lung disease (ILD) was evaluated. Fifty-five to 95% of COPD patients and ILD patients were included into the study. Echocardiography was used to evaluate pulmonary arterial pressure (PAP). Serum ADMA levels were measured by ELISA. Association between OPAP and serum ADMA levels were evaluated by Pearson correlation test. Mean ADMA levels of patients have normal and high OPAP were compared by student-test. Mean serum ADMA levels of patients have increased OPAP was found significantly higher than that of patients that have normal OPAP (p=0.05). A positive correlation (Pearson r=0.6, p<0.01) was found between serum ADMA levels and OPAP. Evaluation of COPD and ILD patients separately showed that significantly higher ADMA levels were found in pulmonary hypertension secondary to COPD (p<0.05) in both groups. COPD and ILD groups showed correlation between serum ADMA levels and OPAP (COPD and ILD Pearson r=0.47 and 0.72 consequently) also exist. ROC analysis was used to evaluate the value of serum ADMA levels measuring in diagnosis of pulmonary hypertension. Area under curve was found 0.7.
Conclusion: Serum ADMA levels measurement may be an indicator for PH secondary to COPD.Area under curve was found 0.7.

P558
Pneumothorax secondary to chronic obstructive pulmonary disease
Nadia Fetta, Abdessemed Taleb. Pulmonary, University Hospital, Sidi Bel Abbes, Algeria
Spontaneous pneumothorax is defined by the presence of air in the pleural cavity without history of trauma. This is a significant clinical problem. COPD is a common cause of pneumothorax. The risk of recurrence of spontaneous pneumothorax secondary to COPD is high and various studies have quoted values 20-60%.
Methods: Retrospective cohort study of all patients COPD admitted with pneumothorax to the pulmonary department between January 2004 and September 2011. The aim: to assess the frequency of pneumothorax in the COPD and describe its clinical profile and scable.
Results: In a study period of 6 years, 248 cases with a diagnosis of pneumothorax were observed at the pulmonary department secondary to COPD was 67% (80 patients COPD developed 167 pneumothorax). Our series is composed mainly of men, mean age 59.6 years. The notion of smoking was found in 100%; ex-smokers 67% and active smokers 33%. The most frequent initial symptom was dyspnea 100% with pleuritic chest pain 42% The episode of pneumothorax revealed the disease COPD in 32% and was responsible of exacerbation of COPD in 68% According to GOLD classification, Fifty five (68%) had moderate COPD and twenty five (31%) had severe COPD. All patients received tube chest drainage and hospital stay mean was 12 days range (6-23 days). Twenty eight patients (52%) had recurrence of pneumothorax. Forty two patients (52%) had emphysema. Four patients developed empyema, six had emphysema subcutaneous and two had pneumonia after chest operation. The evolution of the study was favorable in 74 cases and 6 patients died in an array of acute respiratory failure.
Conclusion: Pneumothorax represents a factor of mortality for patients suffering of COPD and the surgical treatment is needed to prevent recurrence.

P559
Endocrinopathies and related with COPD exacerbation
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Osteoporosis, metabolic syndrome, thyroid dysfunction are common in COPD. Results related with Vit D Deficiency associated with COPD exacerbation are common and controversial.
This study is planned to investigate the levels of Vit D, thyroid hormones and bone densitn COPD in related exacerbation numbers, hospitalization duration related with exacerbation, and the number of antibiotics for exacerbations.
70 subjects with the mean age of 69.1±10.02 years (57.5% of the patients) and the mean FEV1/1.38.75±16.91 were included in the study. Diabetes Mellitus (DM) has found in 13 and hyperlipidemia has found in 9 patients. Vit D Levels was reduced in 90% and thyroid hormones abnormalities were seen in 50% (1 hypothyroidi, 34 subclinic hypertyroidi) of the patients. Bone mineral density was normal in 21 (30%) and osteopenic in 24 (34.3%) and osteoporotic in 25 (35.7%) of the patients. These abnormalities did not relate with FEV1, exacerbation numbers in the last year, ICU admission rate and the duration of hospitalisation.
Endocrinopathies in COPD have been encountered frequently however the impact of these abnormalities of disease outcomes have not elucidated thoroughly. This study has not showed any relation of endocrin abnormalities with parameters of exacerbations.

84. Respiratory infections: a clinical point of view

P560
Prognostic biomarkers in severe community-acquired pneumonia (SCAP) patients, requiring intensive care unit (ICU) admission
Öksana Onyshlayenko1, Alexander Makarevich1, Paulina Jagus2, Joanna Chorostowska-Wymisk1, Tatjana Rybina1, Elena Amelchenko1,2 1st Department of Internal Diseases, Belarussian State Medical University, Minsk, Belarus; 2Laboratory of Molecular Diagnostics and Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; 2Clinical Laboratories of Occupational Diseases, Republican Scientific and Practical Center of Hygiene, Minsk, Belarus
Background and aim: Measurement of prohormones representing different pathophysiological pathways could enhance risk stratification in SCAP pts. The aim of the study was to investigate procalcitonin (PCT), adrenomedullin (AMD), copeptin (CP), B-type natriuretic peptide (BNP-32) levels in ICU SCAP pts and their relationship with in-hospital outcomes (in-hospital mortality (BIM), length of in-hospital stay (LOS),duration of ICU stay,disease specific complications,need for invasive mechanical ventilation (IMV) and vasopressor support (VS)).
Methods: 20 ICU pts with proven SCAP CURB-65 class 3.4 were enrolled to the study. Serum PCT, AMD, CP, BNP-32 values were measured within the 24 hours after admission.
Results: Increasing CAP severity was associated with increased PCT values (p=0.04; p=0.05). PCT in CURB-65 3 and 4 class pts was [median] 0.73 vs 5.94 ng/ml, respectively (p=0.03). CP levels on admission appeared to be higher in CURB-65 4th class pts vs the 3rd class pts -74.8 vs 47.6 pg/ml, respectively (p=0.03). PCT values demonstrated statistically significant correlation with BIM (p=0.74; p=0.005), were higher in non-survivors than those in survivors [5.94 vs 0.73 ng/ml, p=0.01]. PCT and CP values correlated with need for VS (p=0.74; p=0.005 and r=0.54; p=0.02) and showed higher concentrations in pts requiring VS compared with those with stable haemodynamics [102 vs 0.73 ng/ml, p=0.01] and [74.8 vs 47.6 pg/ml, p=0.03]. AMD levels on ICU admission were associated with need for IMV (p=0.47; p=0.04). BNP-32 values correlated with LOS (p=0.56; p=0.02), PCT - with duration of ICU stay (p=0.81; p=0.001).
Conclusion: PCT and CP appeared to be the most reliable prognostic biomarkers in ICU pts with SCAP.

P561
Cat-scratch disease mimicking lymph node tuberculosis about four cases
Jean-Baptiste Obstler, Elodie Verger, Elodie Barra, Caroline Claret, Olivier Lelou. Pneumology, CH Abbeville, Abbeville, France
Cat-scratch disease (CSD) is a bacterial infection due to Bartonella henselae. It’s usually present as isolated lymphadenopathy. Lymphadenopathy histological examination is often non specific. It can be revealed an epithelioid necrotizing granuloma just like lymph node tuberculosis. We report four cases referred in our institution for tubercular lymphadenitis suspicion, which were in fact CSD. Patients were aged between 15 and 61 years old, healthy, without biologic inflam mation. Regional lymphadenopathy without any other lesions was confirmed by CT scans. Biopsy were realized for all patients. Histological analysis was necrotizing epithelioid granuloma and giant cell. Zielh-Neelsen method and quantiFERON-TB GOLD test were negative whereas serologic tests for Bartonella henselae were positive. One patient does not remember contact with cat. Two patients were treated by antibiotic. Outcome of all cases was favorable.
Cat-scratch disease stays a difficult diagnostic. Clinicians must keep this diagnosis possibility in mind when lymph node presents an necrotizing epithelioid granuloma with giant cells. A systematic clinical and laboratory testing approach is necessary. Serology is the best initial test and can be performed by immunoperoxidase assay. Moreover polymerase chain reaction can be useful. Indication of antibiotic treatment is reserved to complicated CSD.
P562
Serotyping, multilocus sequence typing and antibiotic resistance of Streptococcus pneumoniae isolates in China
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Introduction: Streptococcus pneumoniae is a major causative agent of severe infections, which has become a major public health concern.

Objectives: A prospective study was performed to investigate the serotype distribution, genetic relationship and antimicrobial resistance in Streptococcus pneumoniae (S. pneumoniae) isolates from patients in China.

Methods: 21 Blood/cerebrospinal fluid (CSF) isolates and 18 sputum isolates were collected from patients admitted to the Peking University People's Hospital and Fujian Provincial Hospital were analyzed for investigating the serotypes, the multilocus sequence typing (MLST), and their susceptibilities to antibiotics.

Results: The most frequent serotypes of blood/CSF isolates were 14 (38.1%), 19A (14.3%), 23F (9.5%), 18C (9.5%), and in the sputum isolates the most frequent serotypes were 19F (33.3%), 23F (16.7%), 19A (11.1%), 3 (11.1%). The coverage rates of the blood/CSF and sputum isolates for the 7-valent pneumococcal conjugate vaccine (PCV7) were 66.7% and 61.1%, respectively. 4 of 5 isolates determined as 19A were collected from patients <5 years old. The MLST analysis showed that all the 5 isolates were ST320. All the 21 blood/CSF isolates, the resistance rates of erythromycin and penicillin were 83.3% and 61.1%. Of the 18 sputum isolates, the resistance rates of erythromycin and penicillin were 83.3% and 66.7%. All of the isolates of serotype 19A were resistant to both penicillin and erythromycin.

Conclusions: The introduction of PCV13, in which the 19A conjugate is included, will be necessary in China because of the high rates and severe antibiotic resistance of 19A.

P563
Pulmonary manifestation of lassa fever and the impact on mortality
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Background: Lassa fever is associated with multi-systemic clinical disease in severe cases, with consequent increase in mortality. The respiratory system has been shown, both clinically and pathologically, to be involved. However, there is little information on the impact of this on mortality. This study aims to determine the impact of pulmonary involvement on mortality.

Materials and methods: The medical records of 65 RT-PCR confirmed cases of Lassa fever patients with respiratory symptoms (cough and/or breathlessness) admitted to the medical wards of our hospital between January 2009 and February 2011 were reviewed. There were 34 males and 31 females. Of the 65 patients, 10 had both physical and chest x-ray features of pulmonary involvement. Case fatality rates (CFR) were compared between the sub-groups of patients with and those without pulmonary involvement. Significance level was set at P value < 0.05.

Results: The pulmonary features were pneumonia (5); pneumonia with pleural effusion (3); ARDS (2). Among the 10 patients with pulmonary involvement, 7 died, giving a CFR of 70%, while with the group without pulmonary involvement 21 died out of 55, with a CFR of 38.2% (p=0.06; Odds ratio 0.26; 0.04-1.34 (2-tailed Fisher exact)). Over all CFR was 44.6% (2005).

Conclusions: Lassa fever with respiratory features is associated with high CFR especially when the lungs and pleura are involved.

P564
Obesity as the most considerable risk factor for death due to influenza A(H1N1)-09 viral infection
Natasa Lezaja, Elena Luzina. Department of Internal Medicine, Chita State Medical Academy, Chita, Russian Federation

Objective: The aim of this study was to assess the complications of A/H1N1-09 viral infection in died patients in dependents of body mass.

Methods: We reviewed medical records and postmortem examination reports of 33 pts who died in 2009 in Zabavsky region of RF. A/H1N1-09 viral infection was confirmed by transcription- polymerase chain reaction method.

Results: 14 men and 19 women (average age 39.8±12.5 years) were included. All patients were divided into 2 groups: 22 patients with BMI 32.3±4.185 (the 1st group) and 11 patients with BMI< 25 (the 2nd group). There was no difference between the groups in age and gender structure. Causes of death were pneumonia and progressive respiratory failure. Pneumonia developed more rapidly in the 1st group (5,3±1.75 vs 4,09±1.13 days, p=0,049). The rate of acute respiratory distress syndrome was similar in both groups. Thrombosis of various locations was seen more often in obese patients (31,7% vs 0%, p=0,037). A tendency was found to a higher rate of rhabdomyolysis, acute canalicular necrosis and intravascular blood coagulation syndrome in obese patients. Additional risk factors were determined in 77,3% pts of the 1st group (diabetes mellitus, pancreatitis and arterial hypertension). We suppose that possible reasons of severe course of influenza A/H1N1-09 viral infection in obese people were alveolar hypventilation, production of proinflammatory cytokines by the fat tissue resulting in poor immune response.

Conclusions: Thus, obesity was the most considerable risk factor for death during influenza A/H1N1-09 virus infection in Zabavsky region due to aggravation of underlying metabolic disorders by specific effects of A/H1N1-09 virus strain.

P565
Seasonal variation of viral lower respiratory tract infections in immunocompromised patients undergoing diagnosis bronchoscopy
Kathleen Jahn1, Lilian Junke2, Jorg Halter2, Daisia Stolz1, Michael Tammi3, 1Clinic for Pneumology, University Hospital, Basel, Switzerland; 2Clinic for Haematology, University Hospital, Basel, Switzerland; 3Clinic for Pneumology, Hospital Thun, Thun, Switzerland

Pulmonary infections and non-infectious complications are frequent in immunocompromised patients. Multiplex PCR allows to detect a broader spectrum of viral infections in immunocompromised patients suffering from respiratory symptoms. We analysed the types of viral infection in a large cohort of patients undergoing diagnostic bronchoscopy for symptoms of LRT infection. Multiplex PCR for respiratory viral infection consisted of 13 viruses. 670 patients underwent a bronchoscopy with BAL from October 2009 to January 2012. 351 of the patients suffered from haematologic disorders, 157 underwent solid organ transplantation (including 137 lung transplantation, 10 kidney transplantation, 5 heart transplantation and 5 liver transplantation) and 174 were immunocompromised for other reasons (HIV, rheumatological diseases, interstitial lung disease). Overall respiratory viral infection could be documented in 212 cases (31.6%). The most frequent viruses were rhinovirus in 109 samples. A single viral infection was found in 196 cases (29.3%) whereas at least two viruses were detected in 16 patients (2.4%). Rhinovirus was found throughout the whole year. Coronaviruses, parainfluenza, RSV and IMPV were documented from November to April. There were only nine cases of adenovirus and eight cases of influenza respectively. H1N1 was only present in the winter of 2009.

Summary and conclusion: Multiplex PCR in BAL allows to diagnose rapidly viral infection in a high percentage of immunocompromised patients suffering from respiratory tract infection. Except for rhinovirus most viruses show seasonal pattern. However the “winter” period lasts for at least 6 months.

P566
Risk factors for tuberculosis in patients with early gastric cancer: Is gastrectomy a significant risk factor for tuberculosis?
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Since 1940s, many studies suggested the strong relationship between gastrectomy and the development of TB. But there is no study about the association between TB development and gastrectomy in patients with early gastric cancer (EGC). We used our EGC cohort confirmed pathologically by gastrectomy (pT1N0M0) or endoscopic mucosal resection (EMR) (pT1) between Jun 2001 and Dec 2008 and followed (2). We searched an active TB case developed at least 3months after gastrectomy and EMR in EGC cohort retrospectively. Of total 1395 patients with EGC, 1495 patients were classified as gastrectomy cohort and 440 patients as EMR cohort. While one patient (0.2%) was diagnosed as active TB in EMR cohort, 26 (1.7%) were diagnosed in gastrectomy cohort during the follow-up period. TB cumulative incidence showed significant difference between the two cohort (Log-Rank test p=0.030). Cox proportional multivariate analysis after adjustment with age, sex, and BMI group in EGC cohort showed hazard ratio of old TB lesion was 4.911 (95% CI 2.213-10.901) and that of gastrectomy was 8.599 (95% CI 1.155-64.000). In subgroup analysis using gastrectomy cohort, Cox proportional multivariate analysis after adjustment with age and sex showed hazard ratio of old TB lesion was 4.570 (95% CI 2.041-10.231) and postoperative weight reduction (per 10% compared with weight before gastrectomy) was 2.240 (95% CI 1.452-3.486).

Gastrectomy and old TB lesion on chest radiograph were significant risk factor for TB development in EGC cohort and old TB lesion on chest radiograph and body weight loss after gastrectomy were too in gastrectomy cohort.

P567
Identification of bacterial pulmonary infection by a PCR based rapid molecular diagnostic assay in bronchoalveolar lavage
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Rapid PCR based diagnostic tools have been developed to diagnose early bacterial respiratory tract infections. If there is a suspicion of pneumonia patients are usually empirically treated. Bronchoscopy with BAL is advocated in patients with nonresolving pneumonia.
Bacterial PCR might allow to find bacterial pathogens in patients with nonresolving pneumonia under current treatment. In a pilot-study we analysed the diagnostic yield of a new PCR and microarray-based rapid molecular diagnostic assay (Prove it 41 with 35 samples at BAL-fluid including patients with non-resolving pneumonia.

Most of the patients are already pretreated before a sampling with BAL could be done. We included 22 patients (group A) undergoing bronchoscopy with BAL with a strong clinical suggestion of bacterial infection (purulent bronchial secretions) and 13 patients (group B) with no evidence of bacterial infection and no inflammatory signs in the peripheral blood. A were under antibiotic treatment as compared to 15% in group B. Conventional microbiological cultures showed no growth in group B. In group A there were bacteria grown from 10 samples (43%). The Prove it assay identified additional bacteria in 7 BALs of group A with negative culture results (mainly haemophilus influenzae). 3 cases were cultural positive (pseudomonas aeruginosa, klebsiella oxytoca, enterobacter) without detection in Prove it assay. On the other hand bacteria were identified by Prove it in 6 cases of group B.

Conclusion: Bacterial Multiplex PCR (Prove it) might be an interesting tool to diagnose bacterial infection in the BAL of patients with nonresolving pneumonia under current treatment with antibiotics.

P568 Early diagnosis and causal treatment of pneumonia associated with pandemic influenza A (H1N1) virus

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Introduction: In the conditions of epidemic of highly pathogenic virus a special role is taken away to early aetiologic diagnosis of the disease. Meanwhile, expectation or absence of the result of RT-PCR can’t be the reason for a delay of appointment of the antiviral therapy.

Aim: The aim of the study was to investigate early diagnostic features of pneumonia associated with influenza A (H1N1) and the role of antiviral therapy.

Methods: Retrospective analysis of the medical records of 135 patients with pneumonia associated with influenza A (H1N1) during October-December 2009 in Chita, RF. In all patients high resolution CT was developed. Antiviral therapy consisted of oseltamivir 150-300 mg or zanamivir 20 mg per day.

Results: The greatest diagnostic value in laboratory confirmed cases of pneumonia associated with influenza A (H1N1) possessed following indicators: myalgia, leukopenia (4.0 or less), and a symptom of “matte glass”

Diagnostic value of indicators of pneumonia associated with influenza A (H1N1)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Myalgia</td>
<td>56.8</td>
<td>78.7</td>
</tr>
<tr>
<td>Leukopenia (4.0 or less)</td>
<td>59.0</td>
<td>82.9</td>
</tr>
<tr>
<td>“Matte glass”</td>
<td>62.5</td>
<td>93.6</td>
</tr>
</tbody>
</table>

Antiviral therapy in the first 48 hours received 25 pts (18.5%). Duration of hospitalization in those patients was shorter - 8 [6; 11] in comparison of patients not receiving early antiviral therapy - 12 [9; 14.5] (p<0.05). An early initiation of oseltamivir reduced the risk of lethal outcome in 3 times, zanamivir - in 3.2 times (p<0.03).

Conclusion: The greatest sensitivity and specificity in early diagnostic of influenza A (H1N1) is a symptom of “matte glass”. Antiviral medications, prescribed in due time can reduce risk of lethal outcome.

P569 Biomarkers in community-acquired pneumonia (CAP)

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Introduction: Many investigators have tried to identify a simple blood test or predicting rules that can help physicians to make more rational decisions to identify patients who are at risk for adverse outcomes or death.

Aim: The aim of this study was to investigate the prognostic value of plasma D-dimer, CRP and some other biomarkers levels in patients with CAP.

Materials and methods: In this study were enrolled 72 patients admitted on Sept - Dec 2011 with clinical and radiological evidence of CAP. Within 24 hours after admission and on the 4-th day blood samples were taken for analysis. CURB-65 and PSI severity scores were calculated at admission. Statistical analysis is made with SPSS 19.0.

Results: Mean age 62.7±16.6 years (range 25-92). Mean D-dimer on the first day resulted 2621ng/ml (range 206-9000), on the 4-th day 2585 ng/ml (range 120-9000). Mean CRP on the first day resulted 198 mg/l (range 0.76 - 743), on the 4-th day 72 mg/l (range 0.10 - 316). On admission mean value of fibrinogen was 811mg/dl and on the 4-th day resulted 2621ng/ml (range 296-9000), on the 4-th day 2585 ng/ml (range120-9000).

Conclusion: Even though mean values of D-dimer and CRP are higher, no significant correlations resulted between them and CURB-65 and PSI score. Significantly mean values of D-dimer and CRP are higher on groups of patients with complicated CAP (p < 0.004).

P570 Tuberculosis in Esbjerg. High risk group of persons from Greenland

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Introduction: Tuberculosis among immigrants in Denmark decreased with 50% as the immigration decreased. However, tuberculosis among persons from Greenland is increasing and in the period 2006 to 2010 an increased number of persons from Greenland immigrated to Denmark.

Material and method: In the period of two years from january 2009 to december 2010, 24 patients were treated for active tuberculosis, 32 treated for latent tuberculosis as new positive and four before treatment with TNF-alpha-inhibitor: M.Brimon (2),SA (1), Pfortasi (1). Sexratio M/F 2.0, mean age 43 years, range 7-80 years in the group with active tuberculosis. Sexratio 0.4, mean age 16 year, range 10-43 years in the group with latent tuberculosis. Nationality noted.

Results: In the group treated for active tuberculosis patients were born in Greenland (5), Somalia (2), India (1), Vietnam (1), Burma (1) and Denmark (13) In the group with latent disease as new positive patients were born in Greenland (5), Somalia (2), Venezuela (1) and Denmark (24).Only 1 of 4 treated with TNF- inhibitor and latent disease was born in Denmark. Discussion.Uptake area for the hospital in Esbjerg include 210.000 persons. In the town 400 persons are born in Greenland. About 75 persons of them have social problems with abuse of alcohol and drug. The number of persons from Greenland is increasing in Denmark and the frequency in Esbjerg. The frequency of active disease and latent disease of tuberculosis in 2009-2010 was 20.8% and 15.6%.

Conclusion: Tuberculosis in Denmark an increasing problem for persons born in Greenland as the uptake area of the hospital include 210.000 persons. In Esbjerg 60 patients through a 2 year period 2009-2010 were treated for active disease and latent disease. 16.6% of the patients from Greenland.

P571 A case of HIV-associated multicentric Castleman disease with pulmonary involvement

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Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder that is increasingly diagnosed in patients with HIV infection. The course of the disease is unpredictable, ranging from a rapidly progressive form that can be fatal within weeks to a long course of a remitting and relapsing disease. Its principal manifestations are diverse but are almost always include fever, malaise, lymphadenopathy and hepatosplenomegaly. Pulmonary complications are rare.

We report a case of HIV-associated MCD that relapsed after being on remission for 30 years. The patient presented with recurrent "attacks" of classical symptoms (fever, night sweats, polyadenopathy), accompanied by thorarica, shortness of breath and cough. A diffuse interstitial pneumonitis was found on CT-scan of the chest, described as a ground-glass infiltrate with peribronchial micronodules and interlobular thickening that affected mostly the inferior third of both lungs. A slight bilateral pleural effusion was also noted. Lung function tests were normal. Final diagnosis of MCD was made on lymph node biopsy. We first treated this patient with Rituximab alone which led to a rapid relief of his symptoms and radiologic improvement. However, as he relapsed twice following this treatment, each time with systemic symptoms accompanied by a radiologic progression of the diffuse interstitial pneumonitis, we opted for a combined regimen of Rituximab and chemotherapy (CHOP). He is still on remission (6 months) and a follow-up CT-scan shows an almost complete regression of the pulmonary interstitial anomalies. The long term management of MCD presenting with pulmonary involvement has yet to be defined, as long term prognosis.

P572 The resistance rates of Acinetobacter baumannii at endotracheal aspirate cultures

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Introduction: The long term management of MCD presenting with pulmonary involvement

AIM: We aimed to determine the rate of Acinetobacter baumannii resistance in intensive care unit (ICU).

Method: We analyzed 34 cases’ (30 entubated and 4 nentubated) files who had positive cultures for Acinetobacter baumannii at endotracheal aspirate.

Results: The mean age of patients was 65.5, 73.5% (n=25) was male. The most hospitalization 9.65 days (range 0-35).Mean values of D-dimer and CRP resulted in correlation with complications events. Even though mean values of D-dimer and CRP are higher, no significant correlations resulted between them and CURB-65 and PSI score. Significantly mean values of D-dimer and CRP are higher on groups of patients with complicated CAP (p < 0.004).

Conclusion: D-dimer and CRP level cannot replace CURB-65 or PSI scoring for assessment in CAP patients, but are useful to predict clinical outcome, especially complications in patients with CAP.
common comorbidities were COPD and CVD. In 27 patients, blood culture was taken concurrent with endotracheal aspirate culture and 22.2% (n:6) was positive with same agent. 52.9% (n:18) of patients were dead. The rate of Acinetobacter baumannii resistance and MICs presented in Table 1 and 2.

Table 1. The rates of Acinetobacter baumannii resistance to broad spectrum antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC</th>
<th>S</th>
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<tbody>
<tr>
<td>Amikacin (n=34)</td>
<td>&gt;8</td>
<td>25</td>
</tr>
<tr>
<td>Gentamycin (n=34)</td>
<td>&gt;8</td>
<td>100.0</td>
</tr>
<tr>
<td>Piperacillin-tazobactam (n=24)</td>
<td>&gt;8</td>
<td>95.8</td>
</tr>
<tr>
<td>Ciprofloxacin (n=21)</td>
<td>&gt;4</td>
<td>71.4</td>
</tr>
<tr>
<td>Ceftazidime (n=25)</td>
<td>&gt;4</td>
<td>100.0</td>
</tr>
<tr>
<td>Cefepime (n=34)</td>
<td>&gt;4</td>
<td>100.0</td>
</tr>
<tr>
<td>Meropenem (n=32)</td>
<td>&gt;2</td>
<td>58.8</td>
</tr>
<tr>
<td>Imipenem (n=32)</td>
<td>&gt;2</td>
<td>58.8</td>
</tr>
<tr>
<td>Ciprofloxacin (n=34)</td>
<td>&gt;8</td>
<td>100.0</td>
</tr>
<tr>
<td>Levofloxacin (n=33)</td>
<td>&gt;8</td>
<td>100.0</td>
</tr>
<tr>
<td>Tigecycline (n=8)</td>
<td></td>
<td>no resistance</td>
</tr>
<tr>
<td>Colistin (n=9)</td>
<td></td>
<td>no resistance</td>
</tr>
</tbody>
</table>

Table 2. The MICs of Acinetobacter baumannii resistance to broad spectrum antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (n=28)</td>
<td>&gt;8</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Gentamycin (n=28)</td>
<td>&gt;8</td>
<td>28</td>
<td>100.0</td>
</tr>
<tr>
<td>Levofloxacin (n=28)</td>
<td>&gt;4</td>
<td>28</td>
<td>100.0</td>
</tr>
<tr>
<td>Ciprofloxacin (n=28)</td>
<td>&gt;2</td>
<td>28</td>
<td>100.0</td>
</tr>
<tr>
<td>Meropenem (n=28)</td>
<td>&gt;8</td>
<td>16</td>
<td>57.1</td>
</tr>
<tr>
<td>Cefotaxime (n=22)</td>
<td>&gt;4</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Cefepime (n=28)</td>
<td>&gt;4</td>
<td>16</td>
<td>57.1</td>
</tr>
<tr>
<td>Ceftazidime (n=28)</td>
<td>&gt;4</td>
<td>4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Conclusion: Higher resistance rates for broad spectrum antibiotics in Acinetobacter baumannii infections explains higher mortality rates in these patients. Higher resistance rates for carbapenems seems to limit of these antibiotics usage for ICU patients in time.

P573 Thoracic actinomycosis changing with time

Dietmar W. Geiger, Dietmar W. Geiger; 1Thoracic actinomycosis changing with time

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Dietmar W. Geiger, Dietmar W. Geiger; 1Thoracic actinomycosis changing with time
Conclusion: Although ESRD patients suffered from pneumonia caused by multi-resistant pathogens compared with previous CAP studies, including S. aureus, drug resistant organisms were the most common pathogens. The prevalence of pulmonary hypertension and the related factors in hemodialysis patients

Methods: In this study, 76 chronic hemodialysis patients with pleural effusion admitted in hospital between June 2005 and May 2011, and evaluated for the etiology of pleural effusion and associated clinicopathological findings. Statistical tests of Chi square, ANOVA and Kruskal Wallis were used to compare patient’s data with the most common etiologies of pleural effusion.

Results: Parapneumonic effusion (23.7%), urticarial pleuritis (23.7%) CHF (19.7%) volume overload (6.6%) tuberculosis (6.6%) and malignancy (5.4%) were the most common causes of pleural effusion. There was not any significant difference in the frequency of presenting symptoms such as: Dyspnea, cough, weight loss, anorexia, chest pain and fever, in patients with CHF and urticarial pleuritis. Moreover, pleural Adenosine Deaminase levels were not different in patients with tuberculosis, bronchitis, parapneumonic effusion and CHF.

Conclusion: Infectious disease including parapneumonic effusion and tuberculosis can be the most common causes of pleural effusion in hemodialysis patients. This study showed that some inflammatory pleural reactions such as increase in pleural leukocyte count and ADA may be attenuated in hemodialysis patients.

85. Respiratory manifestations of systemic disease: a holistic approach

P577 Pulmonary brucellosis detected during treatment of active tuberculosis in a patient with operated lung cancer (Case report)

Fatma Erboy1, Fatma Erboy1, 2, chest Disease, Bezmi Alem Vakif University Medical Faculty, Istanbul, Turkey; 3, Infectious Diseases, Bezmi Alem Vakif University Medical Faculty, Istanbul, Turkey; 4, Infectious Diseases, Abant Izzet Baysal University, Bolu, Turkey; 5, Chest Disease, Bilisil Public Hospital, Bilisil, Turkey

P578 Copetin application in severe community-acquired pneumonia (SCAP) severity assessment and outcomes

Joanna Chorostowska-Wynimko1, Tatyana Rybina3, Elena Amelchenko3, 1, 1st Department of Internal Diseases, Belarusian State Medical University, Minsk, Belarus; 2, Laboratory of Molecular Diagnostics and Immunology, National Institute of Tuberculosis and Lung Diseases, Warszaw, Poland; 3, Clinical Laboratory of Occupational Diseases, Republican Scientific and Practical Center of Hygiene, Minsk, Belarus

Background: Appropriate early prognostic assessment is crucial for SCAP patients management.

Aim: We aimed to investigate copeptin levels in SCAP patients and their relationship with in-hospital outcomes (in-hospital mortality (IHM), length of in-hospital stay (LOS), duration of ICU stay), disease specific complications, need for invasive mechanical ventilation (IMV) and vasopressor support (VS).

Methods: 20 ICU patients with proven SCAP CURB-65 class 3, 4 were enrolled to the study. Serum CP values were measured within the first 24 hours after the hospitalization.

Results: Increasing CAP severity was associated with increased CP values (r=0.53; p<0.02). CP levels on admission appeared to be higher in CURB-65 scores 4 vs 0-3 (p<0.03), CP values on ICU admission correlated with need for VS (r=0.54; p=0.02 respectively) and showed higher concentrations in patients requiring VS compared with those with stable haemodynamics (74.8 vs 47.6 pg/mL, p=0.03) respectively. CP correlated with duration of ICU stay (r=0.43; p<0.005).

Conclusion: CP could add prognostic information in SCAP patients.

P579 Neuropsychiatric side effects of tuberculosis

L. Fekih, W. Ben hammad, D. Greb, H. Abdeghaffar, H. Hassene, Mahamed Lamine Megdiche. JNB NAFIS, Abderrahmen Mami Hospital, Ariana, Tunisia

Accur e knowledge of microbiological or psychiatric complications secondary to the administration of antituberculosis may be of the origin of diagnosis and therapeutic problems. This work aims at studying the frequency of these manifestations, their clinical presentations and their therapeutic approach.

P580 Pleural effusion in hemodialysis patients with chronic kidney disease

Giunti Prząkówki1, Farm Rashid Farokhi2, 1, Chronic Respiratory Disease Research Center, NRITLD, Mashh School Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran; 2, Department of Nephrology, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Background: Uremic patients are susceptible to many causes of pleural effusions. Moreover, uremia directly creates a kind of exudative pleural effusion. Uremic pleuritis has been introduced as a clinicopathologic entity for the past few decades. However, knowledge of pathogenesis, clinical course and management of this complication is still limited.

Materials and methods: In this study, 76 chronic hemodialysis patients with pleural effusion admitted in hospital between June 1996 and May 2011, and evaluated for the etiology of pleural effusion and associated clinicopathological findings. Statistical tests of Chi square, ANOVA and Kruskal Wallis were used to compare patient’s data with the most common etiologies of pleural effusion.

Results: Parapneumonic effusion (23.7%), urticarial pleuritis (23.7%) CHF (19.7%) volume overload (6.6%) tuberculosis (6.6%) and malignancy (5.4%) were the most common causes of pleural effusion. There was not any significant difference in the frequency of presenting symptoms such as: Dyspnea, cough, weight loss, anorexia, chest pain and fever, in patients with CHF and urticarial pleuritis. Moreover, pleural Adenosine Deaminase levels were not different in patients with tuberculosis, bronchitis, parapneumonic effusion and CHF.

Conclusion: Infectious disease including parapneumonic effusion and tuberculosis can be the most common causes of pleural effusion in hemodialysis patients. This study showed that some inflammatory pleural reactions such as increase in pleural leukocyte count and ADA may be attenuated in hemodialysis patients.

P581 The prevalence of pulmonary hypertension and the related factors in hemodialysis patients

Ali Sharifpour, Omid Sedighi, Samad Golshani, Fatemeh Mahjoob. Pulmonary, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran Nephrology, NRITLD, Mashh School Hospital, Shahid Beheshti University of Medical Sciences, Sari, Islamic Republic of Iran Cardiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran

Background and purpose: Pulmonary hypertension (PH) has been reported in hemodialysis patients, but there are scant studies about its prevalence and mechanisms. The aim of this study was to determine the prevalence of pulmonary hypertension in hemodialysis patients and to study some of its possible etiologic factors.

Materials and methods: In this cross-sectional study, the prevalence of pulmonary hypertension was determined by Doppler echocardiogram in 100 patients on hemodialysis via arteriovenous fistula at least for 6 months. All the patients underwent a thorough clinical evaluation. The laboratory findings including mean of three-month hemoglobin and serum level of calcium, phosphorus, albumin, alkaline phosphatase, parathormone (PTH), triglyceride and cholesterol were all recorded.

Pulmonary hypertension was defined as systolic pulmonary artery pressure higher than 35 mmHg.

Results: Pulmonary hypertension was detected in 44 patients (44%) with a mean
systolic pulmonary artery pressure of 52.09±7.33 mmHg. No significant differences were found between those with and without pulmonary hypertension with regard to age, gender, duration of hemodialysis and all the biological parameters.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>FVC</th>
<th>Supine FVC</th>
<th>FVC difference</th>
<th>PIM/PFEM</th>
<th>PaO2/PaCO2</th>
<th>AH/EMT CO2</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/M</td>
<td>52%</td>
<td>37%</td>
<td>–28%</td>
<td>36/54</td>
<td>85/57</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>59/F</td>
<td>94%</td>
<td>91%</td>
<td>–3%</td>
<td>51/65</td>
<td>72/44</td>
<td>&lt;5/47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61/F</td>
<td>77%</td>
<td>53%</td>
<td>–31%</td>
<td>34/43</td>
<td>75/45</td>
<td>&lt;5/47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>50%</td>
<td>37%</td>
<td>–26%</td>
<td>53/59</td>
<td>72/49</td>
<td>&lt;5/47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57/F</td>
<td>59%</td>
<td>25%</td>
<td>–57%</td>
<td>25/30</td>
<td>84/39</td>
<td>&lt;5/33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>19/F</td>
<td>90%</td>
<td>90%</td>
<td>–1%</td>
<td>51/51</td>
<td>88/39</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>53/F</td>
<td>90%</td>
<td>90%</td>
<td>–27%</td>
<td>53/59</td>
<td>72/49</td>
<td>–5/47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46/M</td>
<td>86%</td>
<td>86%</td>
<td>–112/126</td>
<td>80/38</td>
<td>13</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53/F</td>
<td>90%</td>
<td>90%</td>
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<td>76/44</td>
<td>74/44</td>
<td>&lt;38/62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PS84 Predictors of pulmonary artery hypertension in patients with systemic sclerosis**

M.C. Sabir, Shahjahan P. Sulaiman, Davis Paul Chelangara, Nikhula K. Govind, Aneesh C. Retheditram, Raghunath D. Vijayan. Pulmonary Medicine, Medical College, Kottayam, Kerala, India

**Introduction:** Pulmonary Arterial Hypertension (PAH) is the leading cause of death in patients with systemic sclerosis1. Newer treatment modalities have improved the outcome; hence the early identification of this complication is important.

**Aim:** To study the predictors of PAH in patients with Systemic Sclerosis who attended the out patient service of Pulmonary Medicine, Medical College, Kottayam.

**Methods:** We studied 28 cases of systemic sclerosis patients who had diffuse form. All of them had PAH.

**Results:** Among patients with PAH (diffuse and overlap form), 7 had ILD (63%) and 3 had PAH (38%).

No patient with limited form had PAH but, all the two had PAH (100%).

**Conclusions:** Prevalence of PAH was observed in patients with limited variety when compared with diffuse form and overlap syndrome.

In diffuse form PAH was associated with ILD and no such association was found in overlap syndrome.

A decreasing DLCO is an excellent predictor of the development of PAH in diffuse systemic sclerosis2.

**References:**


**PS85 Respiratory problems in late onset Pompe disease**

Mehtup Ertas, Zuleyha Bingol, Guler Okumus, Piraye Serdaroglu, Esgen Kiyani. Pulmonary Department, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey; Neurology Department, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey

**Introduction:** Pompe disease (glycogen storage disorder type II) is associated with functional deficiencies in skeletal, heart and respiratory muscles due to glycogen deposition. While progression and mortality rates are fast in early onset (first year) Pompe disease, late onset (adult) Pompe disease is related with slow progression and proximal myopathy. In this disease respiratory muscle involvement is independent from severity of skeletal muscle weakness. Here, we present the respiratory evaluation of 10 patients with Pompe disease who are followed up in our clinic.

**Table 1. Characteristics of the patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>FVC</th>
<th>Supine FVC</th>
<th>FVC difference</th>
<th>PIM/PFEM</th>
<th>PaO2/PaCO2</th>
<th>AH/EMT CO2</th>
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<td>–28%</td>
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<td>85/57</td>
<td>44</td>
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<td></td>
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<tr>
<td>2</td>
<td>59/F</td>
<td>94%</td>
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<tr>
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<tr>
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<td>50/F</td>
<td>50%</td>
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<td>–26%</td>
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<td>&lt;38/62</td>
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</table>

**Conclusion:** Respiratory muscle involvement especially diaphragm muscle dysfunction and respiratory disorders in sleep are common in late onset Pompe disease even the respiratory symptoms are recessive.

**PS86 Ankylosing spondylitis: Pulmonary manifestations**

Fıratufar Karakus1, Aylin Rezvani2, Muhammet Emin Akköyulu1, Mehmet Bayram1, Fatih Kothyab Ozczyel1, Murat Sezer1, Levent Kari1. 1Department of Chest Disease, Bezmiuml Vakif University Medical School, Istanbul, Turkey; 2Department of Physical Therapy and Rehabilitation, Bezmiuml Vakif University Medical School, Istanbul, Turkey.

In present study we aimed to assess the spirometric and pulmonary radiological findings of the patients with ankylosing spondylitis.
Methods: 35 outpatients with ankylosing spondylitis were evaluated in terms of demographic characteristics, smoking status, tuberculosis history, respiratory symptoms, HLA B27 status, activity of illness. X-ray, HRCT, spirometry, body plethysmography and DLCO tests were evaluated. 

Results: The characteristics of all the subjects are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31 men; 4 women</td>
<td>90%</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>39.6±15.9</td>
<td>94.3%</td>
</tr>
<tr>
<td>Smoking history</td>
<td>23 smoker, 12 non-smoker</td>
<td>62%</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>21 patients had no TB history; 11 unknown</td>
<td>30%</td>
</tr>
<tr>
<td>HLA B27</td>
<td>5 negative; 16 Positive; 13 unknown</td>
<td>62%</td>
</tr>
</tbody>
</table>

Chest X-ray was normal at 24 patients (% 68.6) and abnormal at 8 (%22.9) patients. The HRCT findings of all the subjects are shown in Table 2.

<table>
<thead>
<tr>
<th>HRCT findings</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15</td>
<td>42.9%</td>
</tr>
<tr>
<td>Bilateral apical pleuroparenchymal lesions</td>
<td>7</td>
<td>20%</td>
</tr>
<tr>
<td>Upper lobe fibrosis</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Groundglass attenuation</td>
<td>3</td>
<td>8.6%</td>
</tr>
<tr>
<td>Nonspecific interstitial lesions</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Nodular density</td>
<td>1</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nonspecific interstitial lesions + nodular density</td>
<td>1</td>
<td>2.9%</td>
</tr>
<tr>
<td>Fibrotic pleuroparenchymal lesions + nodular density</td>
<td>3</td>
<td>8.6%</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>91.4%</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>8.6%</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100%</td>
</tr>
</tbody>
</table>

Lung Volumes were normal at 20 (%57.1) patients, abnormal at 3 (%8.6) patients. DLCO were normal at 16 (%45.7) patients, abnormal at 10 (%28.6) patients. PI max and PE max were normal at 17 (%48.6) patients, abnormal 13 (%33.7) patients.

Conclusion: Disease activity determined by BASDAI Index has no significant correlation with Chest Expansion and value of PI max-PE max (p=0.388). There is no significant correlations between chest expansion and normal or reduced intrathoracic pressures (p= 0.509).

PS87 Diffuse aspiration bronchiolitis diagnosed on transbronchial lung biopsy in a case of thymoma with dysphagia

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2Department of Histopathology, Max Super Specialty Hospital, New Delhi, India; 3Department of Radiology, Max Super Specialty Hospital, New Delhi, India.

Background: Diffuse aspiration bronchiolitis (DAB) is a form of aspiration related lung disease and has unique clinicoro-radio-pathologic features. It has heretofore been reported on autopsies or surgical biopsies. We report a case of DAB diagnosed on trans-bronchial lung biopsy (TBLB).

Case: A 72 year old previously healthy male, smoker (150 pack-years) presented with hoarseness of voice and vertigo for 4 months, dyspnea and swelling in the neck for 1 month. Examination revealed a firm, non tender swelling in the right side of the neck, extending into the superior mediastinum, encasing the trachea, abutting and displacing the esophagus to the left and normal lung parenchyma. A CT-guided transbronchic percutaneous biopsy of the mass revealed an immature lymphocyte rich thymoma. Patient developed sudden breathlessness, after 3 weeks from the start of radiotherapy. A CT-pulmonary angiography was negative for pulmonary embolism. HRCT showed bilateral disseminated centrilobular nodules with ‘tree-in-bud’ appearance suggestive of diffuse bronchiolitis. A TBLB revealed necrotising alveolitis with foreign body giant cells containing refractile material, suggestive of aspiration. A final diagnosis of DAB/aspiration alveolitis secondary to occult chronic aspiration was made. Patient improved on nasogastric feed and treatment with clidamycin. A repeat CT-thorax after 2 months showed normal lung parenchyma.

Conclusion: DAB is an underrecognised, yet an important differential diagnosis, which should be considered in any patient having risk of aspiration and a HRCT showing diffuse bronchiolitis.

PS88 Evaluation of pulmonary function and functional capacity in patients with liver cirrhosis

Olga Corlateanu, Eugen Tcaciuc, Alexandru Corlateanu

Internal Medicine, State Medical and Pharmaceutical University "Nicolae Testemitanu", Chisinau, Republic of Moldova

Background: Various changes can be detected by pulmonary function tests in patients diagnosed with chronic hepatic diseases. These changes characterize the hepatopulmonary syndrome result in hypoxemia and affect one-third of all patients diagnosed with cirrhosis.

The aim of this study was to evaluate and compare the pulmonary function and functional capacity in patients with liver cirrhosis according to the Child-Pugh score and to correlate these variables within each group.

Methods: 40 patients with liver cirrhosis were enrolled into the study. Spirometry (FEV1, FVC, FEV1/FVC), hemoglobin levels, dyspnea by BORG scale, exercise capacity by 6 min walking test (6MWT), blood gas analysis were evaluated. Blood gases were measured in supine and sitting positions.

Results: The patients were classified into three groups, according to cirrhotic severity, using Childs-Pugh classification (A - 7 patients; B - 24 patients; C - 9 patients). There were significant differences (p<0.01, ANOVA) in FEV1 between 3 groups: there was observed a decrease of pulmonary function with progression of cirrhosis from 107±13.1% in group Childs-Pugh A to 89±17.4% in group Childs-Pugh C. Also there was detected a diminution of PaO2 in supine and sitting positions with progression of cirrhosis. The longest 6MWD was 435±17.8 m by group A; then group B (352±43.4 m) and group C (310±63.6 m). There was a strong negative correlation between 6MWD and Child-Pugh classification (r=-0.55, p<0.01).

Conclusion: The progress of liver disease contributes to the onset of several complications which together appear to contribute to the reduction of pulmonary function and functional capacity of patients.

PS89 Assessment of dyspnoea in patients with liver cirrhosis

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Internal Medicine, State Medical and Pharmaceutical University "Nicolae Testemitanu", Chisinau, Republic of Moldova

Background: Pulmonary involvement is a common complication of liver cirrhosis, mainly owing to a decreased hepatic clearance of toxins or increased hepatic production of circulating inflammatory mediators. The connection between the severity of lung manifestations and liver impairment is not well characterized.

The aim of this study was to evaluate and detect predictors of dyspnoea in patients with liver cirrhosis according to the Child-Pugh score.

Methods: 40 patients with liver cirrhosis were enrolled into the study. Spirometry (FEV1, FVC, FEV1/FVC), hemoglobin levels, dyspnea by BORG scale, exercise capacity by 6-min walking test (6MWT), blood gas analysis were evaluated.

Results: The patients were classified into three groups, according to cirrhotic severity, using Childs-Pugh classification: A - 7 patients; B - 24 patients; C - 9 patients. There were significant differences (p<0.01, ANOVA) in dyspnoea assessed by BORG scale between 3 groups: there was the demonstrated the increase of dyspnoea with progression of cirrhosis from 0.7±1.9 points in group Childs-Pugh A to 2.4±4.9 points in group Childs-Pugh C. Dyspnoea correlated better with 6-minute walking distance (r = 0.67, p = 0.001) in cirrhotic patients. Also a significant positive correlation between dyspnoea and Child’s-Pugh classification (r = 0.60, p = 0.01) was demonstrated. The forward stepwise regression analysis shows that the stage of cirrhosis and level of hemoglobin are important predictors of dyspnoea in patients with liver cirrhosis which explains 60% of the dyspnoea.

Conclusion: The Child’s-Pugh stage of cirrhosis and level of hemoglobin in patients with liver cirrhosis are independent risk factors for worsening of dyspnoea.

PS90 Evaluating airway obstruction in patients admitted to general medicine wards by bedside spirometry

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Study objectives: Airway obstruction is found to coexist with other medical conditions. This study attempts to assess airway obstruction in patients admitted in general medicine wards.

Methods: A cross-sectional study of 52 patients admitted to medicine ward of a tertiary hospital was carried out. Bed-side spirometry was performed in each of these patients after taking consent and recording a detailed history.

Results: A remarkable 52% of the patients were found to have airway obstruction (FEV1/FVC<70%) on performing spirometry, including 11.5% with very severe (FEV1<30% predicted), 17.3% with severe (FEV1 30%-49%), 11.5% with moderate (FEV1 50%-69%) and 9.6% with mild (FEV1>70%) obstruction respectively. A diagnosis of obstructive airway disease was present only in 28% of these patients at the time of admission. A considerably higher prevalence of airway obstruction than average was observed in patients admitted for respiratory (70%), cardiac (62.5%) and neurological (58.8%) disorders, while a lower prevalence was seen in those with nephrological (40%), haematological (0%) or other (22%) conditions. No patient was additionally diagnosed with airway obstruction during the hospital stay and only 26% of patients with airway obstruction received bronchodilator therapy.

Conclusions: Airway obstruction co-existing with other medical conditions is grossly under-diagnosed. A routine bedside spirometry performed on hospitalized patients could be a useful tool for detecting and treating airway obstruction.


**PS91**

Is it GER? Different diagnostic approaches for detection of gastroesophageal reflux in patients with chronic cough

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**Background:** Gastroesophageal reflux (GER) is a common cause of chronic cough. Different methods can be used to detect it. The limited accessibility of some devices or difficulties in assessment of relationship between GER and cough may influence their practical usefulness.

**Objectives:** To assess the utility of different methods in the diagnosis of GER in patients with chronic cough.

**Methods:** We included 60 consent, nonsmoking, adult patients, with history of cough longer than 8 weeks, with normal chest radiograph. We used the Carls-

son questionnaire (CQ), assessment of abnormalities in larynx mucosa (Belafsky reflux finding score, RFS), upper gastrointestinal tract radiography, 24-hour-pH monitoring and multichannel impedance (MI) of esophagus.

**Results:** Sixty patients were included (M/F = 1:1.86), mean age 48.8 yrs, mean cough duration 260 weeks (range 16-1440). Sixteen subjects were excluded from further studies due to consent withdrawal or technical problems with pH probe insertion. Positive results of CQ and RFS were observed in 13 and 50/54 cases respectively. Mean calculated RFS was 11.7 points. Exophagasemia herina or reflux during radiography was shown in 6 and 7/54 pts, respectively. Increased esophagus exposure to acid reflux was diagnosed in 43/58 pts using pH monitoring alone, and in 37/54 on the basis of MI. Time-relationship between GER and cough was found in 23 and 21 cases, respectively. MI probe was slightly worse tolerated.

**Conclusions:** Diagnosis of GER was most frequent on the basis of RFS and MI. Combination of few methods allows to recognize GER more precisely. The time relationship between GER and cough, can be assessed by not all used devices by us.

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**PS92**

Platypnea-orthodeoxia syndrome precipitated by kypho-scoliosis: An unusual case of refractory hypoxia

Arun Khanna, David Reed, Gillian Lowrey, Chris Whale. Respiratory Medicine, Derby Hospital NHS Trust, Derby, United Kingdom

**Introduction:** Platypnea-Orthodeoxia syndrome is caused by intra-cardiac, pulmo-

nary artery-right or pulmonary parenchymal shunt. It’s first clinical manifestation in

an elderly lady as a result of a ‘masking’ of a patent foramen ovale (PFO) attributable to her worsening kypho-scoliosis is a novel and poorly understood presentation.

**Case Summary:** An 85 year old lady presented with breathlessness and hypoxia (PaO25.6kPa, PaCO25.2kPa, pH7.4). Clinical examination was normal apart from

marked kypho-scoliosis. Her ECG, chest X-ray, High resolution chest CT, CT pul-

monary Angiogram, Ventilation/Perfusion scans and Trans-thoracic ECHO were all

normal. In particular, she had normal pulmonary pressures. Her lung functions demonstrated a restrictive defect with a normal single-breath diffusion capacity of carbon monoxide. She subsequently exhibited orthodeoxia prompting a ‘bubble’ ECHO study. This revealed a large PFO with a prominent ‘right to left’ shunt, confirmed on Trans-oesophageal ECHO. Percutaneous transcatheater closure of the PFO reduced her oxygen saturation to within normal limits enabling rehabilitation.

**Discussion:** Symptomatic Platypnea-Orthodeoxia syndrome without pulmonary hypertension can be caused by altered intra-thoracic anatomy and physiology. It is postulated that kyphoscoliosis resulting in right atrial compression and alterations to caval flow may result in ‘right to left’ shunt unmasking a ‘silent’ PFO. PFO’s, reported at the time of discharge. The analysis covered the period from 01’2008 to 10’2011.

**Conclusions:** TO present frequently with chronic or acute non specific respiratory symptoms, but with pathognomonic characteristic features in FBS. Thoracic CT scanner is a non invasive diagnostic method. The treatment is symptomatic.

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**PS93**

Pulmonary complications in patients with hematologic diseases

Hiroshi Ohboshi, Kazuo Togitani, Miru Sukai, Ayako Taniguchi, Takayuki Bezoe, Tetsuya Kubota, Akihito Yokoyama. Department of Hematology and Respiratory Medicine, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan

**Patients with hematologic diseases may complicate with various respiratory dis-

ases, such as infections, lung involvement of hematologic diseases, alveolar hemoptoe, and drug-induced pneumonitis. The aim of this study is to clarify the recent incidence and the risk factor for pulmonary complications in patients with hematologic diseases. Medical records and chest computed tomography of patients with hematologic diseases, who were treated in our university hospital during 2010-2011, were reviewed and analyzed retrospectively by hematologists and pulmonologists. Diagnosis of respiratory complications was confirmed by pulmonologists. One hundred sixty six patients with hematologic diseases were admitted mainly for chemotherapy of malignant lymphoma (51.2%), multiple myeloma (17.5%), and leukemia (15.7%). Forty six patients (27.7%) suffered from pneumonia (27 cases, 51.9%), pleural effusion (8 cases, 15.4%), drug-induced pneumonitis (3 cases, 5.7%), acute respiratory distress syndrome (ARDS, 2 cases, 3.8%), alveolar hemorrhage (2 cases, 3.8%), and/or others (10 cases, 19.2%). Six patients (3.6%) were deceased because of respiratory complications (3 cases with pneumonia, 2 cases with ARDS, and a case with alveolar hemorrhage). Pulmonary complications developed significantly higher in current or recent smokers than never smokers. Pulmonary complications in hematologic diseases may be de-

creased by recent introduction of prophylaxis for infections, but are still important in the management of hematologic diseases. Smoking status may be related to the development of pulmonary complications during treatment of hematologic diseases.

**Conclusions:** TO present frequently with chronic or acute non specific respiratory symptoms, but with pathognomonic characteristic features in FBS. Thoracic CT scanner is a non invasive diagnostic method. The treatment is symptomatic.

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**PS94**

Tracheobronchopathia osteochondroplastica – Analysis of 10 years period

Mitsi Nomoto, Jolanda Nikolla, Hasan Hatira. Internal Medicine, University Hospital of Respiratory Diseases “Sh. Ndroqi”. Tirana, Albania

**Background:** Tracheobronchopathia osteochondroplastica (TO) is a pulmonary orphan disease and consists at the presence of multiple osseseous or cartilaginous nodules localized in the submucosa of the tracheobronchial wall. These nodules protrude into the lumen of the trachea and the large bronchi, leading to the airway obstruction. The disease does not involve other organs.

**Method:** We studied in retrospective all cases of TO diagnosed with fiberoptic bronchoscopy for the period 2001 - 2011. In our hospital we realise approximately 1200 bronchoscopies per year.

**Results:** We found 17 cases, 52% were female and 48% male. The average age was 40.6 years, 42% were smokers (~40 UPA) without family history for TO. The duration of symptoms till the diagnostic was 2.3 years. The most frequent symptoms were: cough 100%, sputum 64%, dyspnea 41%, haemoptisis 5%, and erythema nodosa 5%. The laboratory findings demonstrate an increase of sedi-

ment in 58% of cases, 11% leukocytosis and all the others were normal. Proteus mirabilis was the most frequent microbiological strain (17%). Functional respira-
tory tests resulted: 35% obstruction, 11% restriction, 5% mixed and 17% normal.

**Conclusions:** TO present frequently with chronic or acute non specific respiratory symptoms, but with pathognomonic characteristic features in FBS. Thoracic CT scanner is a non invasive diagnostic method. The treatment is symptomatic.
Results: 1779 sarcoidosis patients were hospitalized during almost four years. Majority (79.2%) were diagnosed as pulmonary and/or lymph node sarcoidosis (D86.0, D86.1, D86.2). Sarcoidosis of other and combined sites (D86.8) were diagnosed in 15.8% and unspecified sarcoidosis (D86.9) in 5.0% of patients. At least one comorbidity was noted in 54% of patients. The most frequent reported comorbidities are presented in figure below.

Using linear regression models the association between the number of comorbidities and age and extent of the disease were found (p < 0.001).

Conclusion: Comorbidities in sarcoidosis patients are more frequent in multiorgan disease.

P596 Pulmonary alveolar proteinosis due to mycopnehalone and cyclocoprine combination therapy in a renal transplant recipient
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Since the first case of Pulmonary Alveolar Proteinosis (PAP) was described in 1858 about 500 cases have been reported. We describe a case of PAP occurring in a renal transplant recipient due to mycopnehalone and cyclocoprine combination therapy.

Five years ago, a diagnosis of acute-on-chronic kidney disease was made in a 36 year old woman who eventually underwent renal transplantation then triple-drug immunosuppression. Subsequently she was in maintenance regimen with mycopnehalone and cyclocoprine. Several years ago, she had been treated for tuberculosis of the cervical lymph nodes. Chest X-ray showed a bilateral perihilar infiltrate sparing the costophrenic angles (Figure 1). CT-scan showed bilateral diffuse ground-glass haziness with superimposed interlobular septal thickening, predominantly in the perihilar areas (Figure 2).

Transbronchial lung biopsies showed dilated alveoli filled with PAS-positive granular eosinophilic material with deeply eosinophilic structures, resistant to de-colorization with diastase, consistent with alveolar proteinosis. The appearance of the symptoms after a few months of the commencement of immunotherapy suggested causality.

Immunosuppressive agents are capable of decreasing macrophage numbers and use of these agents in the post renal-transplant patient has been known to produce PAP. This patient was described a combination of mycopnehalone and cyclocoprine.

P597 Effect of respiratory pathology on the quality of life for patients, suffering from rheumatoid arthritis
Tatyana Pertseva, Lyutsa Botvinikova, Yulia Guba. Internal Medicine Department, Dnepropetrovsk Medical Academy, Dnepropetrovsk, Ukraine

Aim: To study the influence of pulmonary pathology on the quality of life (QoL) in patients suffering from rheumatoid arthritis (RA).

Methods: 58 patients with RA (42 women, middle age 57,1±3,17) were investigated by routine, clinical, functional tests and were divided into 2 groups: 1'st – 31 patients who had the respiratory discomfort (breathlessness, cough) and 27 patients without respiratory symptoms (and any disturbances of the function of mycopnehalone and cyclocoprine).

Tests were: unencumbered room air, NIOV+air, NIOV+O2, or O2 via standard nasal cannula. Data collected included exercise time, SpO2 and transcutaneous (Tc) PCO2.

Results: Significant decreasing of the QoL for patients with RA in comparison with patients of the control group and the general population: the low level of QoL was registered in all scales in the patients of the 1-st group – (Symptoms 68,5±4,41, Activity 60,2±1,34, Consequences 63,4±2,11, total score was correspondently decreased: 49,5±2,12, Primary reason of lowering indexes of the SGRQ in patients with RA was a dyspnea. Established multifactor origin of dyspnea in patients with RA upon significant role of lung pathology, which registered in RA-patients.

Conclusions: Pulmonary pathology shows unpleasant effect on QoL, and level of general health of patient with RA, significantly decreased them. The perspective direction for increasing the QoL for patients with RA with pulmonary pathology depends on saving the respiratory function of lungs, adequate control of the activity of the RA, correction of violations of psychosomatic disorders and depressive level of patients.

P598 Venous thromboembolic disease and bronchial cancer

Venous thromboembolic disease (VTE), defined by the occurrence of a deep thrombosis and/or lung embolism. It is a frequent complication of cancer, particularly during chemotherapy. On average, it occurs with 15 to 20% of the patients, and is one of the main causes of death (one hospitalized cancer patient out of seven). We have retrospectively evaluated the occurrence of VTE in 139 bronchial cancer patients treated at the pneumology service of CHU Bab El Oued over a twelve-month duration. The incidence was of 8.6% (twelve cases out of 139), 50% of the VTE were present at the time of diagnosis and 90% appeared during the three following months. Among the twelve VTE diagnosed cases (three women and nine men), we found a predominance of the adenocarcinoma type (41.66%). All cases were stage III and IV and had received chemotherapy, with complementary surgical treatment for two patients. The twelve VTE cases had received an anticoagulant treatment with six deaths occurring after six months of treatment, three recoveries and three patients still under anticoagulants in continuation.

Conclusions: bronchial cancer predisposes the occurrence of a venous thromboembolic event which, once associated to neoplasia, is a factor of high mortality risk. VTE is more frequent with advanced stages, bronchial cancer patients, in adenocarcinoma and with patients under chemotherapy. Response to anticoagulant treatment is uncertain and death can occur after stopping the treatment, which justifies discussing the continuation of anticoagulants, and sometimes even their prescription as preventive treatment.

P599 Nutritional status in patients with bronchiectasis
Leila Boussofara, Nadia Bouadara, Imen Touil, Mounia Ben Khelifa, Mourita Sakka, Zaed Khnani. Pneumology Department, Tahar Sfar Hospital, Mahdia, Tunisia

Introduction: The association between nutritional depletion and chronic respiratory diseases has been recognised for years and mainly documented in chronic obstructive pulmonary disease. However little information is available regarding nutritional depletion in patients with bronchiectasis.

Aims of the study: This study was carried out to determine the nutritional status in patients with bronchiectasis and the relationship between the extent of these bronchiectasis on the C-T scan and nutritional depletion.

Methods: In 45 patients with bronchiectasis, body mass index (BMI), serum albumin, C-reactive protein and spirographic indexes were studied.

Results: BMI was <20 kg/m2 in 17% of patients and serum albumin was <35 g/l in 15% of patients. C-reactive protein was >5 mg/l in 80% and were higher essentially in patients who had more than one pulmonary lobe affected by bronchiectasis. BMI was not correlated to the extent of bronchiectasis, but serum albumin was correlated with p=0.02. BMI and serum albumin were not correlated with Post-bronchodilator FEV1 and long-term oxygen therapy.

Conclusion: Malnutrition is coming to be highly prevalent in patients with bronchiectasis. Assessing this nutritional depletion may be offers benefits to patients with bronchiectasis.

86. The latest insights in chronic care

P600 Effects of a novel noninvasive open ventilation system during constant work rate exercise in COPD
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Exercise intolerance limits daily activities of COPD patients. Noninvasive ventilation improves exercise capacity in severe COPD, but previous systems are impractical for ambulatory use. This study evaluated a 0.45 kg noninvasive open ventilation (NIOV) system (Breathe Technologies), designed for nasal delivery of compressed O2 with each inhalation. This was a randomized single-blinded study of 10 men with severe-to-very severe COPD and exercise desaturation. Following a test day in which a cycle ergometer constant work rate (CWR) was established, subjects completed 3 additional days in which 2-3 CWR tests (separated by 1.5 hrs) were performed in random order. Tests were: unencumbered room air, NIOV+sair, NIOV+sO2, or O2 vs standard nasal cannula. Data collected included exercise time, SpO2 and transcutaneous (Tc) PCO2.
Subjects ages were 67±9y, with FEV1/FVC20±6% and FEV1=30±12% pred.

Responses to CWR exercise

<table>
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<th>No O2</th>
<th>P value</th>
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<tr>
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<td>5.2±2.0</td>
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<td>SpO2 (%)</td>
<td>87±5.2</td>
<td>92±4.7</td>
<td>87±3.9</td>
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<tr>
<td>TcPCO2 (mMg)</td>
<td>45.7±7.6</td>
<td>42.6±4.5</td>
<td>44.5±6.5</td>
</tr>
</tbody>
</table>

Mean (SD). One-way, repeated-measures ANOVA. **Time**.

Exercise endurance was dramatically enhanced using the NIO2 system+O2. These data suggest that this system is a practical means to improve tolerance of everyday activities in oxygen-dependent severe COPD.

P601

The minimal clinically important difference (MCID) for the 6 minute walk (6MW) test in COPD in relation to death

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Introduction:
The 6MW is used to assess interventions in COPD but existing esti-
mates of the MCID for this test have been derived from narrow cohorts where a non-blinded
intervention, for example pulmonary rehabilitation, has been applied.

Objective:
To define the MCID for 6MW distance in an unselected population.

Methods:
Data from the ECLIPSE cohort were used. Briefly 2112 patients were
prospectively followed for 3 years in a multicentre study. We defined an index
event as death or first hospitalisation and calculated the change in 6MW (Δ6MW)
in the last 12 month period before the event occurred. If a patient did not have an
event as death or first hospitalisation and calculated the change in 6MW (Δ6MW)
requiring hospitalisation in the EB group (mean difference -0.5, 95% CI -0.8 to -0.2, p=0.003) but not the B group (mean difference
were recorded as outcomes. Exacerbations were defined by changes in the 14-item,
Exacerbations of Chronic Pulmonary Disease Tool (EXACT), which was filled
by patients who were discharged with the EDS-AA service. There was a significant reduction in
the 12 month exacerbation rate requiring hospitalisation in the EB group (mean
difference -0.5, 95% CI 0.8 to -0.2, p=0.003) but not the B group (mean difference
0.0, 95%CI -0.4 to 0.3, p=0.865). Mortality was not different in patients on the
EDS-AA service compared to those that were not (13% vs. 9%, p=0.43)

Conclusion:
The institution of a specialised EDS-AA service at our hospital was
associated with reductions in COPD exacerbations requiring hospitalisation & has
significant cost implications.

P603

Doctors’ awareness of the Gold standard framework (GSF) for palliation in chronic obstructive pulmonary disease (COPD)

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1Aintree Chest Centre, University Hospital Aintree, Liverpool, Merseyside, United Kingdom; 2Respiratory Department, Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom

Background:
The GSF aims to improve the quality of patient care in the final
year of life, to reduce hospitalisation by reducing length of stay, to facilitate rapid
discharge and admission avoidance thereby reduce costs and improving
cost effectiveness.

Aims:
To assess the awareness of the GSF programme in COPD amongst the
doctors and nurses working in various grades from February 2011 to February 2012 in two University hospitals.

Methods:
An anonymous questionnaire was administered to doctors and nurses who had EXACT-defined COPD exacerbations (mean change = 15 units) over 1200+
total patient-days of observation. Exacerbation durations ranged from 1 to 11 days.

Mean daily physical activity on exacerbation days tended to be lower than on
non-exacerbation days: moderate activity, 70±12 vs. 74±10 minutes (p=0.01); and very vigorous
activity, 6±4 vs 1±3.3 minutes (p = 0.07). in summary, this longitudinal study suggests that physical activity decreases during COPD exacerbations.

P604

Early discharge COPD experience: Reduction of severe exacerbations requiring hospitalisation

Joanne King, Rachel Arnold, Richard Russell, Mona Rafaetheus, Respiratory Medicine, Heatherwood & Wexham Park Hospital NHS Foundation Trust, Slough, Berkshire, United Kingdom

Introduction:
Hospital at home schemes for COPD exacerbations are used but
evidence to support them with reductions in exacerbations or mortality has not
been well validated

Method:
Data 12 months pre & post instigation of an early discharge with admis-
sion avoidance service (EDS-AA) was available to COPD exacerbation patients
hospitalised at our hospital, providing care to a population of 450000, covering
the Bucks (B) & East Berks (EB) area. Currently only patients from EB qualify
for care with the EDS-AA team. The EDS-AA team takes patients home within 5
days of admission & offer support for 10 days after. Subsequent to this, patients
are offered direct EDS-AA team access, including home visits,telephone advice &
self-management strategies

Result:
Data was available in 95 COPD patients hospitalised with a severe COPD
exacerbation. The mean (range) age was 75 (48-99) years & severity of COPD was
classified as GOLD I, II, III & IV in 5%, 33%, 31% & 31% of patients. The
mean (range) exacerbation frequency prior to the EDS-AA service was 1 (0-4)
in all patients. 64% of exacerbations occurred in patients from the EB group &
were discharged with the EDS-AA service. There was a significant reduction in
the 12 month exacerbation rate requiring hospitalisation in the EB group (mean
difference -0.5, 95% CI 0.8 to -0.2, p=0.003) but not the B group (mean difference
0.0, 95%CI -0.4 to 0.3, p=0.865). Mortality was not different in patients on the
EDS-AA service compared to those that were not (13% vs. 9%, p=0.43)

Conclusion:
The institution of a specialised EDS-AA service at our hospital was
associated with reductions in COPD exacerbations requiring hospitalisation & has
significant cost implications.
P605 Factors affecting physical activity in patients with air pollution-related illness compared to patients with COPD

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Background: The survival of chronic obstructive pulmonary disease (COPD) patients has been reported to be associated with physical activity (PA). However, there have been no reports concerning PA in patients with air pollution-related illness (API), who have symptoms of dyspnea similar to COPD patients.

Objective: We investigated the factors affecting PA in patients with API compared to COPD patients.

Methods: The study subjects were 30 patients with API and 38 COPD patients. The MRC dyspnea scale (MRC), pulmonary function, muscle strength, six minute walking test (6MWT), incremental shuttle walking test (ISWT), ADL score, SGRQ, CES-D and PA were measured. PA was assessed using a multisensor accelerometer that records steps and energy expenditure for 7 consecutive days after admission for pulmonary rehabilitation. An analysis was performed to examine the differences between the two groups in order to identify the factors that influence PA in patients with API.

Results: Patients with API had significantly better pulmonary function compared with COPD patients (p<0.001). However, their leg strength, exercise tolerance and QOL were significantly worse (p<0.01), and a higher incidence of depression symptoms were seen in patients with API (p<0.05). On the other hand, the differences of MRC and PA were not significant between the two groups. PA of patients with API was correlated with the MRC, %VC, ISWT and ADL score, while PA of COPD patients was not. PA of patients with COPD did not differ from inactive by gender, age, smoking status, somatic co-morbidities, or BMI. Activity correlated significantly with patients’ reported dyspnea (r=0.32, p<0.001), quality of life (r=-0.25, p<0.001), mobility disability (r=-0.37, p<0.001), and bronchial obstruction (r=0.18, p<0.001). Sensation of dyspnea related to physical inactivity. When COPD patient suffers from dyspnea, actions should be taken to promote physical activity.

P606 Mortality of the COPD, a two years retrospective study

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Results: The survival of chronic obstructive pulmonary disease (COPD) patients, indicate that the diagnosis of COPD is made late. The generally high length of life together with short time with COPD in women is a consequence of COPD.

Aim: To describe the disease and the care of COPD patients during their last two years. The aim was also to find out whether there is gender and/or regional differences with regard to terminal COPD care in Sweden.

Method: Retrospective collection of data from patients records from all patients who died due to COPD in 2003 and 2004, in one urban and one rural area, covering 19% of the Swedish population. A questionnaire was developed for collection of information.

Results: Out of 822 deaths from COPD, sufficient information was found for 729 (89%) records who died in 2003-2004 with COPD as the underlying cause of death. Median disease duration was 6.0 (range 0.36-36 years) with no difference by gender or area and the diagnosis was based on lung function measurement in 47% of the patients.

Median age at death was 78 (range 52.96) years in women and 80 (51.99) in men (corresponding figures for all who died in 2003 in Sweden were, 82.6 and 78.1, respectively). The proportion of current smokers at the time of death was 41% in women and 33% in men (p=0.02).

Most of the patients died at hospital (68%) while 13% died at home. Care days during the two last years were in average 23 days and in 63% of the patients a history of one or more exacerbations were reported.

Conclusions: In Sweden women become 4 years older than men but women with COPD had shorter length of life than had men. This indicates a faster COPD-course in women. The generally high length of life together with short time with COPD diagnosis, indicate that the diagnosis of COPD is made late.

P607 Subjective sensation of dyspnea relates to physical inactivity in COPD

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Background: The importance of physical activity in COPD has been recognised. Physical inactivity relates to exacerbations, hospitalisations and mortality. We don’t know why significant proportion of patients who have severe disease can maintain physical activity, while others turn inactive at early stages of the disease. More information is needed about the factors behind physical activity.

Aim of the study: The aim was to study physical activity in well defined COPD patient cohort. We asked about daily life activity, history in sports and barriers for exercising.

Methods: The study was postal survey of the COPD cohort (N=719) recruited in Helsinki and Turku University Central Hospitals and followed since 2005. Validated questions were chosen to evaluate physical activity, dyspnea, and quality of life.

Results: Fifty percent of the participants exercised >2 times a week throughout the year. Participants showed great variation in activity and sport choices. Active patients did not differ from inactive by gender, age, smoking status, somatic co-morbidities, or BMI. Activity correlated significantly with patients’ reported dyspnea (r=0.32, p<0.001), quality of life (r=-0.25, p<0.001), mobility disability (r=-0.37, p<0.001), and bronchial obstruction (r=0.18, p<0.001). Sensation of dyspnea related to physical inactivity. When COPD patient suffers from dyspnea, actions should be taken to promote physical activity.

P608 Increase motivation and efficiency in cystic fibrosis teenagers using sport activities, respiratory muscle training and airway clearance techniques

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Purpose: This study is aiming to demonstrate the efficiency of combined physio-therapy techniques: clearance techniques, respiratory muscle training (RMT) and sport activities, in order to improve clinical outcomes and quality of life in cystic fibrosis (CF) teenagers.

Method: This prospective study was conducted in the Romanian Cystic Fibrosis Centre and included a number of 40 patients, aged between 12 and 18 years. We have used classic techniques of clearance in the daily physiotherapy: the active cycle of breathing techniques, autogenic drainage, oscillating PEPP, high frequency chest wall oscillation (5 times a week), sport programmes (2-4 times a week) and RMT (3 times a week using TrainAir computer system). We have evaluated at baseline and after 24 months of intervention the quality of life (using CFQOL questionnaire) and functional respiratory parameters FVC, FEV1, FEV2,75-95. The statistical processing of data was made using a non-parametric test: the Wilcoxon matched pairs test.

Results: On a long term we noticed a substantial improvement in the clinical outcomes (less acute respiratory hospitalization and medication) and CFQOL scores. We also noticed significant statistical difference (p<0.05), from initial vs. final evaluation in de functional respiratory parameters.

Conclusions: All cystic fibrosis patients should be encouraged to combine airway clearance techniques with respiratory muscle training and sport activities for better inclusion and quality of life.

Acknowledgements: This paper was supported by a research grant from UEFIS-CDI Romania, code TE 36.
Mortality has decreased by 12% compared to previous data (Pilcher et al Thorax 2005). Mortality is lowest in the NMD and other neurological conditions groups. Complete ventilator independence was most common in the COPD and post surgery groups. The data indicates improved survival and weaning success in the group admitted to the LPU compared to those accepted but not transferred.

P610
The impact of COPD care bundles on compliance of care in northwest London
Lauren Lennes, Urvashi Sharma, Hannah Musgrave, Medicine, Imperial College, NIHR CLAHRC for Northwest London, London, United Kingdom

Background: Chronic Obstructive Pulmonary Disease (COPD) is one of the most common respiratory diseases in the UK, causing around 25,000 deaths a year and with a large portion of patients not receiving ideal care for COPD exacerbations. Care bundles, a sequence of evidence based interventions, have been identified as a way of delivering consistent patient care.

Aims: National Institute for Health Research (NIHR) Collaboration for Applied Health Research and Care (CLARHC) for Northwest London implemented COPD discharge care bundles across 7 sites over 18 months (beginning in April 2009) to improve compliance to existing evidence based interventions.

Methods: The COPD discharge care bundles initially included smoking cessation, pulmonary rehabilitation, patient information on self-management, inhaler technique training, and follow-up appointment. Each of the sites adapted the bundle according to available resources and local settings. Weekly data on compliance was entered into a web reporting tool.

Results: The results from the data showed that 1052 patients were discharged with the care bundle, 668 of these patients were discharged having received all the elements of the care bundle (63.5% were fully-compliant). The bundle element with the highest overall compliance was smoking cessation with 92.5%, and lowest was recorded with the follow-up appointment at 77.8%. Overtime improvement to overall compliance was seen across all sites.

Conclusions: This study reveals aspects that impact compliance of care with COPD care bundle elements. The findings offer valuable lessons to future sites interested in implementing COPD care bundles and should be considered in order to improve COPD care.

P611 COPD acute exacerbation care self-audit in public hospitals in Catalonia (Spain)
Joan Escarrabill, Elena Torrente, Cristina Esquinas, Carme Hernández, Eduard Monsó, Montserrat Freixas, Pere Almagro, Ricard Tresserras. Evaluation Area & Master Plan for Respiratory Diseases (PDMAR), Catalan Agency for Health Technology Assessment and Research (CAITAS), Barcelona, Catalonia, Spain Evaluation Area & Master Plan for Respiratory Diseases (PDMAR), Catalan Agency for Health Technology Assessment and Research (CAITAS), Barcelona, Catalonia, Spain, Spain Evaluation Area & Master Plan for Respiratory Diseases (PDMAR), Catalan Agency for Health Technology Assessment and Research (CAITAS), Barcelona, Catalonia, Spain, Spain Evaluation Area & Master Plan for Respiratory Diseases (PDMAR), Catalan Agency for Health Technology Assessment and Research (CAITAS), Barcelona, Catalonia, Spain, Spain

Aims: To carry out a self-audit to survey the quality of care provided to patients admitted with Chronic Obstructive Pulmonary Disease (COPD) acute exacerbation.

Methods: All 48 acute hospitals with chest unit in Catalonia were invited to complete a retrospective clinical self-audit comprising up to 40, 30 or 20 consecutively admitted episodes of COPD exacerbation (according to the size of the hospital measured through the annual COPD discharges: >400 (Group 1), 100-400 (Group 2), <100 (Group 3)). Results are presented as median, mean or ± standard deviations. Comparisons between hospitals were performed using one way ANOVA.

Results: Data for 910 episodes from 30 hospitals (62.5%) were received (a sample of >70% of discharges). Age 74.9±9.8, males (83.3%), FEV1 41±15, mean of Charlson index by age 4.5±2. Median previous year respiratory admissions=2, IQ=1.3. Mortality: inpatient (4.4%), 90 days (4.4%). Readmission rate (RR) at 90 days: 23%. Mean length of stay (LOS): 8 days (SD=7). A significant variation was observed between the 3 hospitals groups: 8 (SD=6), 9 (SD=4), 7 (SD=5), (p<0.0001). There were no significant differences in inpatient mortality but there were significant differences in 90 day hospital RR (26% vs 23% vs 16%, p<0.045) and 90 day mortality (4% vs 5% vs 8%, p=0.050). In the discharge report there was information on smoking habit (35%, in smokers’ patients), ABG room air (18%) and lung function (52%).

Conclusion: We observed a considerable variation in the care provided between hospitals with a high variability in LOS, 90 day RR and 90 day mortality. The information in discharge report should be improved.

P612 Effect of cough on health-related quality of life in COPD
Helene Bellas 1,2, Bronwen Connolly 3, Surinder Biring 3, Billie Hurst 2

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Background: Current disease-specific health related quality of life (HRQL) measures in COPD focus on symptoms such as breathlessness, fatigue, mastery and social disease aspects. HRQL is known to be affected in idiopathic cough patients and given the reported prevalence of cough in COPD, determining its effect on HRQL is justified.

Aim: Determine the relationship between cough and HRQL in COPD.

Method: Consecutive, unselected participants with COPD were recruited from outpatient clinics. Those who met eligibility criteria completed a set of questionnaires; COPD Assessment Questionnaire (CAT) to determine the presence of cough. The Leicester Cough Questionnaire (LCQ) as a cough-specific, HRQL measure and Cough Visual Analogue Scale (VAS) to indicate self-reported cough severity.

Results: Forty participants were recruited. Baseline demographics showed a mean (±SD) age of 65.2 (±11.9) years, mean (±SD) FEV1% predicted of 49.0% (±18.6), the majority of the sample was of Caucasian background (80%) and the group was well matched in terms of gender (M:F, 22:18). Median (IQR) CAT cough score (5) was shown to be 3 (2-3.5), no participant selected 0 which would indicate ‘no cough at all’. Mean (±SD) VAS score 50.0 (±27.0). Median (IQR) LCQ scores (2/1) were found to be 16 (11.8-18.6), for the group as a whole with the physical domain showing the poorest score of all domains. Median LCQ score decreased with an increasing CAT score. A significant inverse relationship was evident between median LCQ score and VAS (r = 0.70, p<0.0001).

Conclusions: Cough was prevalent in a cohort of stable COPD patients with moderate to severe disease severity. Furthermore, increasing cough severity is associated with greater impairments in HRQL.

P613 Physical activity and sleep duration following hospitalisation with exacerbation of COPD vs. stable COPD & age matched controls
Dilber Yilmaz 1, James Dodd 1, Dinesh Shrikrishna 2, Nick Hopkinson 2

1Clinical Sciences, St. George’s University, London, United Kingdom; 2Muscle Laboratory, Royal Brompton Hospital, London, United Kingdom

Background: Exacerbations are known to reduce physical activity, but little is known about their effect on sleep.

Aim: This study measures physical activity and sleep quantity in participants recovering at home following hospitalisation for a COPD exacerbation and compares them with stable COPD patients and controls.

Methods: We recruited 23 COPD patients immediately following hospital admission for exacerbation (Acute), 34 stable COPD patients (Stable) and 19 age-matched people (Control). Physical activity and sleep duration were measured...
P614 Changes in physical activity and sleep duration following hospitalisation with acute exacerbation of COPD

Dilber Yılmaz1, James Dodd2, Dinesh Shrikrishna3, Nick Hopkinson3.

Objective: To investigate the effects of the past year of a home care based, respiratory therapist centered transition of care program for patients who require home oxygen therapy following hospital admission for an exacerbation.

Methods: To evaluate the effects over the past year of a home care based, respiratory therapist centered transition of care program for patients who require home oxygen therapy following hospital admission for an exacerbation. The 30 day rehospitalization rate (5%) for those patients who required supplemental oxygen on discharge was significantly lower than the historically observed rates (25%) in the Western Pennsylvania area.

Results: 555 patients from 23 different hospitals in the Western Pennsylvania area were enrolled into the program from March 2010 through February 2012. The primary discharge diagnosis was: COPD 69%; CHF 14%; hypoxemia 6%; pneumonia 4%; and other 7%. The overall readmission rate for the entire group was 5%. The 30 day readmission rate for those with COPD was 3% and for those with CHF was 3%.

Conclusions: With the use of this novel respiratory therapist based transition of care program, the 30 day rehospitalization rate (5%) for those patients who required supplemental oxygen on discharge was significantly lower than the historically observed rates (25%) in the Western Pennsylvania area.
at HH can be useful to improve functional capacity and quality of live in these patients. Nevertheless, to assess exercise tolerance at home complexity is complex. The modified Glittre ADL-Test is a measure of functional status that we have adapted to patient’s home.

**Objective:** Analyze the modified Glittre ADL-Test as a tool to measure exercise tolerance during an AECOPD at HH.

**Method:** 17 AECOPD patients, 15 males (median (ICR): 66 (60-84) years, FEV1 38% (29-44) predicted) attended at HH accepted to participate and completed 3 visits (V1: HH discharge, V2: 10 days post discharge, V3: 1 month post discharge). Outcomes: 3) Modified Glittre ADL-Test: laps (m), VO2 and VE; 2) COPD Assessment Test; 3) MMRC and London Chest Activities of Daily Living (LCADI); 4) Modified Baecke (V1 and V3); 5) Handgrip.

**Results:** Modified Glittre ADL-Test laps increased (4 vs 5 l/min, p<0.005), VO2 per lap (242 vs 229 vs 177 mL/min, p<0.03) and VE per lap increased (7 vs 7 vs 5 L/min, p<0.01). CAT (18.5 vs 11.5 vs 12, p<0.01), MMRC (2 vs 1.5 vs 1, p<0.01) and Modified Baecke (4 vs 14, p<0.01) also significantly improved between each assessment. There were no differences in Handgrip or LCADI.

**Conclusion:** Modified Glittre ADL-Test was suitable to measure exercise tolerance following an AECOPD attended at patient’s home.

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**P619 Six minute walking test in chronic respiratory failure: Which reflects the patient clinic status, walking distance or %predicted value?**

Zuhal Karakurt, Gökay Güngör

**Aim:** Six minute walking test (6MWT) with limited values are limited for the patients who has been prescribed noninvasive mechanical ventilator due to chronic respiratory failure (CRF).

**Methods:** 6MWT is performed in patients during June–December 2011 who were already using HMW due to CRF and followed in our polyclinic. WD, ideal and lower limit of normal WD according to gender, age, BMI and %predicted of ideal values were calculated. Parameters that recorded during standard 6MWT and %predicted values were compared according to arterial blood gas (ABG), spirometry values and concomitant diseases.

**Results:** Correlation of WD and %predicted values for spirometry and ABG values of 144 patients were shown in Table 1.

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Patients diagnosed were grouped as COPD, OHS, kyphoscoliosis and parenchymal lung diseases and their 6MWT were compared in Table 2.

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**Conclusion:** Predicted % values of 6MWT are better correlated with respiratory functions than WD for patients who use HMV due to CRF.
Objective: To compare functional (torque) and metabolic (deoxygenation) effects of NMES at increasing levels of stimulation in patients with COPD and age- and gender-matched controls.

Methods: Fifteen males with moderate-to-severe COPD (FEV1 = 46.2±18.1% pred) and 10 controls underwent high-frequency (50 Hz) NMES at 20 to 50 mA. Torque was measured by isokinetic dynamometry, muscle deoxygenation (HHb) by near infrared spectroscopy, and muscle mass by DEXA.

Results: Maximal voluntary contraction (MVC) was significantly higher in patients than controls; these differences, however, disappeared after muscle mass correction (p = 0.05). There were progressive increases in torque and HHb with amplitude of stimulation in both groups. Although absolute torque at given level of stimulation was systematically lower in patients, MVC-corrected values were similar (20 ± 50 mN and 57 ± 3±7% and 24.4±8.4% in patients and 64±5±2 and 22.4±10.0% in controls, respectively). Moreover, there were no between-group differences in HHb (% cuff-induced maximal) across the stimulation intensities (p = 0.05).

Conclusions: Our results indicate preserved functional and metabolic responses to NMES in non-depleted patients with moderate to severe COPD. These data suggest that they might derive full physiological benefit from this intervention.

Phyllis Murphie
CREWS – A validation pilot
suggest that they might derive full physiological benefit from this intervention.

Conclusions: We interrogated the Patient Outcomes and Information Service (POINTS) database of participating practices in the UK. The POINTS provided by GlaxoSmithKline UK Ltd as a service to medicine is delivered by Quintiles Data was collected between 2007-08 and 2009-10.

Results: 1265 GP practices had a list size of 7 million with 160000 COPD patients. 911 practices returned total list sizes (1.7% prevalence of COPD) 51,000 (32%) had a COPD review recorded yet 85,000 (53%) had spirometry recorded within 15 months, 124,600 had flu and/or pneumococcal vaccination status recorded (82%) which only 15% had exacerbation frequency recorded. Increases in MRC dyspnoea score (MRCD) recording occurred from 2007 at 28% to 44% in 2009 (p < 0.001). The most common prescription was short acting β agonist SABA in 67%, ICS/LABA combi inhaled in 47%, LAMA in 30%, 24,000 (15%) were prescribed an ICS inhaler (outside of licence and against NICE guidelines). 19000 patients with mild airflow limitation were on ICS-LABA beyond licence (FEV1 60-80%). We found 10,000 potentially misdiagnosed patients with FEV1 < 80%; of these 38% were on ICS-LABA and 20% were on LAMA.

Conclusions: Over-treatment of mild COPD with ICS-LABA or LAMA is frequent. Exacerbations rates were poorly recorded suggesting incomplete COPD reviews which may lead to failure of appropriate management. Exacerbation frequency recording should be incorporated into QOF pay.

P625
Current COPD care in the UK – Data from 160000 patients in the POINTS database
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Background: COPD is a major UK healthcare cost. Differing standards of care exist e.g. those qualifying for payment. Quality & Outcomes Framework (QOF) vs. patient-focused incentivised NICE guidelines.

Aims: To define a large UK wide COPD cohort and describe their primary care management compared to these standards.

Methods: We interrogated the Patient Outcomes and Information Service (POINTS) database of participating practices in the UK. The POINTS provided by GlaxoSmithKline UK Ltd as a service to medicine is delivered by Quintiles Data was collected between 2007-08 and 2009-10.

Results: 1265 GP practices had a list size of 7 million with 160000 COPD patients. 911 practices returned total list sizes (1.7% prevalence of COPD) 51,000 (32%) had a COPD review recorded yet 85,000 (53%) had spirometry recorded within 15 months, 124,600 had flu and/or pneumococcal vaccination status recorded (82%) which only 15% had exacerbation frequency recorded. Increases in MRC dyspnoea score (MRCD) recording occurred from 2007 at 28% to 44% in 2009 (p < 0.001). The most common prescription was short acting β agonist SABA in 67%, ICS/LABA combi inhaled in 47%, LAMA in 30%, 24,000 (15%) were prescribed an ICS inhaler (outside of licence and against NICE guidelines). 19000 patients with mild airflow limitation were on ICS-LABA beyond licence (FEV1 60-80%). We found 10,000 potentially misdiagnosed patients with FEV1 < 80%; of these 38% were on ICS-LABA and 20% were on LAMA.

Conclusions: Over-treatment of mild COPD with ICS-LABA or LAMA is frequent. Exacerbations rates were poorly recorded suggesting incomplete COPD reviews which may lead to failure of appropriate management. Exacerbation frequency recording should be incorporated into QOF pay.

P626
The need for the integrated care for advanced COPD patients in the northern Poland (Pomerania)
Iwna Dampa-Konstanska1, Lidia Werachowska4, Amelia Szymanowska-Narloch3, Piotr Krzakowski3, Małgorzata Kaczmarsk2, Ewa Jassem1, 1Department of Allergology, Medical University of Gdansk, Poland; 2Department of Pneumonology, Province Hospital, Chojnice, Poland; 3Department of Sociology, and Education, University Nicolaus Copernicus, Torun, Poland; 4Department of Nursing, Medical College, Chojnice, Poland

COPD is one of the most prevalent chronic disease, significantly increasing morbidity and mortality in developed countries. Symptom control and preventing risk of exacerbation is the main goal in the management of COPD. Poor compliance and insufficient self-management, especially in the more advanced patients are recognized causes of increased exacerbation rate. Currently, in the Northern Poland the model of integrated care for advanced COPD patients is to be introduced. However little is known about the need and acceptance for such a care among patients and their relatives. Thus, the aim of this initial study was to assess the QoL (using SGRQ) in 30 consecutive advanced COPD patients living one of the small towns in Pomerania and their acceptance for continuing support (two times a week during one month) delivered in their homes (assessed by specially constructed questionnaire). Home intervention included two-hours meeting (structured as follows: 30 min of education including assessment of the proper use of inhalators and medications intake, 30 min of physical activity, 30 min of small-talk focused on the subject proposed by patient, and 30 min of the assessment of symptoms, palsoximetry and PEF measurement) with medical caregiver. Results demonstrated poor QoL in the study group during the stable period of the disease (total score of SGRQ – mean: 71; range: from 24 to 91) and the full acceptance for the home support (28 patients were very satisfied, 2 were satisfied). These findings confirmed the need for integrated care in Pomerania and chance for realization of the program.
P627 Family care in advanced COPD: Perceived difficulties and expectations of support from services
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Chronic Obstructive Pulmonary Disease (COPD) is an incapacitating, highly prevalent disease which often requires intensive support from patient’s family members. However, knowledge about the difficulties experienced by family members in their caregiving role remains scarce. This study aimed to explore the difficulties experienced by family carers, and their expectations towards social and health support services.

A qualitative, cross-sectional study was conducted with 21 family carers of COPD patients at advanced grades (GOLD 3 and 4). Semi-structured interviews were performed to collect data. Participants were mostly female (n=20), with a mean age of 60.9±12.35 years old, spouses (n=12) and caring for more than 4 years (n=18). All interviews were audiorecorded, transcribed and submitted to content analysis by 2 independent judges.

The major difficulties reported are related to: i) provide support in basic [washing (n=1), dressing (n=2)], and in instrumental activities of daily living [preparing meals (n=4)]; ii) communication with patient (n=2); and iii) restrictions in social activities (n=2). Six carers did not identify any difficulty. Most of participants (n=12) could not identify how formal support services could help them. They lack of information about community resources might explain these results. Strategies towards effective flow of information must be addressed in order to prevent caregivers’ burden.

P628 Rehospitalization rates for patients with pneumonia who require supplemental oxygen therapy following hospital discharge
Brian Carlin1, Kim Wiles2, Dan Esleby1. 1Pulmonary and Critical Care Medicine, Allegheny General Hospital, Pittsburgh, PA, United States; 2Medicine, Klingensmith HealthCare, Ford City, PA, United States

Objective: To compare the hospital readmission rates for patients with pneumonia who require supplemental oxygen therapy following an exacerbation who are entered into a home-care based, respiratory therapist centered transition of care program.

Method: Patients with a diagnosis of pneumonia who required supplemental oxygen therapy on hospital discharge were entered into a post hospitalization transition of care program (Discharge, Assessment and Summary @ Home (D.A.S.H., Klingensmith HealthCare, Ford City, PA)). Patients with a diagnosis of COPD were excluded from this analysis. The program consists of face to face visits by a respiratory therapist with the patient on days 2, 7, and 30 following hospital discharge. Education, behavior modification, skills training, oxygen titration during performance of activities of daily living, clinical assessment, and adherence data collection are components of the program. The 30 day readmission rates following discharge for those patients entered into the program over a twenty four month period were evaluated.

Results: 22 consecutive patients with pneumonia from 23 different hospitals were enrolled into the program over the two year period. None (0%) of the patients were rehospitalized within the first thirty days following hospital discharge.

Conclusions: The use of a multiple visit respiratory therapist based patient centered management program resulted in a significant decrease in the 30 day readmission rates for those patients who were discharged following a hospitalization for pneumonia.

P629 Psychological distress in asthma and COPD
Bransilava Milenevkov1,2, Aleksandra Ilic1,2, Sanja Dunic-Ianic1,2. 1Faculty of Medicine, University of Belgrade, Serbia; 2Clinic for Pulmonary Diseases, Clinical Center of Serbia, Belgrade, Serbia

Background: The effective control of asthma requires a treatment regimen that may be compromised by psychological factors, such as anxiety and depression.

The aim of our study is to estimate the prevalence of anxiety and depression among adults with stable persistent asthma.

Methods: We analyzed the data from 50 adult patients with persistent asthma (group A). Fifty patients with COPD (GOLD II-IV) were the control group (group B). The pulmonary function test was performed by spirometry. Depression and anxiety scores were assessed by Hospital Anxiety and Depression Scale. The prevalence of anxiety and depression was calculated in both groups and the difference between groups was estimated. The correlation between pulmonary function parameters and psychological distress was calculated.

Results: The anxiety score in Group A was 6.2±2.3 and in Group B 7.87±2.35. The depression score in Group A was 4.9±2.4 and in Group B 7.97±4.04. The difference between groups was significant for both anxiety and depression (p<0.05).

There was no correlation between psychological status and pulmonary function tests in group A (p>0.05) and in group B (p>0.05).

Conclusion: This research suggests the importance of psychological distress screening for patients with persistent asthma, as COPD also. Further studies are needed to examine the correlations between the severity of the respiratory disease and mental status and to target the psychological factors that contribute worsening asthma and COPD.

P630 Influence of anthropometric characteristics in respiratory reserve volume of morbidly obese subjects
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Introduction: The reduction of the respiratory reserve volume (ERV) is considered the most consistent finding for changes in lung function in morbid obesity. The importance of decreased ERV in morbid obesity is attributed to the known association between these volumes with the closure of small airways, which causes hypoxemia.

Objective: To correlate ERV with anthropometric characteristics of morbid obese women.

Methods: Cross-sectional study with morbidly obese (BMI=40kg/m2) and control (BMI between 18.5 and 24.9 kg/m2), both with normal lung function. The body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), and neck circumference (NC) were measured. Subsequently, pulmonary function test were performed.

Results: A total of 30 morbidly obese (BMI 44.1±14.1 kg/m2) and 30 lean women (BMI 22.1±1.18 kg/m2) were evaluated. ERV was significantly lower in obese [0.28 (0.14-0.60 L) when compared to lean women [0.74 (0.51-1.08 L)]. The percent-age of predicted values of forced expiratory volume in one second (FEV1) were significantly lower in morbidly obese (88.31±4.31L/min) when compared to lean women (102.75±13.2L/min). There were no differences in forced vital capacity (FVC), the ratio FEV1/FVC. There was negative correlation between body mass index, BMI, waist circumference (WC), waist-to-hip ratio (WHR) and neck circumference (NC) with ERV, respectively (r= -0.3757, -0.4112, -0.4711, -0.3456, -0.5145).

Conclusions: The ERV is influenced by body mass, BMI, WC, WHR and NC.

P631 Association between the mini nutritional assessment and the COPD assessment test
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Background: The Mini Nutritional Assessment® (MNA) has not been studied extensively in COPD patients.

Objectives: We evaluated whether COPD patients with impaired health status as determined by the COPD Assessment Test (CAT) have poor nutritional status according to the MNA.

Methods: We recruited clinically stable male COPD outpatients (age, ≥65 years) as a cross-sectional study. We conducted the following examinations: pulmonary function tests, nutritional assessment using the MNA questionnaire (high scores indicate good nutritional status), the CAT, and dyspnea evaluation. The patients were divided into 2 groups: (A) those with CAT scores ≥10 and (B) those with CAT scores <10. We also calculated 4 scores exploring the domains of the nutritional status from the MNA questionnaire: anthropometric, general, dietary, and subjective scores.

Results: The study included 68 patients (mean age, 75.4± years). The total score was significantly correlated with FEV1% predicted, BMI, the modified Medical Research Council dyspnea score, and the CAT score (Spearman’s rank correlation coefficient, ρ = 0.298, p = 0.013; ρ = 0.701, p < 0.0005; ρ = −0.373, p = 0.002; and ρ = −0.363, p = 0.002; respectively). Group (A) (n = 47) had significantly lower total, general, dietary, and subjective scores than group (B) (n = 21) (p = 0.003; p = 0.029, p = 0.045, and p = 0.014, respectively, Mann Whitney U-test).

Conclusions: The nutritional status as determined by the MNA was associated with pulmonary function, dyspnea, and the COPD-related health status. In addition, the nutritional status as determined by the MNA was significantly lower in COPD patients with CAT scores ≥10 than in those with CAT scores <10.

P632 Usability of digital media in patients with COPD: A pilot study
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Digital media can serve as the main interface between the patient and the care-
Long-term oxygen therapy (LTOT):Retrospective audit on ten years prescriptive appropriateness

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Background: Guidelines focus on three key issues for appropriate prescription of LTOT: patients should be nonsmokers, in a stable condition, and they should use oxygen for at least 15 h/day.

Aim: To evaluate prescriptive appropriateness in a group of patients with Chronic Respiratory Failure during a period of ten years.

Methods: 702 patients (mean age 74.1±11, 56% males) were prescribed with LTOT between 2002 and 2011. Prescriptive appropriateness based on PaO2 or non invasive SaO2, as indicated by the ERS guidelines.

Results: O2 source: 84.1% liquid, 13.5% concentrator, and 2.3% gas. Main reason for prescription was pulmonary: 88.4%, 69.1% for COPD. Among patients with PaO2 and SaO2 traceable values (n=60), the prescription resulted appropriate for 240 (39.4%). Pneumologists showed higher prevalence of LTOT inappropriate than other prescribers: difference not significant. We noted low appropriateness in the first third of the study, followed by a constant improvement: at that time we performed an educational program for all prescribers. On 2011 we noted a new drop in appropriateness.

Conclusion: The results confirm that a considerable amount of patients are inappropriately prescribed. Efforts need to improve the adherence to the published international guidelines for LTOT prescription through continuous educational programs aimed to all prescribers.
short burst, 53% ambulatory, 47% long term). The oxygen was prescribed mainly by Respiratory Nurses (40%) and General Practitioners (31%).

Methods: We enrolled 138 consecutive patients with chronic lung diseases who underwent a PR in a monocenter, prospective study (CEPRO 2011-036). The global score of the VSRQ (scored from 0 to 80 with 8 questions), SGRQ (scored from 0 to 100 with 8 parts) and HAD (scored from 0 to 42 with 7 questions for anxiety evaluation and 7 for the depression) were measured at the beginning and the end of a six week outpatient PR. HRQL improvement was measured by the increase of the VSRQ score and the decrease of the SGRQ and HAD scores.

Results: The VSRQ correlated with the SGRQ (r=-0.49, p<0.01) and the HAD (r=-0.47, p=0.01). After PR, there was a significant improvement of the VSRQ (46 vs 39, p<0.001), SGRQ (38.3 vs 42.3, p=0.019) and HAD (14 vs 15.1, NS). The VSRQ increase correlated with the SGRQ decrease (r=-0.39, p<0.01).

Conclusions: The VSRQ score correlates with the SGRQ and HAD scores. Our data demonstrate the clinical interest of this simplified test to evaluate the HRQL in PR.

88. Standard of care, incidental findings, image acquisition
In this study, we have successfully validated relative alveolar sizes as measured with the use of predictive correction factors. Lung tissue, the experimentally obtained OFDI measurements could be re-scaled on average. We discovered that the relative change in size between alveoli was extremely on potential refraction effects that are not visible in micro-CT images. Therefore, we compared the cross-sectional area, perimeter, volume, and surface area of matched subpleural alveoli from micro-CT and OFDI images. Furthermore, we developed a ray-tracing model that approximates the reconstructed alveolar size within OFDI images based on fast imaging speed (>10fps). In order to enable quantitative comparisons about alveolar behavior under various ventilation strategies or pathologies, it was crucial to investigate the validity of alveolar size measurements obtained from OFDI images. Therefore, we compared the cross-sectional area, perimeter, volume, and surface area of matched subpleural alveoli from micro-CT and OFDI images. We fixed air-filled swine samples. Furthermore, we developed a ray-tracing model that approximates the reconstructed alveolar size within OFDI images based on potential refraction effects that are not visible in micro-CT images. We observed that the relative change in size between alveoli was extremely well correlated between the two imaging techniques (r=0.9, p<0.0001), but OFDI images underestimated absolute sizes compared to micro-CT images by 27% (area), 5% (perimeter), 46% (volume), and 25% (surface area) on average. Using our model and OFDI measurements of the refractive index for fixed and fresh lung tissue, the experimentally obtained OFDI measurements could be re-scaled to approximate the micro-CT measurements with dramatically reduced error (<10% for all size parameters). In summary, we have successfully validated relative alveolar sizes as measured within OFDI images and show the potential to obtain absolute size measurements with the use of predictive correction factors.

Efficacy of chest CT in establishing the cause of primary spontaneous pneumothorax
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Background: The cause of primary spontaneous pneumothorax (PSP) is thought to be a rupture of a subpleural bleb or bulla (BB). Thoracoscopy is considered the gold standard in determining the presence of BB, but this is an invasive procedure that has limitations. Recent studies have shown CT to be almost as sensitive for detecting subpleural blebs and bullae as thoracoscopy. We found CT to be a very sensitive method of diagnosing PSP in patients who underwent preoperative non-contrast chest CT followed by wedge pulmonary resection and pleurodesis through mini-thoracotomy. Results of CT, surgery, and pathological study of resected tissue were compared.

Methods: The study included 42 patients with PSP who underwent preoperative non-contrast chest CT followed by wedge pulmonary resection and pleurodesis through mini-thoracotomy. Results of CT, surgery and pathological study of resected tissue were compared.

Results: The sensitivity and specificity of CT was 96.4% and 76.5% respectively. Correlation was also found comparing the size of BB measured on CT and the pathological study. In 14 cases (30%) no BB were found on CT, during surgery or pathological examination. In all of these cases a finding known as “apical lines” (AL) was demonstrated on CT. The pathological examination of the resected lung specimens showed fibrosis and emphysema.

Conclusions: We found CT to be a very sensitive method of diagnosing BB in PSP patients. The study also demonstrated the presence of AL in PSP patients which were the radiological manifestation of limited fibrotic and emphysematous changes in the apex which may be the cause of PSP in our series of patients. Preoperative diagnosis of the cause of PSP helped to employ the proper surgical technique and to prevent recurrence of PSP.

Assessing the standard and accuracy of chest x-ray reporting by medical physicians in an acute medical take
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Introduction: The reporting of CXRs for medical patients admitted to hospital was across Europe. Comparison between physicians and radiology reporting has suggested radiologists provide improved quality (1) and accuracy (2) of reporting. In our trust the radiologist report on all the admission CXRs but this may not be available at the time of physician review.

Aim: To assess if disagreement in reporting between general physicians and a radiologist would have an impact on the medical management of a patient.

Method: We retrospectively compared the reporting of 50 CXRs by the medical physician with that of a radiologist.

Results: The overall concordance of reporting was 78%. There were 21/50 normal CXRs of which the physician correctly reported 20/21 (95%) as normal. The remaining were either acute changes (somewhat severe change) or chronic changes (15/50, 30%). Only 6/14 (43%) acutely abnormal CXRs were reported correctly and 11/15 (73%) reported on chronic changes by the physician.

Conclusion: Correctly identifying an acute diagnosis was less than 50%, particularly differentiating between pneumonia and heart failure, yet many trusts require the physician to report on CXRs. Undergraduate and post-graduate training in internal medicine does not formally train or examine in radiology and given these findings more training and service development needs addressing for patient safety.

References:

X-ray interpretation: A self-assessment survey
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Aim: To assess the confidence of hospital based doctors in reviewing plain radiographs.

Methods: An online e-survey tool collected responses from 600 doctors from the West Midlands area, UK. They were asked to rate their confidence as: not confident, will always need senior help; somewhat confident in interpreting some conditions; confident of routine and common conditions; very confident, seek radiology advice occasionally; highly confident, almost never seek radiology advice. We also asked them to self assess their confidence in identifying some common findings on x-rays; and collected data on any formal or informal training they had received.

Results: 241 (40%) responses were received; of these 165 were from medical and 76 from non-medical specialties. The level of confidence expressed by medical doctors in interpreting chest x-rays (48.5%) was significantly higher than abdominal (17.4%) and skeletal x-rays (6.2%). Doctors in non-medical specialties were better with skeletal x-rays (22.5%). Of the 241, 70 had been to a radiology course, 127 had some form of formal and 57 had informal training. 11 (9 medical trainees) did not have any form of training. 17/241 felt that there should be radiology training for all doctors, and it should be a compulsory part of the training portfolio.

Conclusion: There was variability in confidence amongst hospital doctors in interpreting x-rays across training grades and clinician groups. Basic radiology training as a separate competency may need to be considered in the training programmes and e-portfolio of hospital doctors. Training in chest radiograph interpretation should merit focused attention in the respiratory specialty training as well as the HERMES curriculum.

Lung ultrasound as an ambulatory investigation tool in respiratory medicine: An audit of clinical practice
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Introduction: Lung ultrasound is an imaging tool which is increasingly used by nonradiologists physicians in the intensive care unit and the emergency department. However, there is a lack of data concerning lung ultrasound directly provided by the pulmonologist during ambulatory investigations.

Methods: The study is an audit of clinical practice of the respiratory diseases ambulatory of a tertiary care university hospital. Consecutive lung ultrasounds, performed by pulmonologists, were prospectively recorded from April 2011 to...
February 2012. The main indication, methods and clinical consequences were registered on a web-database.

**Results:** 8 experienced operators performed 112 exams on 92 patients (aged 66.4 years, mean ± 49 females). The mean duration of the exam was 8.2 minutes. B-mode was used in all patients, while functions such as M-mode and Color-Doppler were needed in 10% and 4%, respectively. Convex probe was the most used as a single transducer (82% of the cases); linear probe was used in association with the convex or as a unique probe in 22% of the exams. The main indications were: pleural effusion (32%), chronic obstructive pulmonary disease (12%), pneumothorax (10%), chest pain (8%), acute exacerbation of COPD (6%), heart failure (4%), and epigastria dysplasia (2%). The pneumologist who executed the exam reported that in 72% of the cases lung ultrasound had a clinical impact, even if minor, on patient management.

**Conclusions:** The execution of lung ultrasound is a rapid and feasible imaging tool which may often provide clinically relevant data during ambulatory consultations. Further studies will be needed to evaluate the impact of lung ultrasound on the patients’ management.

**P646**

One year’s experience of mobile bedside chest ultrasound service for pleural diseases in a district general hospital

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**Introduction/Objectives:** The role of chest ultrasound for the management of pleural diseases has evolved rapidly over the last few years. The National Patient Safety Agency’s rapid response report and the latest British Thoracic Society guidelines have recommended the use of chest ultrasound prior to intervention in pleural effusion. We describe our experience with using mobile bedside chest ultrasound including complication rates, impact on waiting time and length of hospital stay.

**Methods:** Prospective data from all patients receiving mobile chest ultrasound over a 12 month period in 2011 was collected. Scans were performed by an acute medicine physician and respiratory registrars with level 1 competency in chest ultrasound as classified by the Royal College of Radiology. Case notes, coding and radiology data were assessed, and comparisons made to waiting time and length of hospital stay for those receiving chest ultrasound in the radiology department.

**Results:** Overall 126 scans were evaluated with 123 performed the same day as requested and 3 the next day. Of those, 24 were followed by chest drain insertion, 56 by pleural aspiration and 46 with no intervention. Two patients had small pneumothoraces post aspiration (3.8%) whilst 1 chest drain insertion and 2 pleural aspirations failed. Average hospital stay was 13.3 days compared to 18.6 days for those having scans in the radiology department.

An average time of 21 minutes which included scanning duration, collecting and returning the device was documented in 71 patients.

**Conclusion:** Mobile bedside chest ultrasound when performed by level 1 competent physicians appears to be safe and considerably reduces length of hospital stay.

**P647**

Incidental findings on CTPA at a district general hospital

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**Background:** CT Pulmonary Angiogram (CTPA) is the gold standard investigation for Pulmonary Embolism (PE) in the UK.

**Aims:** Due to the quality of CTPA imaging, incidental findings are often identified. We investigated the incidence of these findings on CTPA studies done at a large district general hospital.

**Methods:** CTPA reports over a 12 month period in 2011 were reviewed retrospectively. Data was collected regarding PE, incidental findings and chest x-ray (CXR) reports at time of CTPA.

**Results:** A total of 216 CTPA reports were analysed. Results are seen in Table 1. Of the patients who had consolidation on CTPA, 9 (17%) had no consolidation seen on CXR. In those with a pleural effusion on CTPA, 42 (67%) had no effusion on CXR and of the patients who had a malignancy, 21 (75%) had not had this detected on CTPA.

**Discussion:** Out of 216 patients, 15 (6.9%) had no CXR prior to CTPA and 13 (6%) had no formal CXR report.

**Conclusion:** At our centre, CTPA yielded 11% diagnosis rate for PE. A sizeable number of incidental findings were detected resulting in further investigations and treatments of patients. The sensitivity of CXR is not sufficient to rule out consolidation in this set of patients. This study emphasises that CTPA is important in the diagnosis of PE, but also in identifying alternative pathologies not seen on routine CXR.

**Reference:**


**P648**

Evaluation of incidental findings other than PE on CT pulmonary angiogram

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**Background:** PE is a common cause of admission to hospital, with CTPA increasingly being used to make this diagnosis. However, incidental findings other than PE are frequently noted. Our objective was to investigate the incidence of these, and the implications in patient management.

**Method:** This was a retrospective study which involved all inpatients who had undergone CTPA from June until November 2009. Data was obtained from PACS and electronic records. Abnormalities other than PE was identified and new lesions were differentiated from old.

**Results:** A total of 112 patients were identified with the majority being male (67%). The mean age was 61 years (range 23 to 97). SOB was the most prevalent presenting symptom in 62 (55.3%) followed by chest pain 37 (33%). Chest radiographs were performed in 110 (98.2%) patients, of 52.7% were normal. PE was found in 28 (25%) patients. Incidental findings were seen in 56 (50%) patients, 40 (71.4%) of these were new of which 28 (70%) of them needed further interventions. The most prevalent findings were pneumonia 22 (39%) followed by fibrosis 12 (5.5%), effusions 5 (8.9%) and lung masses 4 (7%). 10 patients had both PE and incidental findings.

The average length of stay was 7.3 days. Patients with additional pathology stayed a day longer (7.5 days) than those without (6.9 days).

**Conclusion:** In patients with suspected PE, CTPA has become a routine investigation with a yield of 25% in our study. Incidental pathology was evident in 50% of scans, which is in keeping with other studies. The addition of these findings on CTPA impacts on the length of stay of patients in hospital by one day, and has important implications for the acute clinical management of these patients.

**P649**

Audit of the investigation of suspected pulmonary embolism in pregnancy

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**Introduction:** The diagnosis of pulmonary embolism (PE) in pregnancy relies upon criteria based clinical assessment supported by the use of appropriate imaging modalities. There is wide discrepancy between clinicians in the way the condition is investigated and this may have profound implications for diagnosis, resource allocation and radiation dose delivered to the mother and foetus.

**Methods:** Using the radiology database, all pregnant women who were investigated for PE were reviewed retrospectively. Data was collected regarding PE, incidental findings and chest x-ray (CXR) reports at time of CTPA.

**Results:** A total of 216 CTPA reports were analysed. Results are seen in Table 1. Of the patients who had consolidation on CTPA, 9 (17%) had no consolidation seen on CXR. In those with a pleural effusion on CTPA, 42 (67%) had no effusion on CXR and of the patients who had a malignancy, 21 (75%) had not had this detected on CTPA.

**Discussion:** Out of 216 patients, 15 (6.9%) had no CXR prior to CTPA and 13 (6%) had no formal CXR report.

**Conclusion:** The audit shows that there is a lack of standardisation pathway for suspected PE in pregnancy and the choice of investigative modality was clinician dependent. There is a need for the international medical community to develop robust guidelines to all standardised care, effective use of resources and minimize maternal and foetal radiation exposure.

**P650**

MDCT in tracheal stenosis assessment


**Purpose:** MDCT assessment of the degree and extent of tracheal cicatricial stenosis (CTS) in comparison to the results of endoscopic examination and intraoperative data.
P651 The difference in upper airway morphology between supine and upright posture
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Introduction: The effect of upper airway (UA) morphology and especially the effect of the minimal cross sectional area (CSA) on lung deposition of inhaled medication (IM) is significant. However since IM is used when a patient is upright, conventional computed tomography (CT) data may not provide accurate information on the influence of the UA on lung deposition. The objective of this study is to evaluate variability in UA morphology for supine posture using CT vs. upright posture using cone beam CT (CBCT).
Materials and methods: A total of 20 normal subjects were included. 15 valid CBCT scans could be included as the rotating gantry of the CBCT touched the shoulders of the broad-shouldered subjects, causing motion artifacts. The UA CT scans were performed using the GE VCT LightSpeed scanner and the CBCT scans were performed using the SIEM i-CAT scanner.
Results: The UA CSA in the CT scan was characterized by lower CSAs as compared to CBCT (Minimal CSA, p = 0.036, Average CSA, p = 0.006). The minimal CSA in the CT scan could accurately predict the difference in minimal CSA between CBCT and CBCT as indicated in the figure.

Conclusions: It can be concluded that the UA morphology is different between supine and upright position. From the supine CT image, it can be predicted how large the minimal CSA will be when the subject is in an upright position. This function can be used to generate a correction factor for assessing lung deposition of IM.

P652 The relationship between NT proBNP and CT lung density in long term smokers
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Introduction: Cardiovascular conditions are reported to be the most frequent cause of death in COPD.

Aims and objectives: The relationship between NT-terminal prohormone of brain natriuretic peptide (NT-proBNP) as a surrogate marker of congestive heart failure (CHF) and CT lung density remains unclear. Pulmonary oedema leads to increased CT lung density. Little is known about milder CHF and CT lung density. Lung cancer screening provides an opportunity to study this relationship.

Methods: 500 long-term smokers were selected from the Danish Lung Cancer Screening Trial (DLCST). Smoking habits were recorded and spirometry was performed. CT lung density was measured automatically by in-house developed computer software and expressed as the volume adjusted 15th percentile density (V15). NT proBNP with p<0.05 as part of a panel of biomarkers. The 194 persons, who had the CT scan and the blood sample performed the exact same day, were included in a multiple regression model. The model included gender, pack years, number of cigarettes a day during the last month, COPD severity, and NT proBNP with PD15 as outcome variable.

Results: Female sex (+0.5 g/l, SE 1.9, p<0.001), high number of cigarettes a day (+0.6 g/l, SE 1.1, p<0.001) and no or mild COPD (+0.2, SE 0.1, p<0.001) were associated with a higher PD15, but there was no correlation with NT proBNP (+0.001, SE 0.002, p=0.959).

Conclusions: PD15 was not correlated to NT proBNP. Therefore milder degrees of CHF seem to have little influence on CT lung density. Lung density is higher in females, in people without COPD and in heavy current smokers.

P653 Pulmonary emphysema: Qualitative assessment at CT of presence and subtypes
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Pulmonary emphysema is defined by morphology and is a heterogeneous disease with variably defined subtypes. We hypothesized that reliable detection of the presence of emphysema and its subtypes by visual CT assessment could be achieved by application and training on standard definitions of subtypes and severity. CT scans from 40 participants were selected randomly from a population-based cohort of participants ages 60-80 years with ≥10 pack-year smoking history. Non-contrast CT scans (120 kVp, 100 mAs, 0.75 mm) were performed at full inspiration and sharp filter reconstruction. Standard definitions of centrilobular (CLE), paraseptal (PSE) and panlobular (PLE) emphysema subtypes and severity were developed and three readers (2 chest radiologists, 1 pulmonologist) trained. The three readers independently assessed the 40 scans plus 10 replicates. Intra- and inter-reader agreement were assessed using unweighted Cohen’s κ and intraclass correlation coefficient (ICC), respectively.

Results: The 40 participants had a mean age 68±5 years, 40% were current smokers, and 55% had chronic obstructive pulmonary disease. The κ statistic was 0.57-0.84; inter-reader agreement was good for CLE (κ = 0.67), moderate for PSE (κ = 0.32) and absent for PLE (κ = 0.06).

Conclusions: This protocol for the visual assessment of chest CT can reliably detect the presence and extent of emphysema, in addition to selected emphysema subtypes.

P654 MDCT and MRI DWI early signs of COPD
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Cigarette smoking is the leading cause of COPD. Most people who have COPD smoke or used to smoke some form of tobacco. But nonsmokers can develop COPD also.

Purpose: The main aim is to find early MDCT or MRI signs of COPD in young population of smokers, before developing the first clinical symptoms.

Material and methods: We examined 5863 patients from 18 to 35 years old. 3101 were male, 2762 female. All patients were examined on 16 or 64 MDCT using all advanced methods like virtual bronchoscopy, emphysema software we created, histogram, huge variation of filters and MDCT pulmonary angiography and MDCT perfusion. Patients with signs of COPD were examined by 1.5 T MRI with DWI.

Results: Patients were examined by MDCT because of different reasons, some of them because of acute respiratory symptoms and some also groups of patients voluntarily screened for lung cancer. We find signs of early COPD in 603 (10.28%) patients. All patients with signs of any other chronic disease or lung cancer were not matter of this study. Also we did not use patients with history of hemoptysis, even small one. In patients we find signs suspect for COPD we performed MDCT pulmonary angiography to find any signs of vascular abnormalities which could mislead us. MRI with DWI was performed to determine small vessels. In all patients we find areas of lower density then lung parenchyma. All areas were in peripheral parts of the lung, on left side of the lung in 61%. We
also had control examination after two years in 6 patients, in all patient areas of emphysema were bigger.

Conclusion: Signs of COPD can be found earlier than first symptoms are visible. MDCT with variety of tools and MRI with DWI are very useful for early diagnosis.

P655 A functional and radiological multiparametric approach to the study of parenchymal features of chronic obstructive pulmonary disease Riccardo Battistelli1, Andrea Sinisgalli1, Giulia Patricelli1, Giuseppe Macio2, Anna Rita Larcì1, Michele Amato1, Salvatore Valente1, Giuseppe Battistelli1, Monica Nona Duma1, Florent Baty1, Michal Devecka3, Giuseppe Macio2, Anna Rita Larcì1, Michele Amato1, Salvatore Valente1.

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Chronic obstructive pulmonary disease (COPD) includes a range of changes ranging from chronic bronchitis to emphysema. We evaluated if integration of lung function tests and computed tomography (CT) scan allows a better characterization of patient with COPD.

23 patients (5 females) underwent lung function test and six-minute walk test (6mWT).

We used a third-generation, continuous-rotation helical 64-rows CT scanner with Siemens b30f and b50f convolution kernels. For each broncho-pulmonary segment of the lung, we can assess different features, such as length and diameter of the first airway generations, and lobar volumes (in terms of percentage of the functional residual capacity).

Results: Comparisons with experimental measurements have been done for total, tracheobronchial (TB) and lobar deposition, showing good correlation between measured and simulated values. For instance, mean experimental TB deposition fraction in the left lung is 14.5±2.4, vs. 14.9±4.1 for simulation results.

Conclusions: This work provides a scientific foundation for addressing both asymmetric and individualized lung morphologies in analytical modeling of aerosol deposition.

P658 Assessment of tumor size and movement trajectories using CT scans with different pitch settings Paul Martin Putze1,2,3, Maricela Nona Duma1, Florent Baty1, Michal Devecik1,2, Mami Bruschi1,2, Ludwig Plasswilm1,2.

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Assessment of tumor size and movement trajectories using CT scans with different pitch settings.

Method: A water filled 40mm table tennis ball serving as a phantom was moved along an ellipsoid trajectory by a custom assembled Locog device based on the cycle duration of 4.2 seconds. The ellipsoid trajectory was tested with a range from “fast” (2.5mm, standard pitch), “fast” (2.5mm, half pitch), and “fast” (0.625mm, half pitch).

Results: The volume of the ball was overestimated with the volume of the tumour phantom growing from 82% for the fast CT, 171% for the intermediate CT and 300% for the slow CT. The phantom trajectory could best be reconstructed in the slow CT. The different sizes can be seen here.

Conclusion: The custom lung phantom proved to work well for the specified task. The effect of CT settings during planning-CT acquisition on the resulting volumes was significant. Acquisition of slow-CT images for radiotherapy planning enables a better targeting of the moving tumor and sparing of normal lung tissue specifically when respiratory gating is not available.

P659 The role of positional CT in detecting adhesive process in the pleural cavity of TB patients under artificial pneumothorax (AP) Raul Amanashevedov, Andrei Perfiliev, Atdajan Ergeshov, Olga Demikhova.

Radiology Department, Central Tuberculosis Research Institute, Moscow, Russian Federation.

We studied 54 patients with different forms of destructive pulmonary TB, which received artificial pneumothorax (AP) during 5.5 (+1.5) months. Out of them 54.8% had infiltrative, 24.0% cavitory, 16.2% fibrocavitary, and 4.8% disseminated pulmonary TB. Sputum positive TB was established in 83.6% cases. Adhesive process in the pleural cavity was detected using polypositional computed tomography (CT). We developed the algorithm for radiographic monitoring of AP and detecting adhesions in the pleural cavity. We established pleural adhesion in 70.3% cases; thoracoacous was performed in 52.6% cases, with 100.0% effectiveness of AP.
In 47.4% cases thoracoscopic was not administered to the patients with adhesive process; out of them 55.5% had effective AP, 16.6% – partially effective AP, and 27.9% – ineffective AP. Thus, polyposidal CT demonstrated effectiveness in detecting adhesive process in the pleural cavity of TB patients.

89. From the laser through the stent to the valve: the broad spectrum of interventional pneumology

P660

Confocal laser endomicroscopy in diagnosis of solitary and multiple pulmonary nodular inflammation

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Background: Probe-based confocal laser endomicroscopy (pCLE) is a new method used during bronchoscopy by means of special minprobe Alveoflex and based on the visualization of intralveolar structures which possess autofluorescence. Till now the only lung pathology for which specific diagnostic signs are established at the visualization of intraalveolar structures which possess autofluorescence. Results: Patients diagnoses have been as follows: sarcoidosis (17), central lung cancer (1), pneumonia (5), usual interstitial pneumonia (1), bronchiolalveolar carcinoma (BAC) (4), other peripheral tumors (8). In all patients with BAC the cancer (1), pneumonia (5), usual interstitial pneumonia (1), bronchioloalveolar carcinoma (4), other diseases we haven’t found any significant difference between healthy and cancer (1), pneumonia (5), usual interstitial pneumonia (1), bronchioloalveolar carcinoma (4), other diseases.

Conclusions: pCLE could be used as an additional method of noninvasive diagnostics of BAC in vivo.

P661

Airway injury after intubation for lung surgery: Double lumen tube compared to EZ blocker

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Background: Double lumen tubes (DLT) or bronchial blockers (BB) are used for isolated lung ventilation. DLT’s can be positioned faster and remain firmly in place, but are more difficult to introduce. BB’s are more difficult to position and need more frequent intraoperative repositioning. The design of a Y-shaped BB, the EZ-Blocker (AnaesthetIQ BV Rotterdam Netherlands, EZB) combines advantages of both techniques. This randomized study investigated efficiency, efficacy and safety of DLT’s vs EZB and focused on airway injury caused by intubation.

Methods: 100 patients were randomly assigned to DLT or EZB group. Incidence and severity of damage to laryngeal, tracheal and bronchial structures were analysed by bronchoscopy before and after surgery. All procedures were recorded and injury was scored by a pulmonologist blinded for intubation type. Further the ease and time of placement, incidence of malpositions, quality of lung deflation, postoperative hoarseness and sore throat were assessed.

Results: There was a significantly higher incidence of airway injury after DLT compared to EZB. Marked tracheal and bronchial hematomas were found in 58% vs 26% (P=0.002) and 31% vs 6% (P=0.007). No differences were found in vocal cord and main carina injury. Placing single lumen tubes and EZB’s took more time but was rated easier. The majority of EZB’s and DLT’s were initially malpositioned (42/49 DLT, 37/50 EZB). Lung deflation was comparable. Fewer patients in the EZB-group complained of sore throat.

Conclusions: The EZB is an efficient and effective device for lung isolation and causes less injury and sore throat than DLT. Bronchoscopic control is recommended for both devices to ensure correct positioning.

P662

Preoperative endobronchial photodynamic therapy improves surgical radicalism for locally advanced NSCLC

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Objective: We describe the result of prospective randomized trial comparing neoadjuvant chemotherapy with and without endobronchial photodynamic therapy (PDT) followed by surgery for locally advanced NSCLC.

Methods: From Jan 2008 to Dec 2011, 42 pts with stage III central NSCLC (main bronchus/distal tracheal involvement) were randomized to either endobronchial PDT or no PDT. PDT was done with photosensitiser chlorine E6 and 662 nm laser light before each of the three courses of chemotherapy. Patients assigned to PDT (n=21) and no PDT (n=21) were similar with respect to age, sex, tumor stage, and histology.

Results: No PDT complications were observed. After neoadjuvant treatment partial remission revealed in 19 pts (90%) in PDT and 16 pts (76%) in no PDT group; these patients underwent thoracotomy. Surgery in PDT group: 14 pneumonectomies and 5 lobectomies; surgery in no PDT group: 10 pneumonectomies, 3 lobectomies and 3 exploratory. There was one postoperative death in each group. Completeness of resection was significantly higher in PDT (R0-89%, R1-11%) vs no PDT (R0-54%, R1-46%) group.

Conclusions: Combination of chemotherapy with endobronchial PDT increases effectiveness of neoadjuvant treatment and surgical radicalism for locally advanced central NSCLC.

P663

Clinical experience with a new self-expandable metal stent, SILMET, in tracheo-bronchial stenosis

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Introduction: The Implantation of Tracheo bronchial stents is a recognised treat- ment option in the management of airway disease. However, stent related side effects and complications are still an unresolved issue and are object of intense investigation. Research is currently focusing on the delivery mechanism and on biomaterials.

Aims: We evaluate the clinical result and effectiveness of the Silmet stent for treatment of benign or malignant bronchial disease.

Methods: Clinical data were collected retrospectively from 21 consecutive pa- tients. Each patient implanted were underwent to clinical monitoring, according to our protocol, consisting in endoscopic and microbiological testing at 1 day, 1 month, 3 months and 6 months after the procedure. For the evaluation of mucus plugging we used our 4 points endoscopic scoring: 0 = no secretions; 1 = moderate amount of secretions easily removable by suction; 2 = severe amount of secretions removable using a biopsy forceps, mucolytic agents instillations or other devices in addition to the suction; 3 = complete stent obstruction or deposit of thick and non-removable secretions.

Results: At the end of follow-up we recorded a single death which was not respiratory related. In one patient under chemotherapy we observed dislocation of the stent after significant tumor mass regression. No patient developed airways stenosis or trauma, airway wall damage or major complications. Nineteen patients had endoscopic score 0 and two patients score 1 in the last visit. One patient had a mild not obstructing granuloma.

Conclusions: These new Silmet stent have proved effective and free of severe complications in the treatment of tracheo-bronchial stenosis.

P664

Incidence and management of anastomotic complications after bronchial resection: A retrospective study

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Background: Bronchial resection and re-implantation in the surgical management of.
of lung cancer are intended to spare lung parenchyma, with curative intent. We studied the incidence and management of anastomotic complications after such procedures.

**Methods:** We retrospectively reviewed charts of patients referred to our center for lung tumors, who underwent bronchial resection and re-implantation from 1991 to 2011.

**Results:** A total of 108 patients were included. Sixty-eight percent were male, and mean age was 58 years. Sleeve lobectomies were performed in 100 patients, bronchial resections without lung parenchymal resection in 8 patients. Squamous cell carcinoma represented 46.3%, carcinoid tumors 22.2%, and adenocarcinoma 18.5%. Mean time between surgery and the first bronchoscopy examination was 4.47 days, with anastomotic abnormalities detected in 20.4%. Twenty-three patients underwent therapeutic bronchoscopy for malacic or fibrotic bronchial stenoses in 9 cases, for dehiscences in 7, for obstructive granulomas in 3, and for bronchopleural fistulas in 3. Endoscopic treatment consisted in stent placement in 5 cases, mechanical dilations in 3, laser treatment for one case of bronchomalacia, and resection of granulomas in 3. No risk factors were identified as predisposing for bronchial complications. There was a trend towards lower 1-year survival in patients with bronchial complications compared to those without (71.9% vs. 83.4%, p=0.114).

**Conclusions:** Bronchial resection and re-implantation is a surgical procedure associated with an anastomotic complication rate of 21%. Regular endoscopic surveillance is advised in order to detect and treat early complications.

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**P665 Optimizing the treatment of inflammatory tracheal stenosis according to a morphometric classification**

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**Introduction:** A multivariable classification with its corresponding multimodality treatment has not been described in inflammatory tracheal stenosis.

**Objectives:** 1. To describe the distribution of patients according to a morphometric classification. 2. Identify the rate of success according to its corresponding treatment variables.

**Method:** Only patients with post intubation (PITS) or idiopathic inflammatory tracheal stenosis were included. Other benign non inflammatory diseases, granulomas and neoplasms were excluded. Patients were classified based on 3 endoscopic variables (Table 1). Treatment was selected according to the grouping of these variables.

**Results:** 40 patients were included: PITS in 87.5%, idiopathic stenosis in 12.5%. Distribution of patients according to treatment success are presented in Table 2. Endoscopic treatment was performed initially in 95% of patients. The treatment was successful in 45%, 26% underwent further surgical treatment and 29% needed a permanent canula or tracheal silicon stent.

Of the 12 patients who underwent surgery, 2 received no prior endoscopic treatment, and 3 required endoscopic treatment after surgery. Surgical treatment was successful in 83%. 17% of operated patients had tracheal restenosis.

**Conclusions:** 1. The more frequent tracheal stenosis group was S2D3L1 (39%). 2. Success rate with this multimodality approach was achieved in 68% of the patients. Funded partially by FUCAP.

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**P666 Safety of percutaneous dilatational tracheostomy in obese critically ill patients when performed with bronchoscopy assistance**

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**Introduction:** Intensive care unit (ICU) patients, mainly those in need of prolonged mechanical ventilation require tracheotomy. Obese critically ill patients are at greater risk for requiring intubation and prolonged mechanical ventilation. Percutaneous dilatational tracheostomy (PDT) is a well-established procedure that can be performed at the bedside by an intensivist with less surgical equipment required.

**Goal of study:** To evaluate the safety of performing PDT with bronchoscopy assistance in obese patients requiring prolonged mechanical ventilation.

**Method:** Sixty patients 17-79 yrs of age, 23 females and 37 males with body mass index 38±8 kg/m² underwent PDT with bronchoscopy assistance due to prolonged endotracheal intubation between December 2009 and January 2012. The procedures of percutaneous dilatation tracheostomy with guide wire dilator forceps (GWFD) were done bedside under general anaesthesia in the ICU. Operative and post operative complications were observed.

**Results:** Overall complication rate was low and occurred in 10 patients, there was no procedure-related mortality. Subcutaneous emphysema without pneumothorax occurred in three patients, two patients had a transient hypotension related to sedation and five patients had peristomal oozing. The mean time for procedure completion was 1.5 minutes, no patient required conversion to surgical tracheotomy. The bronchoscopy examination that was performed in 24 of the patients 20 days after tracheotomy tube removal showed no scar formation.

**Conclusions:** PDT with bronchoscopy guidance is safe for obese critically ill patients that can be done by an experienced intensivist at the bedside setting.
Conclusions: Interventional bronchoscopy plays definitive role in the treatment of surgery, were subsequently treated bronchoscopically due to anastomotic reestenosis with Nd-Yag laser (25%), electrocautery (37%) and tracheal stenting (44%).

Primary bronchoscopic treatment was the initial approach in 44%, followed by surgical intervention in 57% of cases in which tumor base could be totally visualized bronchoscopically and pathological evaluation revealed diagnosis of TC. Efficacy could be reached by the method. Tumors diagnosed as TC after pathological evaluation cryotherapy and/or coagulation with diode laser or APC tumor tissue was totally removed with core-out technique. Treatment approaches with interventional bronchoscopic methods in carcinoid tumors are non-invasive and effective in the treatment of benign tumors of the trachea. Complete cure can be obtained in all cases. Long follow up and treatment of recurrence is essential in the early period.

P669 Argon plasma coagulation in treatment of post intubation tracheal stenosis
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Background and objectives: Acquired tracheal stenosis can be created by various causes. The most common cause of acquired non-malignant tracheal stenosis is endotracheal intubation for a short period. Argon plasma coagulation (APC) is a non-contact method of thermal hemostasis which can be used easily and fast and has low depth of penetration. Therefore, we decided to evaluate efficacy of this method in treatment of Tracheal stenosis.

Methods: This study is single blinded. Subjects were patients with tracheal stenosis after endotracheal intubation who were selected by non-probability sampling in bronchoscopy unit of Masih Daneshvari Hospital. First, for each patient a diagnostic flexible bronchoscopy was performed to identify the type, location, and severity of the stenosis. Then, under general anesthesia, patients underwent rigid bronchoscopy. After that, the stenosis was removed as possible by APC device. After two weeks a pulmonary function test (PFT) was done to check the obstructive sign.

Results: Of all 34 patients, 24 were asymptomatic for more than 1 year and responded to treatment (70%); 5 were asymptomatic for more than 10 months and less than 2 months (14.7%) and 5 did not have asymptomatic period more than 10 months and did not respond to treatment. In follow-up PFT, FEV1 in all patients was asymptomatic for more than 10 months (29 patients) showed a significant progress. (At the end of the period, FEV1 was more than 90% in 27 patients and 70-90% in 2 patients.)

Conclusion: On the whole, although the surgical treatment remains the main treatment of tracheal stenosis after intubation, if this method is not possible for any reason, APC is useful as a safe and effective method.

P670 Endoscopic approach in the treatment of carcinoid tumors
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Aim: Carcinoid tumors are the neuroendocrine tumors of the tracheobronchial tree. Treatment approaches with interventional bronchoscopic methods in carcinoid tumors have been analyzed and discussed.

Methods: In this study, 20 consecutive carcinoid tumor patient treated between January 2006 to August 2011 in our Interventional Pulmonology Unit were evaluated. All patients undergone rigid bronchoscopy. In all of the patients after coagulation with diode laser or APC tumor tissue was totally removed with core-out method. Tumors diagnosed as TC after pathological evaluation cryotherapy and/or laser was applied as a complementary procedure. Long follow up and treatment of recurrence, and resive ratios, complications, mortality and morbidity were evaluated.

Results: From the 20 cases included into the study, 17 of them were TC and 3 of them were AC. AE mean age of the cases were 56 (between 20-73) and 14 of them were female. Six cases, two of them were AC, were operated after bronchoscopic treatment. Rigid bronchoscopy was applied as a mean of 2.3±1.5 times while fiberoptic bronchoscopy was applied as a mean of 3.2 times. Radial probe EBUS and autofluorescence bronchoscopy were used in bronchoscopic follow up. No mortality due to bronchoscopic treatment was observed.

Conclusion: Bronchoscopic treatment is effective and safe in endobronchial carcinoid cases in which tumor base could be totally visualized bronchoscopically and pathological evaluation revealed diagnosis of TC. Efficacy could be reached by the method. Surgical intervention of the standard bronchoscopic procedure. Close follow up and treatment of recurrences is essential in the early period.

P671 Bronchoscopic treatment of benign tumors of the tracheobronchial tree
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Aim: To evaluate the efficacy of the bronchoscopic treatment approach and follow up results of the treatment of the benign tumors of the tracheobronchial tree.

Method: In this retrospective cohort study, 44 consecutive patient who underwent bronchoscopic treatment between January 2006 to June 2011 in our Interventional Pulmonology Unit were evaluated. All patients undergone rigid bronchoscopy under general anesthesia. In all of the patients firstly mechanical debridement after coagulation was applied and cryotherapy to the base of the tumor for excluding residue were applied.

Recurrence and residue ratios, early and late complications were evaluated.

Results: Most commonly treated benign tumor was hamartoma (38%, n=17). Other than this, procedures were applied to other rare tumors like as adenoma, amyloidosis, etc. In eight of the patients, tumor was located at the trachea. One to six session, even for a short period of 2.3±1.5 times was the duration of treatment. Recurrence and residue ratios, early and late complications were evaluated. In follow-up PFT, FEV1 in all patients was asymptomatic for more than 10 months and did not respond to treatment. In follow-up PFT, FEV1 in all patients with respiratory signs showed a significant progress. (At the end of the period, FEV1 was more than 90% in 27 patients and 70-90% in 2 patients.)

Conclusion: Our reported complication rates are lower than in other similar studies. We believe that a registry can potentially be utilised for database collection, bench marking and quality improvement initiatives and for training purposes in the near future. This paper-based prospective data analysis is feasible and valuable. We plan to extend this database to other French centers and in time to develop a web-based system, which will minimise the missing data fields.

P672 The feasibility of using a prospective multi-institutional database to measure outcomes from advanced bronchoscopy

Background: In France, there is no prospective registry to document activity and outcomes of the new diagnostic and therapeutic bronchoscopic technologies. We assessed the feasibility of a prospective multi-institutional outcomes database of advanced bronchoscopy.

Methods: Over a 2-month period, we have interrogated the procedure of advanced diagnostic (EBUS, EBUS-Mini-Probe, Autofluorescence) and therapeutic bronchoscopy from 5 French institutions. Information on procedure type and lesion characteristics as well as complications were documented.

Results: A total of 943 procedures were performed, of which advanced bronchoscopy represented 25%. The most related complication remains haemorrhage after biopsies, and completed technologies Autofluorescence followed by therapeutic bronchoscopic procedures. The EBUS specific complication was 3.2% in the University Hospitals, compared with a complication rate at 1.85% in the literature. The EBUS-Mini-Probe and Autofluorescence global complication rate was 6.66% and 11.3% respectively. The therapeutic bronchoscopy complication rate was 7.5% in the University Hospitals, compared with the reported global complication rate of 7%.

Conclusions: Our reported complication rates are lower than in other similar studies. We believe that a registry can potentially be utilised for database collection, bench marking and quality improvement initiatives and for training purposes in the near future. This paper-based prospective data analysis is feasible and valuable. We plan to extend this database to other French centers and in time to develop a web-based system, which will minimise the missing data fields.

P673 Interventional bronchoscopic treatment improves quality of life in patients with advanced bronchial cancer
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Objective: Improvement of quality of life (QOL) is a main issue in patients with...
advanced bronchial cancer. Hemoptysis, dyspnea and irritating cough resulting from endobronchial obstruction are the main cause of QOL disturbance in those patients and interventional bronchoscopic treatment may play a role in solving this problem.

Methods: Patients with different symptoms related to endobronchial obstruction due to lung cancer were recruited into two groups. The first group was treated with argon plasma coagulation (APC) and the second group was treated with cryotherapy. All methods were applied via the fiberoptic bronchoscope under local anesthesia. The impact of bronchoscopic treatment on improvement of symptoms, arterial blood gases parameters, pulmonary function tests parameters, QOL and performance scale were evaluated.

Results: Forty five patients were recruited in the study. Twenty five patients were treated with APC and twenty patients were treated with cryotherapy. Bronchoscopic treatment was able to improve symptoms, pulmonary function test and blood gases parameters with subsequent improvement in the performance state of the treated patients.

Conclusions: Bronchoscopic treatment is an effective treatment to deal with symptoms related to endobronchial obstruction with subsequent improvement in the pulmonary function, blood gases, as well as QOL in these patients.

P674 Accurate monitoring of pulmonary air leak closure during endobronchial valve placement
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Introduction: Endobronchial valves may be effective for the treatment of a prolonged pulmonary air leak (PAL). A traditional chest drainage system relying on a subjective and instantaneous assessment of expiratory bubble formation in the water-seal column lacks accuracy to aid assessments during and after valve placement.

Patients and methods: Three patients with a postoperative PAL measuring at least 1000 ml air leakage per minute (ml/min) were evaluated. We attempted air leak closure using endobronchial valves relying on a digital air leak measurement system displaying and recording the expiratory pulmonary air leak in ml/min. The number of valves used was set by either leakage cessation or residual leak of <100 ml/min.

Results: In all patients, the effect of every single valve placed was accurately assessed in ml/min during the procedure. In 1 patient the air leak stopped after lobar exclusion, while in 2 patients the air leak decreased to <100 ml/min after lobar exclusion. The continuous post-intervention assessment accurately indicated air leak cessation in these two patients within 48 hours after valve placement. Chest drain removal was successful after air leak cessation. None of the patients developed respiratory insufficiency requiring subacute endobronchial valve removal. As planned, all valves were removed 3-4 weeks after their placement.

Conclusion: Digital objective air leak assessment guides endobronchial valve placement, indicates the exact timing of air leak cessation, and allows a safe fast-tracking policy of chest tube removal.

P675 Endoscopic bronchial occlusion with Watanabe silicone prosthesis and biological glue for the treatment of alveolectra fistulas
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Introduction: Alveolectra fistula (APF) is the communication of the distal bronchial tree and pleural space, and supposes a serious problem for its associated morbimortality. The objective is to evaluate a endoscopic bronchial occlusion with a silicone prosthesis (Watanabe spigots) and biological glue.

Patients and methods: Observational, retrospective, descriptive study, collecting bronchial occlusion cases in our hospital from 2004 to 2010. General data collected, including details of previous and current illnesses, pleural drainage, fiberoptic bronchoscopy, location of dependent bronchus, spigots implanted, glue instilled, recurrences, pneumonectomies and monitoring.

Results: 6 patients and 7 sessions of bronchial occlusion. Average age 60, 3F/3M. The predisposing diseases were neoplasia, pneumonia and lung abscess. Developing as empyema or pneumonia with a drain placed 23 days on average prior to the occlusion. Performed under general anaesthesia, the responsible bronchus located with balloon catheter, ventilator volumes, dye or sight of bubbling. Two spigots placed per session on 3 occasions, and in 4 others, in sizes M and S. N-butyryl cyanurate was added in 4 sessions. The leak stopped in the operating theatre in all cases, with late recurrence in 3. No complications except expectoration of 2 spigots. Definitive lung re-expansion in 4 patients, with subsequent pleurodesis and drain removal. Two patients died from the progression of their underlying disease.

Conclusions: Endoscopic bronchial occlusion with Watanabe spigots and N-butyryl cyanurate is an effective, technically simple method without complications for the treatment of APF.
P678
Early improvements of Chartis assisted-endoscopic lung volume reduction treatments
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Endobronchial valve (EBV) treatment improves lung function and exercise tolerance in patients with pulmonary hyperinflation related to advanced emphysema. However, collateral ventilation (CV) may strongly limit the efficacy of EBV placement. This is a preliminary assessment of the role of lung volume reduction coil (LVR-C) as a possible alternative to EBV when CV occurs.

The occurrence of CV in the targeted lobes was assessed in 7 male subjects with heterogeneous emphysema by using the Chartis system. Based upon the above system, five subjects (aged 68±12 yrs) were assigned to EBV treatment (Zephyr EBV, 3 to 4 per patient), while two patients (aged 62±4 yrs), in which CV was documented, were assigned to LVR-C treatment under fluoroscopic guidance. (Nitiol coils, a total of 10 coils per patient). FEV1% pred. was 40±10% in the EBV group and 27±15% in the LVR-C group; RV% pred. was 154±28% and 171±29% respectively.

At 30 days, FEV1% pred. improved by 4.8 percentage points in the percent of the predicted value in the EBV group and by 1.5 in the LVR-C group. However, the reduction in RV% pred. was even more impressive in the LVR-C group (mean difference: -50 points) than in the EBV group (mean difference: -36 points). Similarly, the improvement in the 6 min. walking distance was higher in the LVR-C group (mean difference: +47 meters) than in the EBV group (mean difference: +17 meters).

All procedures were well tolerated and no major adverse effects were recorded in both groups. In our preliminary observations, LVR-coil treatment resulted in early improvements in lung function and exercise capacity, and can be proposed for the treatment of patients with severe heterogeneous emphysema when CV is documented.

P679
Assessment of fissure integrity for decision-making in valve treatment of emphysema: Preliminary results
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Objective: To investigate if fissure integrity can determine collateral ventilation and guide endobronchial valve (EBV) treatment of emphysema.

Method: The study is underway. We employ the Apollo software (VIDA Diagnostics) for treatment planning, and developed a visual fissure integrity score using a 3D high-resolution CT scan and 61% an open lung biopsy.

Disease course: 33.3% and 43.3% had slowly progressed. Smoking status: Dyspnoea 78%, cough 63%, constitutional symptoms 25%, pain 22%.

Results: Details on 95 patients (19 deceased, 7 lost to follow-up) received. Clinical information regarding 67 cases has been received; completed by the patient, consultant or both (31 males). Age at presentation 37.1 years (SD 14.4). Presenting symptoms: Dyspnoea 78%, cough 63%, constitutional symptoms 25%, pain 22% and pneumothorax 8%. Smoking status: Ex 71.7%, current 25.0% mean (SD) 19.9 (16.9) pack years. Cannabis use 9.6%: Diagnosis: 93.8% patients had had an HRCT scan and 61% an open lung biopsy. Disease course: Symptoms resolved 23.3%, same 33.3% and 43.3% had slowly progressed. Treatment: None 56%, Steroids 29.6% immunosuppression/chemotherapy 26.5%, pleural surgery 18.7% and lung transplant 6%

Conclusions: This UK dataset indicates a high prevalence of smoking in our cohort and, despite advances in computed tomography a high percentage of patients are still diagnosed with an open lung biopsy.

P680
Pulmonary Langerhans’ cell histiocytosis (PLCH): A new UK register
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Introduction: PLCH is a rare interstitial lung disease, linked to cigarette smoking and may be associated with respiratory failure and death. Limited UK data has been published and little knowledge exists of the diagnostic and treatment practices employed by UK physicians.

Aims and objectives: Our study aims to characterise the epidemiological, clinical, histological, radiological and prognostic indicators in a UK cohort of patients with PLCH.

Methods: 112 cases from 53 centres (65 from the BTS British Orphan Lung Disease database and 47 new or previously unregistered). Consultants provided contact details; Patients were sent an information leaflet, consent form and questionnaire. Once consent obtained, consultants were sent a medical questionnaire. The patients’ GP provided current medication and medical history.

Results: On 95 patients (19 deceased, 7 lost to follow-up) received. Clinical information regarding 67 cases has been received; completed by the patient, consultant or both (31 males). Age at presentation 37.1 years (SD 14.4). Presenting symptoms: Dyspnoea 78%, cough 63%, constitutional symptoms 25%, pain 22% and pneumothorax 8%. Smoking status: Ex 71.7%, current 25.0% mean (SD) 19.9 (16.9) pack years. Cannabis use 9.6%: Diagnosis: 93.8% patients had had an HRCT scan and 61% an open lung biopsy. Disease course: Symptoms resolved 23.3%, same 33.3% and 43.3% had slowly progressed. Treatment: None 56%, Steroids 29.6% immunosuppression/chemotherapy 26.5%, pleural surgery 18.7% and lung transplant 6%

Conclusions: This UK dataset indicates a high prevalence of smoking in our cohort and, despite advances in computed tomography a high percentage of patients are still diagnosed with an open lung biopsy.

P681
Pulmonary manifestations of Sjogren syndrome
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Background: Sjogren syndrome is a chronic and autoimmune disease characterized by lymphocytic infiltrates in all exocrine glands. Dryness of the eyes and mouth are the most common symptoms of this syndrome. Primary pulmonary manifestations of Sjogren syndrome are diffuse lung and airway diseases.

Aim: 131 patients were included in our study between the years 2000-2011 who were diagnosed with Sjogren syndrome. Of these patients, 31 were examined who admitted to pulmonary diseases clinic and had Thorax computed tomography (CT). We aimed to evaluate demographic characteristics, respiratory symptoms, pulmonary function test parameters and Thorax CT findings of patients who have Sjogren Syndrome.

Results: The mean age was 57.3 years and 30 (%96.8) were women. Pulmonary function test was normal in %45.2 of the patients. 7 patients (%22.6) were smoker. 2 patients had COPD and 4 had asthma. 11 patients suffered from dyspnea and 5 from coughing. Thorax CT revealed pathological findings in 22 patients (%71.0). In Thorax CT examination 8 atelectasis, 8 pulmonary nodules, 5 pathological lymph nodes, 3 bullae formation, 2 bronchiectasis, 2 pulmonary embolism, 2 lobars, 2 infarction, 2 ground glass appearance and 2 pleural effusion were reported. Of the 23 patients who underwent echocardiographic evaluation 7 (%22.6) had elevated systolic pulmonary artery pressure (mean 63.3 +2.7mmHg).

Conclusion: Respiratory disorders are common in patients with Sjogren syndrome even if the affected individuals are asymptomatic. Therefore, close follow up of these patients in pulmonary disease clinics are recommended and Thorax CT assessment for lung involvement should be considered for early diagnosis.
Lung function follow-up, yr 5.9

Mean FEV₁ and DLCO were, respectively, ≥70% predicted at diagnosis, and similar mean rate of FEV₁ decline was found in both S-LAM and TSC-LAM groups. Significant improvement of FVC and DLCO was detected in the patients with TSC-LAM and 53 patients with S-LAM diagnosed according to ERS 2010 criteria with a lung function follow-up >2.1 year. Results are shown below:

<table>
<thead>
<tr>
<th>TSC-LAM (mean ± SD)</th>
<th>S-LAM (mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>Women, %</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Age at LAM diagnosis, yr</td>
<td>51±11</td>
<td>40±15</td>
</tr>
<tr>
<td>Initial FEV₁, %pred</td>
<td>72±20</td>
<td>70±20</td>
</tr>
<tr>
<td>Lung function follow-up, yr</td>
<td>5±1.2</td>
<td>5±1.3 ± 8</td>
</tr>
<tr>
<td>FEV₁ decline (pre)</td>
<td>-2±4.28</td>
<td>-3±4.5 ± 0</td>
</tr>
<tr>
<td>FEV₁ decline mL/yr</td>
<td>-103±89</td>
<td>-114±177</td>
</tr>
</tbody>
</table>

Conclusion: Although diagnosed at an earlier age than S-LAM, patients with TSC-LAM had similar mean FEV₁ at diagnosis, and similar mean rate of FEV₁ decline. Lung function follow-up similar to S-LAM may be recommended in TSC-LAM.

Effect of source of inhalation antigen on manifestation and prognosis of EAA patients

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Exposure to moulds in domestic environment leading to EAA is often reported. Inhalation exposure to moulds may lead to development of proliferative Th2 cells.

Aim of the study: To examine influence of inhalation antigen on EAA manifestation and prognosis.

Method: Fifty-four patients of the mean age 55±17.5 were included to the retrospective study. They underwent complex diagnostic program including detailed history assessment, physical examination, serum specific IgE tests, lung function tests (spirometry, diffusing capacity of the lung for CO), HRCT of the chest, broncho抄y with BAL and TBB. Patients were divided into five groups according to their antigen exposure history – unknown source of exposure, professional exposure in chemical industry workers, exposure to moulds, exposure to bird antigens and exposure to mammal’s fur and epithelium.

Results: Patients with mould exposure history had significantly higher FVC (p < 0.05), FEV₁ (p < 0.01) and DLco (p < 0.01) at the time of diagnosis than other exposure groups. Significant improvement of FVC and DLco was detected in the patients with history of exposure to bird antigens. We found no difference in BAL differential cell counts among patient groups. BALF PMN cell count at the time of diagnosis negatively correlated with FVC and FEV₁ a year after diagnosis in the whole group (p < 0.05).

Conclusion: EAA caused by moulds does not have a worse manifestation and prognosis that EAA caused by other inhalation antigens. Better outcome of patients exposed to bird antigens is probably influenced by easy removal of the antigen’s source. The type of inhalation antigen very likely does not influence the manifestation of EAA.

Introduction: Hypersensitivity pneumonitis (HP) is a potentially serious illness that may progress to pulmonary fibrosis and chronic respiratory insufficiency. Reliable methods are needed to diagnose the condition and, if possible, to identify that causative agent. The aim of the study was to establish the diagnostic yield of Specific Inhalation Challenge (SIC) in patients with HP.

Material and methods: All patients with suspected HP in whom SIC were performed between June 1995 and December 2010 (n=113) were included. Diagnosis of HP was established on the basis of internationally accepted criteria (M Girard, et al. Allergy 2009; 64:322-334). The SIC was considered positive in the case of a decrease >15% in FVC and/or a decrease >20% in TLOCO, or a decrease in FVC between 10-15% accompanied by an increase in temperature of 0.5°C within 24h of the inhalation of the antigen (Morell F, et al. Medicine 2006; 85:110-130).

Results: Eighty-eight patients were diagnosed with HP in 68 the SIC test was positive (73%). Of these 53 HP patients (58%) were positive, in 45 negative (51%) and 24 (21%) were recorded. The sensitivity and specificity of the test were 72% and 84% respectively, with a positive predictive value of 94% and a negative predictive value of 47%. Having HP caused by an antigen other than birds or fungi was a predictor of a false negative result (p=0.035).

Conclusions: In HP a positive SIC participating confirms the diagnosis, while a negative result does not rule it out.

Project partially funded by FIS PI 10100571 (Instituto de Salud Carlos III) and Beca SEPAR 2010.

Computer tomography lung density in smokers is correlated to measures of local inflammation in the lung

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Cigarette smoking causes an inflammatory response in the lungs. CT imaging provides means of quantifying pulmonary structure and function. We hypothesized that the inflammation in smokers may be mirrored both by an altered attenuation on CT and by measures inflammation in the lungs.

Materials: Healthy smokers (20 men, 20 women, mean age 54, 35±12 pack years, 40 healthy nonsmokers, age 57 and 40 COPD, age 59 (38±11 PY, 31 current smokers, 9 exsmokers) performed inspiratory CT scans. Values between -500 and -750 HU were considered as high attenuation area, BAL, was performed. Cell concentration were measured.

Result: Attenuation for smokers (44% ±5.7) and nonsmokers (38% ±5.6), COPD exsmokers (33% ±4.5) (p<0.001 and p<0.05 respectively). COPD smokers (41% ±5.0) did not differ from that of healthy smokers. Both smoker groups (healthy smokers: 556±259 x 10⁶/mL (mean±SD); COPD smokers: 458±263) had higher cell concentration in BAL compared to nonsmokers (121±50) and COPD exsmokers (102±29). The difference between the smoking and nonsmoking groups were significant (p<0.001). There was a significant correlation (r=0.0001) between cell concentration in BAL and CT attenuation. There was no significant correlation between cell concentrations in BAL and CT attenuation in smokers and COPD exsmokers.
Conclusion: The increased lung density in smokers compared to nonsmokers may mirror an inflammatory response induced by cigarette smoke. This hypothesis is strengthened by a positive correlation between lung attenuation and cell concentration in the lower respiratory tract. Our results provide a quantitative approach for measuring smoke-related structural changes in the lung.

D967 Determinants of fitness to fly in interstitial lung disease

![Image](https://via.placeholder.com/150)

P687 Different cutoff values of serum SP-D for German and Japanese to diagnose idiopathic pulmonary interstitial pneumonias are related to different SFTPD gene polymorphisms

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Introduction: Surfactant protein (SP) D is a member of the C-type lectin superfamily. Serum SP-D is applied as a diagnostic biomarker for various interstitial lung diseases in Japan, but not in European countries. It is also known that rs721917 single nucleotide polymorphism (SNP) in surfactant protein D (SFTPD) gene might influence serum SP-D levels.

Aims: This study was aimed to evaluate serum levels and genetic backgrounds of SP-D both in German and Japanese cohorts.

Methods: Serum levels of SP-D were measured and compared between patients with idiopathic interstitial pneumonias (IPPs) and healthy subjects (HS) both in German and Japanese cohorts. In addition, rs721917 SNP was genotyped by polymerase chain reaction. The power of serum SP-D to discriminate IPPs from HS was examined by receiver operating characteristic analysis based on ethnicity and rs721917 genotype.

Results: The serum levels of SP-D in IPPs were significantly higher than in HS for both German and Japanese cohort (both p<0.001). The discriminating cutoff values of serum SP-D were higher in the German than in the Japanese cohort. Furthermore, the TT genotype of rs721917 SNP, which is more frequent in German HS than in Japanese HS, was correlated with high levels of serum SP-D, and the cutoff value of serum SP-D was different according to rs721917 genotype.

Conclusions: Our data suggest the possibility of serum SP-D to be used as diagnostic biomarker for IPPs in Germans. The cutoff value of serum SP-D is higher in the German than in the Japanese cohort, and this difference might be related to the difference of rs721917 genotype distribution.

P688 Sarcoidosis associated pulmonary hypertension (SAPH) in the Netherlands

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Background: The development of pulmonary hypertension (PH) is an important risk factor for early mortality in sarcoidosis. The prevalence of SAPH in Europe is largely unknown.

Aim: To investigate the prevalence of and clinical parameters associated with SAPH in the Netherlands.

Methods: We analyzed clinical data and transthoracic echocardiograms (TTEs), made routinely at our PH/Interstitial Lung Disease clinic, from consecutive patients. Sarcoidosis patients with pulmonary hypertension were excluded. The HCT level was noted, along with baseline characteristics of the patients. The HCT levels were compared among patients who had been determined to have sarcoidosis, sarcoidosis associated with pulmonary hypertension (SAPH), sarcoidosis associated with pulmonary hypertension (SAPH) with IBD, sarcoidosis associated with pulmonary hypertension (SAPH) with IBD and fibrosis, sarcoidosis associated with pulmonary hypertension (SAPH) with IBD and fibrosis and sarcoidosis associated with pulmonary hypertension (SAPH) with IBD, sarcoidosis associated with pulmonary hypertension (SAPH) with IBD and fibrosis.

Results: From 139 sarcoidosis patients, 130 were included with stage 0 (11), I (46), II (39), III (7), IV (16). 5 patients (3.8%) had PH and 6 (4.6%) possible PH. Patients with PH were all women, predominantly black (4 out of 5) with stage IV disease (4 out of 5). 4 out of 6 patients with possible PH (3 white, 3 Asian) had stage I disease. TTO % pred was lower in PH compared to no PH (median: 46.0 (18.4 – 78.5) vs 78.50 (28.0 – 119) p < 0.01). FEV1% pred was decreased in PH compared to no PH (median: 84.0 (36.0 – 96.0) vs 82.0 (30.0 – 131.0) p < 0.05). TLP was decreased in PH (median: 61.0 (51.0 – 91.0) vs 82.0 (46.0 – 116.0), but not significantly different. In possible PH pulmonary function showed no significant difference versus no PH. Conclusions: SAPH is uncommon in the Netherlands and mainly found in black women with stage IV disease and associated with decreased lung function. Unexpectedly, suspicion of PH was found in some patients with stage I disease, warranting further investigation.

P689 The influence of TNFα gene polymorphism on the therapeutic response in patients with sarcoidosis

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Sarcoidosis is an inflammatory disease of unclear etiology, with genetic factors playing a considerable factor in both its onset and clinical presentation. In the majority of patients, the disease goes away spontaneously, without treatment. However, longer therapy is necessary in a small number of patients.

The aim of this research was to determine the role of TNF-α-308GA polymorphism in the therapeutic response in patients with sarcoidosis. The research encompassed 66 patients with sarcoidosis, 44 of whom were females and 22 were males, of average age 51.17±1.12, who were treated for sarcoidosis at the Clinic for Lung Diseases NL. TNFa-308 GA gene polymorphism was examined in all patients using the PCR-RFLP method.

Results: 10 patients received no treatment, 48 patients underwent corticosteroid treatment, while 8 patients received combined treatment using corticosteroids and methotrexate. No statistically significant difference in the distribution of TNF-a gene polymorphism genotypes and alleles was detected between the patients receiving corticosteroid treatment and those without treatment. However, the duration of the treatment was statistically considerably lower in patients belonging to AA genotype group (14.83±9.77) when compared to those from GG genotype group (18.0±10.56), p<0.05.

Conclusion: Previous research showed that the presence of TNF-308A allele is a good prognostic sign of sarcoidosis, as it is coupled with the acute form of the disease and the absence of recidives. Our results indicate a great prognostic significance of this allele, given that this could predict a favorable outcome of the disease and a shorter duration of treatment.

P690 Determinants of fitness to fly in interstitial lung disease

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Introduction: The predictors of in-flight hypoxia in interstitial lung disease remain unknown. The hypoxia challenge test (HCT) is widely used to evaluate fitness to fly. We assessed the predictive determinants of airworthiness using HCT.

Methods: 183 patients underwent HCT in 2005-2011 (74 males; mean age 57.6; 73 ex-smokers) of which 126 had idiopathic interstitial pneumonia, 26 hypersensitivity pneumonitis, 23 sarcoid and 8 other ILDs. 164 had lung function tests on the same day. 124 had an echocardiogram within 1 year. The HCT was performed using an inhaled gas mixture containing 15% oxygen. From BTS guidelines, the HCT was positive (in-flight oxygen required) if PaO2 < 6.6 kPa on 15% oxygen.

Results: Median PaO2 on air was 10.3 kPa (range 9.3-14.3), with median percent predicted FVC 68.1% and DLCO 38.3%. On univariate logistic regression, variables associated with a positive HCT were age (p<0.04), PaO2 on air (p<0.0001), FVC%, DLCO% and composite physiologic index (CPI) (p for all<0.0001). Pulmonary hypertension (PH) on echocardiogram was also predictive, although less strongly (p<0.015). On multivariate analysis, variables remaining significantly associated with a positive HCT were PaO2 on air (p<0.0001), lung function markers including CPI (p<0.0001), or in separate models DLCO (p<0.0001), and FVC (p=0.006), while PaO2 on echo was no longer predictive (p<0.13). On ROC analysis, area under the curve was 0.80 for PaO2 on air, 0.75 for DLCO%, 0.72 for CPI, 0.83 for combined CPI and PaO2, and 0.85 for combined DLCO and PaO2.

Conclusion: Our findings highlight the potential of PaO2 on air, DLCO and CPI levels as non-invasive predictors of fitness to fly. Identifying the best combination requires further prospective evaluation.

P691 Diagnostic yield of transbronchoscopic lung biopsy guided by CT in diffuse lung disease

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Objective: The predictors of in-flight hypoxia in interstitial lung disease remain unknown. Hypoxia challenge test (HCT) is widely used to evaluate fitness to fly. We assessed the predictive determinants of airworthiness using HCT.

Methods: Retrospective review of 56 patients clinical files with DLD, who were submitted to TLTB guided by CT between January 2009 and November 2011. Trucut18-20Gauge needles, percutaneous anasthesia and multislice CT Siemens Somatom Sensation were used.

Results: The patients included had an average age of 58.4 years and 32 (57%) were male. Diffuse micronodular was the most frequent CT pattern observed in 41 (75%) patients, consolidation in 25 (47%) patients, ground glass in 14 (25%), reticular in 14 (25%) and cysts in 5.3%. Biopsy confirmed preliminary diagnostic hypothesis in 27 (48.2%) patients and in 13 (23.2%) histological features observed guided to another diagnosis, leading to a diagnostic sensitivity of 71.4% (40/56 patients). In 16 (28.6%) patients this procedure was not conclusive. Diffuse micronodular and consolidation were the higher diagnostic yield patterns. 11 patients had complications, 7 pneumothorax and 4 non-massive hemoptysis. Organizing pneumonia (35%), sarcoidosis (12%) and silicosis (10%) were the most frequent diagnosis.

Conclusions: In this series of patients TLTB guided by CT was safe, quick and...
Background: Lung fibrosis is the most common cause of death in systemic sclerosis. CCL18 is associated with poor prognosis and disease deterioration in fibrotic lung diseases. The prognostic relevance in patients with interstitial lung disease in systemic sclerosis was shown by Tiev et al. (Tiev KP, Eur Respir J 2011 38: 1355-1360).

Objectives: To evaluate the role of CCL18 in patients with or without interstitial lung disease in systemic sclerosis.

Methods: We measured the chemokine CCL18 in sera of 126 patients with progressive systemic sclerosis by ELISA, as well as lung function testing at baseline and every 6 months during follow-up. Pulmonary fibrosis was detected by HR-CT. We computed ROC- and Kaplan-Meier-curves and Cox proportional hazards models to analyze the influence of CCL18 on time to disease progression, defined as decline of the predicted FVC<sub>10</sub>-10% or death.

Results: Patients with serum CCL18 concentrations above 140 ng/ml suffered from a significantly higher chance of disease progression (p<0.001) within one year. The hazard ratio to suffer from a disease progression was 8.9 in the univariate Cox hazard model and 8.7 in the multivariable hazard model (after adjusting for age, gender, and baseline FVC). In the subgroup of patients without pulmonary fibrosis at baseline the hazard ratio was even 21.1 (p<0.001).

Conclusion: CCL18 predicts disease progression of the lung involvement in patients with systemic sclerosis, independent of age, gender or baseline FVC, especially in patients without any evidence of lung fibrosis. CCL18 in sera might therefore be a tool to identify patients who will suffer from lung function deterioration in the future and to guide therapeutic interventions in these patients.

P693 Abnormal heart rate variability in patients with sarcoidosis

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Background: Heart Rate Variability (HRV) can predict cardiovascular events, especially sudden cardiac death and ventricular arrhythmias. Aim of this study was the evaluation of HRV indices in sarcoidosis (Sarc).

Methods: 180 biopsy proven Sarc patients who were not taking antiarrhythmic drugs were included in this study. They were compared with 72 sex and age matched healthy subjects. All participants had cardiac stress tests, cardiac ultrasound, 24-hour Holter monitoring and cardiac MRI and were classified to group A (healthy), group B (cardiac-free Sarc) or group C (cardiac Sarc). The average heart rate (mean HR), the maximum and minimum heart rate (maxHR and minHR), the root mean square of SD of RR (RMSSD) and the standard deviation of all normal to normal NN intervals (SDNN) were calculated during 24-hour Holter monitoring.

Results: Comparison among groups of different parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>101±30</td>
<td>95±60</td>
<td>98±92</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV1</td>
<td>99±32</td>
<td>92±13</td>
<td>88±24</td>
<td>0.001</td>
</tr>
<tr>
<td>TLF</td>
<td>84±65</td>
<td>92±48</td>
<td>89±12</td>
<td>0.001</td>
</tr>
<tr>
<td>TLC</td>
<td>84±17</td>
<td>94±37</td>
<td>82±24</td>
<td>0.004</td>
</tr>
<tr>
<td>DLCO</td>
<td>84±26</td>
<td>93±72</td>
<td>71±10</td>
<td>0.0001</td>
</tr>
<tr>
<td>KCO</td>
<td>100±40</td>
<td>98±35</td>
<td>91±32</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean Heart Rate</td>
<td>73±60</td>
<td>74±60</td>
<td>85±94</td>
<td>0.15</td>
</tr>
<tr>
<td>MaxHR</td>
<td>140±88</td>
<td>140±32</td>
<td>136±17</td>
<td>0.4</td>
</tr>
<tr>
<td>MinHR</td>
<td>45±33</td>
<td>48±35</td>
<td>50±34</td>
<td>0.013</td>
</tr>
<tr>
<td>RMSSD</td>
<td>38±95</td>
<td>28±37</td>
<td>29±30</td>
<td>0.013</td>
</tr>
<tr>
<td>SNN</td>
<td>150±30</td>
<td>127±30</td>
<td>112±30</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In bivariate analysis, SNN is correlated with age (p=0.001, r=−0.397), FVC (p=0.001, r=−0.242), FEV1 (p=0.001, r=−0.261), TLC (p=0.001, r=−0.290) and DLCO (p=0.001, r=−0.264).

Conclusion: HRV is decreased in patients with sarcoidosis compared to the control group. SNN is significantly decreased in patients with sarcoidosis and is correlated with lung function indices.
Materials and methods: A549 and SKMES cell lines were treated with serum from patients with sarcoidosis, COPD and healthy individuals. Their effect on cell proliferation was examined. The influence of cytokines and EGF on cell proliferation was also investigated.

Results: When serum from patients with sarcoidosis was added to the culture medium of both epithelial cell lines, there was a statistically significant increase of cell proliferation (p<0.05). By contrast, serum from normal controls or patients with COPD had no impact. This positive influence of serum from patients with sarcoidosis was annulled by EGFR inhibitor.

Conclusions: Out of control cell growth is a basic step towards malignancy. The increase of epithelial cell proliferation in the presence of sarcoidosis serum, documented in the present study, could represent a link of this disease with neoplasia, under favorable circumstances.

P697 IL-17a expression in transbronchial biopsy samples in sarcoidosis
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Background: Th17 is a new subset of CD4 (+) T cell population and characterized by the release of cytokines such as IL-17A, IL-17F and IL-22. Multiple studies in humans and animals have described the role of Th17 cells in the pathogenesis of several autoimmune and chronic inflammatory diseases such as psoriasis, inflammatory bowel diseases, tuberculosis and lung fibrosis.

Aim: To evaluate the possible role of Th17 cells in the pathogenesis of sarcoidosis by evaluating the IL-17A levels in lung biopsy samples of sarcoidosis patients.

Methods: The IL-17A expression was evaluated with immunohistochemical analysis. The area that had higher IL-17A antibody positivity was evaluated with x40 magnification and the positive staining inflammatory cells (macrophage and lymphocyte) were counted.

Results: A total of 41 sarcoidosis patients (32 [78%] female) with the mean age of 48 years were included in the study. Among them 22 (54%) were diagnosed as Stage 1, 17 (42%) as Stage 2 and 3 as sarcoidosis. In the whole study group only 2 (5%) patients had no IL-17A (+) inflammatory cells. In the remaining, 9 (22%) patients had one IL-17A (+) staining cell, 15 (37%) had 2, 5 (12%) had 3 cells, 9 (22%) had 4 cells and 1 (2%) had 5 cells. The IL-17A (+) staining cells were identified at the periphery of the granuloma. No statistically significant correlation was identified between the number of IL-17A (+) staining inflammatory cells and plasma ACE levels, CD4/CD8 ratio and the stage of the disease (p>0.05).

Conclusion: The identification of IL17A (+) staining inflammatory cells in the periphery of the sarcoidosis granulomas, may indicate that Th17 cells have an important role in the pathogenesis of sarcoidosis.

P698 BALF TNFα level in relation to inflammatory status and phenotype of sarcoidosis
Anna Golan Geremek1, Michał Bednarek1, Elżbieta Puscinska1, Marek Kram1, Urszula Demkow2, Dorota Górecka1

Aim: To evaluate the relation of BALF TNFα levels to the inflammatory status and phenotype of sarcoidosis.

Material and methods: We have measured: TNFα, TGFβ, IL-2, IL-12, IL-10 in BALF and TNFα, TGFβ, IL-2, IL-12, IL-10 levels in serum in 184 sarcoid patients. We checked for the correlations between BALF TNFα and cytokines, selected systemic inflammatory markers and clinical factors (age, duration of the disease, PFT, 6MWT, extrapulmonary involvement).

Results: We have found important positive correlation between concentration of BALF TNFα and:
- BALF: IL-2 (r=0.4676, p=0.0001), IL-12 (r=0.4555, p=0.0001) and serum: IL-12 (r=0.26, p=0.0011), IL-10 (r=0.2832, p=0.0012), TNFα (r=0.1871, p=0.12).
- serum CRP (r=0.2427, p=0.003), γ-globulins (r=0.1685, p=0.033), Dliders (r=0.1685, p=0.035).
- the age of patients (r=0.16, p=0.029).

No relation was found between the BALF TNF alpha and the duration of the disease, PFT (except for FEV1 r=0.1466, p=0.05), 6MWT, extrapulmonary sarcoidosis (liver and spleen dimensions, hepatic enzymes, protrombine), CA and P serum nor urine levels. Weak but important negative correlation was observed between BALF TNFα and monocytosis (r=-0.1788, p=0.015).

Conclusion: Out of control cell growth is a basic step towards malignancy. The BALF cytokine inflammatory status reflects the systemic inflammation (measured by the serum cytokine network and non-specific inflammatory biomarkers).

The BALF TNFα status has no relation to the phenotype of sarcoidosis.

P699 Assessing sarcoidosis: The King’s Sarcoidosis Questionnaire and the minimal important difference
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Introduction: The King’s Sarcoidosis Questionnaire (KSQ) is a brief, validated, multi-organ, health status questionnaire. This study aimed to determine the minimal important difference (MID).

Methods: 60 patients with pulmonary sarcoidosis attending clinic (mean age 52 years; duration 7 years, 50% female, 67% Caucasian, 76% immunosuppressive medications) were asked to complete the KSQ on 2 occasions (change of therapy n=25). Combined Lung-Health Status modules (Lung-HS) consisted of 16 items and impact of medications 3 items; scoring range 0–100, 100=best. At the second visit patients also completed a 15-item global rating of change questionnaire (GRCQ). The MID corresponded to the mean change in KSQ in patients indicating a small change in GRQ (±2/3) and was also estimated by determining 1xSEM and effect size (ES) of 0.3.

Results: Health status was impaired at baseline: mean (SD) Lung-HS 54 (24) and Medication score 60 (29). 20 patients deteriorated, 18 improved and 22 were unchanged. The GRQ scores were associated with change in Lung-HS: r=0.4, p<0.01. There was a significant change in Lung-HS score in patients reporting a change of therapy (p=0.05). Combined Lung-HS MID determined by GRQC for those improving and those deteriorating was 5 and 6 and 5 point change respectively. The MID of individual General HS, Lung and Medication modules determined by GRQ were 5, 9 and 9 respectively.

Conclusion: The KSQ is responsive to changes in health status and can be used for longitudinal assessment of patients with sarcoidosis. The MID of the combined KSQ Lung-Health Status modules is a 5 point change.

91. Diffuse parenchymal lung disease: clinical profiles and collagen vascular disease

P700 Corticosteroid (CS) therapy does not influence immune reactivity in patients with non-specific interstitial pneumonia (NSIP)
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Aim: To assess the influence of CS therapy on immune reactivity in patients with NSIP.

Patients and methods: 27 patients (8 male 19 female, average age 57±3.2 years) with histologically proved NSIP were included. Immunosuppressive medications were used in 11 patients of group 1, the diagnosis was recently established and treatment was not yet started. 16 patients of group 2 received CS during 2–10 yrs. Blood level of IL-15, IL-2, IL-8, TNF-α basal and those deteriorating was assessed by ELISA. NSIP patients also completed a 15-item global rating of change questionnaire (GRCQ). The MID determined by GRQ was calculated for the GRQ scores of change for those improving and those deteriorating was 5 and 6 point change respectively. The MID of individual General HS, Lung and Medication modules determined by GRQ were 5, 9 and 9 respectively.

Conclusion: The KSQ is responsive to changes in health status and can be used for longitudinal assessment of patients with sarcoidosis. The MID of the combined KSQ Lung-Health Status modules is a 5 point change.

P701 Does emphysema influence the application of du Bois score in idiopathic pulmonary fibrosis?
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Idiopathic pulmonary fibrosis (IPF) is the most frequent interstitial pulmonary fibrosis. Development in CT scan technology improved accuracy in lung study. Emphysema can be associated to IPF; the most common form is the “Combined pulmonary fibrosis and emphysema” syndrome (CPFE). The aim of this retrospective cohort study was to assess the impact of emphysema associated to IPF on functional parameters (Forced Vital Capacity FVC and Total Lung Capacity TLC) at baseline (t0) and on the loss of FVC after 6 months (t6) which is used in the du Bois prognostic score.
Data from 73 patients suffering from IPF were collected between 1982 and 2011 in an University Hospital with access to pharmacological studies and lung transplantation. Fifty six patients (M/F; 44/12; age 65.1±8.0) were considered for analysis. Biochemical diagnosis of emphysema was based on CT scan criteria used by Schmidt et al. [1].

IPF

With emphysema | Without emphysema | p
--- | --- | ----
N | 35 | 38
Age(years) | 65.9±9.3 | 65.3±11.8 | 0.39
Tobacco use | 15 (71%) | 24 (69%) | 0.41
History of respiratory hospitalization | 5 (24%) | 9 (26%) | 0.62
FVC ≤0.85 (L) | 86.7±18.4 | 72.6±20.6 | 0.02
TLC ≤1.8 (L) | 86.6±17.2 | 72.6±15.0 | 0.004
FVC ≤70% | -1.2±20.1 | -0.0±11.4 | NS
Du Bois score | 14.6±14.0 | 18.0±13.9 | 0.39

Emphysema seemed to influence significantly TLC and FVC at 0. In Du Bois score was not statistically different between the two groups although they corresponded to different sub domains of mortality risk. According to the Du Bois score, patients with emphysema were at lower risk of mortality than the others.


P702

Telomerase expression in idiopathic pulmonary fibrosis (IPF) and non small cell lung cancer (NSCLC).

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Rationale: Telomeres protect chromosome ends since chromosomes lacking telomeres undergo fusion, rearrangement and translocation. Telomerase dysfunction has been linked with pathologic autoimmune responses and could play a role in both fibrogenic injury and the response to explain telomerase expression (mRNA levels of both subunits TERT and TERC) in Bronchovascular Lavage Fluid (BAL) and lung tissue of patients with NSCLC and IPF, since there are indications of common pathogenetic pathways in both diseases.

Patients and methods: We prospectively studied 44 BALF samples from NSCLC patients, 29 BALF samples from IPF patients and 13 BALF samples from control subjects. We also studied lung tissue samples from 32 IPF patients, 10 NSCLC patients and 21 control subjects. mRNA expression for both TERT and TERC was measured by Real-Time RT-PCR.

Results: (a) Lung tissue: IPF mRNA hTERT levels (0.24±0.14) were significantly lower compared to controls (0.46±0.30) (p=0.030). hTERC mRNA levels were higher in the control group (4.3±1.9) compared to NSCLC (2.8±1.5) and IPF (1.2±0.97), with strong group statistical significance (p<0.0001). (b) BALF: TERT mRNA expression was higher in the control group (0.79±0.06) compared to IPF (0.39±0.14) and NSCLC (0.34±0.29) (p=0.005). TERC mRNA expression was higher in the IPF group (1.09±0.39) compared to controls (0.54±0.40) and NSCLC (0.62±0.19), with no group statistical significance.

Conclusion: The attenuated expression of both telomerase subunits measured in NSCLC and IPF patients when compared to controls, suggests that telomerase genes may play a significant role in fibrogenesis and carcinogenesis, supporting the hypothesis of a common pathway.

P703

Specific features of pulmonary mechanics and gas exchange in patients with histiocytosis X (HX)

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Aim: To assess the changes of pulmonary mechanics and gas exchange parameters, which are typical for histiocytosis X.

Materials and methods: 67 patients with HX have been examined, including 48 men (mean age 29.1±1.4 yrs) and 19 women (mean age 27.1±2.6 yrs). Spirometry, bodyplethysmography, compliance measurement, diffusion capacity (DLCO) and blood gases were carried out for all patients.

Results: For either men or women the mean values of the lung mechanics parameters didn’t overstep the bounds of normal value, except for DLCO. Excluding 39 patients with normal value of indices, two groups of patients were identified. The first group of 20 patients shown signs of airflow limitation: decrease of the forced exhalation FEV1 (59.7±6.5%Pred) and FEF25-75 (39.7±8.9%Pred) and reduction normal TLC (98.4±6.5%Pred) by obstructive type (RV/TLC 168.0±11.2%Pred). The second group contained 8 patients with restrictive respira-

P704

The EDD (exercise, DLco, dyspnea) index in diffuse systemic sclerosis with pulmonary fibrosis

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Introduction: Pulmonary fibrosis secondary to systemic sclerosis (SSc) is the major cause of morbidity and mortality in these patients. The aim of this study was to determine the correlation of important lung function parameters with chest high resolution CT scan (HRCT).

Methods and materials: Thirty-two consecutive diffuse SSc patients (according to the criteria of american college of rheumatology) with pulmonary involvement were enrolled in this cross-sectional study. Patients with pulmonary fibrosis secondary to other reasons, previous restrictive lung disease, and history of smoking were excluded. Complete lung function evaluation was performed. Also the severity of dyspnea was evaluated by Modified Medical Research Council (MMRC) scale EDD index was calculated based on 6MWT, DLco, and MMRC.

The EDD index in scleroderma lung fibrosis

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<tr>
<td>6MWT</td>
<td>≤50</td>
<td>250–349</td>
<td>350–449</td>
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<tr>
<td>DLco</td>
<td>≥80%</td>
<td>60–79%</td>
<td>40–59%</td>
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<td>MMRC</td>
<td>0–1</td>
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The chest HRCT was performed and the Warrick score recorded in all patients. Results: The mean age of the patients was 39.18 years ±9.39 (SD). Seventeen (53%) of patients were in EDD stage 1 (score: 0±0.3), 9 patients (28%) in stage 2 (<score ≤5), and 6 patients (19%) in stage 3 (score >5). The Warrick score was 10.84±6.94 (SD). There was statistically significant correlation between EDD index and Warrick score (p=0.001, r=0.72). Also there was statistically significant relation in EDD stages with Warrick scores (p=0.002).

Conclusion: The EDD as a useful lung function index is completely related to chest HRCT findings in SSc pulmonary fibrosis and can be used in clinical practice.

P705

Increased exhaled nitric oxide precedes lung fibrosis in a murine model of systemic sclerosis

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Background: Exhaled nitric oxide (eNO) increased in patients with systemic sclerosis (SSc) and interstitial lung disease. Reactive oxygen species (ROS) and bleomycin induced skin and lung fibrosis in mice, mimicking the SSc in humans. Objectives: This study aimed to validate eNO measurement method in mice and to study the evolution of lung inflammatory and fibrotic processes in mice injected with HOCI or bleomycin.

Methods: C57BL/6 mice were randomized into 3 groups receiving subcutaneous injections of HOCI, bleomycin, or PBS for 2, 4, or 6 weeks. Exhaled NO was measured at the end of each injection period and after 2 resting weeks without injection (8 weeks). Mice were then sacrificed to obtain skin and lungs tissues for NO synthases (NOS) expression analysis.

Results: Increased exhaled NO, inducible NOS and 3-nitrotyrosine expression in bronchial epithelium, lung neutrophils and macrophages were observed at early phases (2 and 4 weeks) in HOCI- and bleomycin-treated mice. Interestingly, lung vascular endothelial NOS expression decreased significantly at 6th and 8th week. Skin fibrosis was significantly increased from the 4th week and lung fibrosis from 6th week.

Conclusions: Exhaled NO can be used as a sensitive biomarker of lung inflammation in these murine models in which inflammation precedes fibrotic processes in skin and lungs. Mechanisms linking inflammation and fibrosis remain to be clarified.
P706 Elevated serum B cell activating factor belonging to the TNF family (BAFF) in interstitial lung diseases associated with collagen vascular disease.

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Background: BAFF is a vital homostatic cytokine for B cells. Increased serum levels of BAFF were found in a number of different autoimmune diseases and patients with polymyositis with interstitial lung disease (ILD) had higher BAFF levels than those without ILD. However, serum BAFF levels have not been reported in patients with ILD associated with collagen vascular disease (CVD-IP) and idiopathic interstitial pneumonia (IP).

Aim: We investigated serum levels of BAFF in patients with CVD-IP and with IP to determine whether they correlate with pulmonary function.

Methods: Twenty-seven patients with CVD (n=15) and CVD-IP (n=12), who visited our institution from 2008 to 2010 and underwent pulmonary function test, were enrolled. Underlying CVDs consisted of rheumatoid arthritis (n=4), dermatomyositis (n=2), systemic sclerosis (n=2), ANCA-associated systemic vasculitis (n=1), and mixed connective tissue disease (n=1). Twenty-three healthy volunteers were included as a control group. Serum BAFF levels were measured by ELISA.

Results: Serum BAFF levels were 4.4±1.2 ng/ml for CVD-IP, 3.1±0.6 ng/ml for IP, and 2.0±0.1 ng/ml for the control. BAFF was significantly elevated in CVD-IP compared with control subjects. An inverse relationship between serum BAFF levels and DLco was noted in patients with CVD-IP.

Conclusion: We found elevated serum BAFF levels in CVD-IP patients and correlation with severity for ILD.

P707 Grape seed proanthocyanidin extract (GSPE) attenuates bleomycin-induced pulmonary fibrosis in mice.

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Background: Grape seed proanthocyanidin extract (GSPE) has more powerful antioxidative activity than other well-known antioxidants, including vitamin C and E. Idiopathic pulmonary fibrosis is a chronic progressive disorder with a poor prognosis. An antioxidant-antimicrobial imbalance may contribute to the disease process in idiopathic pulmonary fibrosis.

Objectives: To examine whether GSPE which is known to act as an antioxidant has therapeutic effect on bleomycin-induced pulmonary fibrosis in mice, an animal model of idiopathic pulmonary fibrosis.

Methods: Mice were treated by intratracheal instillation of bleomycin. GSPE was administered by intraperitoneal (IP) injections (30, 60, or 90 mg/kg).

Mice were sacrificed on days 21 after bleomycin instillation.

Results: Compared with the BLM/Veh group, histologic findings in mice treated with BLM and IP injection of GSPE (BLM/GSPE) showed less fibrotic lesions in a dose-dependent manner. The mean Aschcroft’s fibrosis score in the BLM/Veh group was significantly higher than in the BLM/GSPE group. The lung hydroxyproline concentration on Day 21 was significantly higher in the BLM/Veh group than in the BLM/GSPE group (62.9 vs 55.3, 51.9, 50.4 ug/ml).

Conclusions: GSPE attenuated bleomycin-induced pulmonary fibrosis in mice. Prophylactic GSPE may be useful in the treatment of idiopathic pulmonary fibrosis.

P708 Clinical impact of irradiated lung volumetric modeling in adjuvant breast radiotherapy (RT).

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Background: No relation with the ILD types.

Methods: (Pt) beginning breast RT between June ’07 & March ’10 were prospectively reviewed. Pt included were women with DCIS or Stage I–III carcinoma, who received RT using a 3D-CRT technique to the breast or chest wall (2-field RT (2FRT) ± supraclavicular/postaxillary boost (4-field RT (4FRT)).

50.4 Gy in 28 fl. Lung DVH parameters, 2D parameters are reported. Post RT all Pt underwent 3 monthly (mo) clinical/PFT & 6 monthly HRCT scan. Modeling equations to predict the PIV from 2D parameters was developed using linear regression analysis. Mann-Whitney U test was used to analyse PFT & HRCT changes over time. Binary logistic regression used to evaluate relation between PIV and Radiation pneumonitis (RP).

Results: 44 Pt met the inclusion criteria: 6 had 2FRT & 38 had 4FRT. With a medium follow-up of 14 months, 5 Pts reported mild respiratory symptoms at 1mo, which resolved completely at 3mo post-RT.A significant decrease of FVC, FEV1, MMEF25-75 & DLco was observed at 3mo,with partial recovery at 9 mo in the Pt treated with 4FRT, but there was no decrease of PFT in Pt treated with 2FRT. In HRCT at 6mo grade I opacity was present in 4 & 1 Pts (PIV 15-19.9 and Mean lung dose 10.1-15) undergoing 4FRT & 2FRT.

Conclusions: Within the range evaluated in this study, the 3D parameters (FV) better predicted an early decrease in pulmonary function, although HRCT detected RP was observed only when > 11% of the lung was irradiated in 4FRT-4FRT is associated with significant reduction in PIV but not 2FRT.

P709 Impact of diagnostic pitfalls on the management of pulmonary sarcoidosis.


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Background: Work-up in patients with sarcoidosis includes differentiation mainly with pulmonary TB, hypersensitivity pneumonitis and community-acquired pneumonia. Usually bronchoscopy is performed with lung biopsy and BAL, but often this option is not available, and thus diagnostic mistakes arise.

Aim: To evaluate frequency and possible impact of diagnostic pitfalls on management of sarcoidosis patients.

Methods: 127 patients with newly diagnosed sarcoidosis based on results of lung biopsy and BAL during bronchoscopy were enrolled into study. We analyzed primary diagnosis and treatment, duration of treatment, age, sex, usage of systemic steroids after the final diagnosis and mean dose of them in patients with correct (controls) and incorrect primary diagnose (study group).

Results: 23 patients (18.1%) had diagnostic pitfalls, from which 12 were treated from pulmonary TB in HRZE regimen around a year (46.57±3.32 wks), 7 treated from pneumonia for 3.11±1.13 wks with further observation for 20,33±5.52 wks, and 4 pts were diagnosed as having a hypersensitivity pneumonitis with mean treatment with steroids 30±5.25±2.89 wks. Groups were comparable for sex and age. In study group, 10/23 (43.5%) pts had relapse of disease versus 30/104 (28.8%) in controls (p<0.05), frequency of systemic steroids use was also higher (15/23 (65.2%) versus 59/104 (56.7%) in controls). The mean dose of prednisone in sudy group was significantly higher than in controls: 21.7±0.9 mg vs 17.2±0.7 mg (p<0.05).

Conclusions: Diagnostic pitfalls in work-up process among sarcoidosis patients are quite frequent, and lead to a more severe disease flow with higher frequency of systemic steroids usage and higher dose of them.

P710 Pulmonary hypertension in different interstitial lung diseases.

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Background: Pulmonary Hypertension (PH) has been proposed a higher incidence in Interstitial Lung Diseases (ILDs). PH in different ILDs has different pathogenesis. PH in patients with ILDs is not well recognized and can occur in the absence of advanced pulmonary dysfunction or hypoxemia.

Objective: To investigate the incidence of pulmonary hypertension in different types of interstitial lung diseases.

Methods: Two hundred and five patients with ILD between 24 and 89 years old (mean age one hundred and four male, one hundred and one female) were evaluated, to discuss the incidence of PH in ILD seems to have no relation with the ILD types.

Results: Two hundred and five ILDs in Beijing Chao-Yang Hospital, ranging from January 1st 2010 to June 8th 2011, 27 were diagnosed as PH, so the incidence of PH in ILD is 13.2%. There was no significant difference of the incidence of PH in ILD between males and females (p=0.901). There was a significant difference of the incidence of PH in ILD between age ≥60yrs and <60yrs (p=0.017).The incidence of PH has no statistically significant difference among different types of ILD (p=0.455).

Conclusion: The total incidence of PH in ILDs is 13.2%, the patients with age ≥60yrs have higher incidence of PH. Whether PH develops in ILD seems to have no relation with the ILD types.
**P711**

Profile of interstitial lung diseases in Pakistan, Karachi pulmonology clinics registry data, 2008 – 11

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Background & Objective: No published data is available about the status of Interstitial Lung Diseases (ILD) in Pakistan. This study ponders to determine the incidence and relative frequency of various ILDs in Karachi, its most populous multi-ethnic city.

Methods: We reviewed data from a registry cataloging to 3 pulmonology clinics in different areas of the city. Based on a detailed questionnaire it records age, gender, exposure history, clinical presentation, HRCT and PFT findings mandatorily and BAL/VATS data if available. It prospectively recorded diagnosed ILD cases between Jan 2008 and Dec 2011 and deaths occurring during follow-up.

Results: In a total of 5600 pulmonology referrals, the incidence of ILD was 2.3% (n=133) with a mean age of 55.1 years (+12.9 SD), mortality of 22.6% and median survival of 3 years. Idiopathic Pulmonary Fibrosis (IPF) (49.6%), Non Specific Interstitial Pneumonitis (NSIP) (19.5%) and Sarcoidosis (17.3%) were the most frequent ILDs followed by Collagen Vascular Disease Related (5.3%), Drug Induced ILD (4.5%) and Hypersensitivity Pneumonitis (3.8%). Reporting females (n=91) outnumbered males (n=42). The incidence of IPF/NSIP was greater in males (76%) while sarcoidosis and other ILDs occurred more in females (34%). Interestingly, out of 45 IPF diagnosed housewives living in congested areas, 42% had chronic avian exposure due to home breeding/pets.

Conclusions: Establishes for the first time the considerable presence of ILD in Pakistani population and describes its salient features. Hopefully this will improve disease awareness and help us expand this registry to other major cities for greater input towards research.

**P712**

BAL protein profiles specific of different interstitial lung diseases

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Interstitial lung diseases (ILD) are an heterogeneous group of lung disorders with different etiopathogenesis, clinical courses and prognosis. In the last ten years our group of research is focusing on the proteomic analysis of BAL in different interstitial lung diseases.

Aims of this proteomic study were to compare protein profiles of Sarcoidosis (S), Idiopathic Pulmonary Fibrosis (IPF), Langerhans cell Histiocytosis (PLCH), pulmonary fibrosis associated with Systemic sclerosis (SSc) patients in order to identify proteins of interest involved in specific pathogenetic networks or potential biomarkers with clinical value.

Methods: Population of patients was composed by 9 S, 7 IPF, 9 PLCH, 7 SSc. Proteomic analysis was performed by 2D-electrophoresis. Image analysis was done by Image Master Platinum 7.0 software. Protein identification was performed by mass spectrometry.

Results: Image analysis revealed distinct expression profiles for each ILD. Among the 280 differentially expressed in our ILD samples there were Complement C3, complement factor B, complement factor I, antithrombin III, angiotensinogen, vimentin D binding protein, Leucin-rich alpha-2-glycoprotein, 14-3-3 protein epsilon, calcyphosin, kiningen N-term, alpha-2-HS-glycoprotein.

Conclusion: The proteomic analysis of BAL confirmed the possibility to use 2D-electrophoresis to highlight different protein profiles among specific ILDs.

**P713**

Idiopathic pulmonary fibrosis: Clinical, radiological and functional significance of biomarkers of proliferation

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Background: Natural course of idiopathic pulmonary fibrosis (IPF) could be predicted by proliferative markers of the fibrotic process, such as myofibroblasts and interleukins (IL)-13 and IL14. Our primary aim was to determine whether these proliferative markers influence the course of IPF course measured by a radiological/functional score.

Methods: Twenty-eight patients with biopsy-proven IPF disease, who underwent pulmonary evaluation by high-resolution computed tomography (HRCT) fibrosis score and pulmonary function tests were studied. Five normal lung tissues (NTL) were included Biomarkers in lung tissues were detected by immunohistochemistry and quantified by histomorphometry for myofibroblasts alpha-smooth muscle actin (α-SMA), anti-interleukin (IL)-4 and IL-13.

Results: Myofibroblast amount, IL-4 and IL-13 expression were higher in IPF than in NLT (p<0.01). Myofibroblast expression of α-SMA was positively correlated to IL-14 and IL-13 expression. Lung tissue from patients with high HRCT fibrosis scores expressed significantly greater α-SMA+, IL-4 and IL-13 when compared with patients with low HRCT fibrosis scores (p<0.05). Negative correlations were found between myofibroblasts α-SMA+ and VC and DLCO.

Conclusions: Proliferative markers, detected by immunohistochemistry, in lung tissue allowed recognizing a dichotomous discrimination of HRCT fibrosis course and influenced pulmonary function tests, suggesting that they may be promising markers of prognosis in these patients. Financial support: FAPESP, CNPq.

**P714**

Significance of protein S in patients with interstitial lung disease

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Background: Protein S exerts anticoagulant activity by acting as a cofactor of activated protein C for the inactivation of coagulation factors Va and VIIa. We have previously reported that protein S protects against lipopolysaccharide-induced acute lung injury by directly inhibiting the local expression of inflammatory cytokines without affecting coagulation (Takagi T, et al. 2009). However, the role of protein S in interstitial lung disease remains unclear.

Objective: The aim of this study is to evaluate the clinical significance of protein S in patients with interstitial lung disease.

Methods: This study comprised 106 patients with interstitial lung disease admitted in our institution between August 2008 and December 2011. There were 39 patients with interstitial pneumonia, 25 with sarcoidosis, 9 with collagen vascular disease-associated interstitial lung disease, 8 with organizing pneumonia, 7 with pulmonary sarcoidosis, 5 with tumour-associated ILD, 4 with hypersensitivity pneumonitis, 2 with IgG4 related multi-organ lymphoproliferative syndrome, 1 with alveolar proteinosis, and 1 patient with alveolar hemorrhage. Levels of protein S in BALF were measured using an enzyme-linked immunosorbent assay.

Results: Significant changes in the BALF levels of protein S were observed among the different types of interstitial lung diseases. The BALF level of protein S was significantly correlated with the number of macrophages, lymphocytes and with the BALF concentration of total protein and albumin.

Conclusion: These results suggest that protein S plays role in the pathogenesis of interstitial lung disease.

**P715**

Combined pulmonary fibrosis and emphysema syndrome (CPFE)

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Introduction: CPFE is a clinical entity which consists in the coexistence of emphysema of the upper lobes and pulmonary fibrosis of the lower lobes.

Method: Retrospective descriptive study of cases diagnosed of CPFE between 2007 and 2012.

Results: 44 patients, all of them men, with an average age of 69 years. All were current or ex smokers. 50% had a UIP (usual interstitial pneumonia) pattern at the HRTC, 11.4% possible UIP pattern, and 36.8% inconsistent UIP pattern. All the patients had emphysema, above all paraseptal and centrilobular. PAH was present in 10 patients. The final diagnosis was: 18 IPF, 1 possible IPF, 1 NSIP, 3 possible NSIP, 6 fibrosis associated connective tissue diseases, 1 asbestosis, 1 hypersensitivity pneumonitis, 1 drug associated fibrosis, and 12 non classificable interstitial pneumonias. During follow-up 8 patients died, 6 were diagnosed of lung cancer.

| Table 1. Results |
|-----------------|-----------------|
| **n** | **s** |
| **Age** | 44 | 69±12 (43-88) |
| **Men** | 44 | 100% |
| **Current smokers** | 15 | 34% |
| **Ex-smokers** | 29 | 65% |
| **PAH** | 10 | 22.7% |
| **PAs** | 10 | 56.3±31.7 (36-90) |
| **FVC (%)** | 38 | 101.7±21.3 (47-152.5) |
| **FEV1 (%)** | 38 | 72.4±12.5 (45.9-78.5) |
| **TLC (%)** | 24 | 89.6±23.1 (45.1-139.7) |
| **DLCO (%)** | 30 | 50.8±12.8 (39.2-104.1) |
| **DLCO/VA (%)** | 34 | 60.7±24.8 (25.4-123.7) |

Conclusions: All of the patients from this study are men with smoking history. These patients have, lung volumes preserved with a severe impairment of gas exchange. The high prevalence of PAH and its important role in the prognosis justify echocardiography. As these patients might have a high prevalence of lung cancer, a close follow-up would be advisable.
P716 Nine cases of interstitial lung disease associated with anti-CADM140 antibody positive dermatomyositis
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Background: Anti-CADM140 antibody (CADM) was found in some amyopathic dermatomyositis (DM) patients in 2005. It was reported that about 50% of CADM positive patients died from acute exacerbation (AE) of DM-related interstitial lung disease (DM-ILD) despite treatment. As compared with CADM negative patients (about 6%), the rate of AE of ILD is clearly high in CADM positive pts. [Objective] To elucidate the clinical characteristics of ILD associated with CADM positive DM.

Methods: Blood examination, arterial blood gas analysis, pulmonary function testing, bronchoalveolar lavage (BAL) analysis and pattern of chest CT were examined in 9 pts who were diagnosed with CADM positive DM in our hospital. Results: Since the average value of FVC and CRP at the time of the first medical examination was 662% of the normal range in 7 pts, slightly high (217 IU/L) in 1, and significantly high (25300 IU/L) in 1. The value of KL-6 was in the nearly cut-off range in 8 pts, and significantly high in 1 (3764). Alveolar-arterial oxygen difference was increased in 3 pts. In 4 pts in which BAL was performed, the lymphocyte differentiation was all high. Concerning chest CT image, patchy shadow or patchy shadow and trabeucular shadow in outside layer of the lung fields were seen in 7 pts, GGO around broncho-vascular bundle in 1, and no abnormal shadow in 1. All of the shade were slight. Although one pt died of AE, 8 pts survive as of February 2012.

Conclusion: In DM-ILD, even if the CT image and data are slight, whenever the CT image is not typical NSIP pattern, we have to take the possibility of CADM into consideration.

P717 Chitotriosidase activity and CHIT1 gene polymorphism in sarcoidosis
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Introduction: Among several biomarkers of sarcoidosis activity chitotriosidase (CTO) has been found to be useful. Some subjects have a 24-base pair duplication in the CTO gene (CHIT1) that results in the production of inactive enzyme which might influence CTO activity.

Aims: The study was conducted 1) to confirm previous observations of increased CTO activity in patients with sarcoidosis and 2) to evaluate the influence of different CHIT1 polymorphism on CTO activity.

Methods: The study comprises 47 patients with newly diagnosed active sarcoidosis (27 females, 20 males, average age 42.3 years). CTO activity was determined in serum and BAL using a standard fluorimetric method. CHIT1 genotyping was done by polymerase chain reaction (PCR).

Results: A normal CHT1 genotype (NN) was present in 61.7% of the subjects. 34.0% were heterozygotes for deleted allele (ND) and 4.3% were homozygotes (DD). The mean serum CTO value was 136 nmol/mL/h (± 583) and was increased in 93.6% of patients. The mean BAL CTO value was 9.01 nmol/mL/h (± 12.8). There was no difference in serum and BAL CTO activities (p =0.70, p < 0.001).

There was no significant difference between NN and ND subjects in serum CTO activity (855±15.02 nmol/mL/h, 4.31±4.507 nmol/mL/h, p=0.001). In BAL there was no difference between CTO activity in normal and homozygotes (348 nmol/mL/h, p=0.331), but a significant difference in BAL CTO activity (12.2±15.02 nmol/mL/h, 4.31±4.507 nmol/mL/h, p<0.001). There was no CTO activity in mutation homozygotes.

Conclusions: The results confirm previous observations that the CTO activity is increased in patients with sarcoidosis. Unexpectedly, there was no significant difference in serum CTO activity between CHIT1 normal homozygotes and heterozygotes which warrants further study.

P718 Safety and tolerability of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF) receiving commonly used concomitant medications
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Introduction: The CAPACITY Program (CAP) included two Phase 3 trials of PFD in 779 patients with IPF. Analyses were conducted to assess the safety of PFD in patients receiving commonly used concomitant medications.

Objectives: To examine the safety/tolerability of PFD in IPF patients receiving commonly used concomitant medications.

Methods: Pooled data from the CAP trials were analyzed. Commonly used concomitant medications were defined as those used by ≥25% of patients in any treatment group between the first and last dose of study drug. The percentage of patients with selected treatment emergent adverse events (TEAEs) while on or within 28 d of cessation of commonly used concomitant medications was assessed. Patients in the PFD 2400 mg daily group were evaluated using a composite safety endpoint that included any Grade 3 or 4 TEAE, discontinuation of PFD, interruption/dose reduction of PFD, or any serious AE.

Results: Commonly used concomitant medications and vaccines included: acetylsalicylic acid, azithromycin, influenza vaccine, multivitamins, omega3, paracetamol, salbutamol, and simvastatin. No evidence of a clinical pattern of TEAEs was observed with the use of PFD and these commonly used medications or vaccines. Patients receiving these medications had similar patterns of safety as those not receiving a commonly used concomitant agent.

Conclusions: These data suggest that PFD is safe and generally well tolerated in patients with IPF when used with a spectrum of commonly used concomitant medications.

P719 Systemic lupus erythematosus (SLE): Cyto- and chemokines as possible serum markers for pulmonary involvement
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SLE is a systemic autoimmune disease associated with high prevalence of lung involvement. Pulmonary manifestations (PM) in SLE are difficult to diagnose and the ability of its detection with serum markers could be useful for early detection and specific treatment.

Twenty three patients with SLE (age: 45.4±14.6 years; 22 female, 10 smokers) were enrolled in pulmonary examination including physical examination, chest X-ray, lung function test, CO diffusion capacity (DLCO) measurement and blood gas analysis. Plasma of 17 patients was analyzed by protein array system with chemoluminescence imaging, including the cytokines and chemokines: 4-IBB, IP-10, IL-12 p70, IL-17, CCL14a, CCL21, CCL28, MCP-1, MCP-4, F-LAT.

PM was diagnosed in 12 patients (52.2%; age:43.1±14.2 years), including pulmonal fibrosis (3), shrinking lung syndrome (1) and ventilatory disorder (8). Ten patients had no PM (47.8%; age:50±12.1 years). In patients with PM significant decrease of static lung volumes and DLCO were noted (TLC % pred: 81.1±3.3 vs. 93.7±3.9 p <0.05, FEV1 % pred: 77.8±5.7 vs. 94.2±5.5 p=0.05, DLCO % (IT): 62.4±4.4 vs. 97.3±6.7 p<0.001). Microarray measurements confirmed significantly higher CCL21 level in SLE patients with PM, negatively correlating with FEV1 (r=0.65, p=0.04) and positively with resistance of the airways (r=0.73, p=0.02). The biomarkers MCP-1 and IP-10 as potential candidates for further analysis of PM in SLE patients.

In lupus patients PMs are prevalent and are associated with decreased lung volumes and DLCO. Microarray results identified CCL21 and MCP1, IP10 as potential candidates for further analysis of PM in SLE patients.

92. Diagnostic insights and decision making in primary care

P720 The usefulness of point-of-care-testing for C-reactive protein in lower respiratory tract infection/acute cough Elena Andreeva, Hasse Melbye, 1Family Medicine, Northern State Medical University, Arkhangelsk, Russian Federation; 2Department of Community Medicine, University of Tromsø, Norway

Background: Respiratory tract infections and acute cough are too frequently treated with antibiotics. Point-of-care test (POCT) for C-reactive protein (CRP) has in one study been shown to significantly reduce antibiotic prescribing for lower respiratory tract infections (LRTI) without compromising recovery.

Aim: The aim of the study was to evaluate the effect of using CRP test in general practice patients with LRTI on the prescription of antibiotics, referral to radiography, and the outcome of the patients.

Methods: Open randomised clinical trial, patients with LRTI/acute cough were included. CRP-test was carried out before treatment was decided in the intervention group, with the use of Afinion test system (Axis Shield). Frequency of prescribing antibiotics and referral to radiography were main outcome measures.

Results: Altogether, 179 patients were included, 101 in the intervention group tested by POCT for CRP and 78 in the control group. No significant difference in

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age, gender, co-morbidity, symptoms and chest findings was found between intervention and the control groups. In the intervention group antibiotics prescribing rate was significantly lower: 37.4%, than in the control group, 60.2% (p=0.005). Referral to chest X-ray examination was also significantly lower in the intervention group, 55.4%, than in the control group, 76% (p<0.01). Two weeks after start of treatment the recovery rate (% fully or almost recovered) was 92% and 93%, respectively.

Conclusion: CRP testing may reduce unnecessary antibiotic prescribing and referral to radiography in patients with LRTI and acute cough without compromising recovery.

P721
Influence of different spirometry interpretation algorithms (SIA) on decision making among primary care physicians
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Background: Typically, the only spirometric data required for clinical decision making are the Forced Expiratory Volume in one second (FEV1) and the Forced Vital Capacity (FVC). Limitations of SIA promoted for adoption in primary care have been described (Can Fam Physician October 2011 57: 1148-1152, 1153-1156).

Aims and objectives: This study examines how different SIA may influence decision making among primary care physicians.

Method: Thirty seven primary care physicians were asked to interpret nine spiromograms presented twice in random sequence using two different SIA (as stand alone aids) and touch pad technology (remote audience response devices) for anonymous data capture and recording.

Results: We observed important differences in the interpretation of the same spiromograms using two different SIA. When the pre-bronchodilator FEV1/FVC decision node in one algorithm prompted referral, the latter SIA did not include a logic string leading to a post-bronchodilator FEV1/FVC so a definitive consideration of COPD could not be made. The absence of a post-bronchodilator FEV1/FVC decision node in one algorithm prompted referral for evaluation of low FVC.

Conclusions: This pilot study suggests that different SIA may influence decision making and lead clinicians to interpret the same spirometry data differently.

P722
Clinical assessment of a portable FEV1/FEV6 meter for the detection of airway obstruction
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Objectives: To evaluate the accuracy of the portable Vitalograph-COPD-6 device in the detection of airway obstruction.

Methods: All participants underwent a measurement of FEV1, FEV6 and FEV1/FEV6 using the COPD-6 meter, and a conventional spirometry measuring FEV1, FVC and FEV1/FVC. Conventional spirometry was performed by highly trained lung function staff, whereas the COPD-6 meter was used by final-year medical students, according to the manufacturer’s instructions. Subjects were randomized to determine which measurement was performed first. The FEV1/FEV6 ratio that corresponded to the optimal combination of sensitivity and specificity was determined from a ROC curve. Agreement was analyzed by calculating sensitivity, specificity, positive and negative predictive values (PPV and NPV), and the kappa-index.

Results: Test results of 147 subjects were analyzed. The prevalence of obstruction was 42%. The area under the ROC-curve was 0.946. The FEV1/FEV6 ratio that corresponded to the optimal combination of sensitivity and specificity was 73%. For this cutoff value sensitivity, specificity, PPV and NPV were 82%, 93%, 90% and 88%, respectively. The kappa-index was 0.76. Lowering the cutoff point to 70% resulted in sensitivity, specificity, PPV and NPV of 65%, 98%, 95% and 79%, respectively. For a FEV1/FEV6 cutoff point of 80%, they were 95%, 69%, 69% and 95%, respectively.

Conclusions: The portable Vitalograph-copd-6 device is an accurate device for detection of airway obstruction. Best sensitivity/specificity for FEV1/FEV6 was obtained with a fixed cutoff point of 73%. For screening purposes, high sensitivity (95%) can be reached when using an 80% threshold for FEV1/FEV6.

P723
Is the COPD assessment test (CAT) useful in our patients?
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Aim: To determine the correlation between scores obtained in the quality of life (QL) questionnaires with functional and clinical parameters.

Methods: Prospective study. 56 moderate-severe COPD patients with exacerbating phenotype admitted from 1/02/11 to 30/10/11. Studied items: symptoms, MRC scale, spirometry, BML, 6MWT, CAT and St.George. Descriptive analysis.

Results: In Table 1 general characteristics are shown. Functional parameters do not correlate with CAT, and have a poor inverse correlation with St.George. BODE, 6MWT and dyspnoea have a good correlation with both questionnaires. Graphic 1: correlation between BODE and SG, Graphic 2: correlation between CAT and SG, Graphic 3: correlation between scores obtained in CAT and SG about dyspnoea in basal situation.

P724
A pilot study on the effects of telepulmonology in primary care on efficiency and quality of care in the Netherlands
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Introduction: Misinterpreting spirometry results can lead to under- and misdiagnosis of obstructive pulmonary diseases. In telepulmonology a general practitioner (GP) digitally consults a pulmonologist. We assessed the effect of the use of telepulmonology (TP) in the daily practice of Dutch GPs on prevented physical referrals and potential quality of care improvement.

Methods: GPs accessed a secured web-based consultation (TC) system (KSYOS); filled in the patient data; added a spirogram; optionally added relevant clinical information. This information was sent to the local pulmonologist. The number of prevented physical referrals was measured by asking GPs the following two questions: Before TC(Q1): “Without TP, would you have physically referred this patient?” After TC(Q2): “Do you refer this patient physically?”

Quality of care was measured by the percentage of TCs sent for second opinion, the percentage of physical referrals resulting from these TCs and the educational effect experienced by GPs.

Results: In total 872 TCs performed from January 2010 until December 2011 were analyzed. Thirty-two percent (n=283) of the TCs were intended to prevent a physical referral (Q1=yes), 70% (n=199) of these were actually prevented. Of all TCs 68% (n=589) were sent for advice or second opinion (Q1=no), 19% (n=111) of these patients were referred after TC. GPs experienced an educational effect in 9% (n=78) of the TCs.

Conclusions: Telepulmonology potentially improves efficiency of care by preventing unnecessary physical referrals. Conversely TP can improve quality of care referral of patients that would otherwise not have been referred and the educational effect experienced by GPs.
P725
Prediction of mortality in the Swiss chronic obstructive pulmonary disease (COPD) cohort using the age dyspnoe and airflow obstruction index (ADO) 
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Background: COPD is associated with significant mortality, being the fourth leading cause of death worldwide. The Age Dyspnoe and airflow Obstruction Index (ADO) is a simplified prognostic assessment tool for patients with COPD which has been developed in specialized settings. Aims: Our objective was to reassess the usefulness of the ADO index as a predictor of mortality in a general practitioners’ (GP’s) based Swiss COPD cohort. Methods: 409 patients with presumed GOLD stages I-IV were enrolled by their GP’s and data was collected during a total period of 24 months. The observed 2-year risk of all-cause mortality in the cohort was compared to the ADO index predicted 3-year risk of death by performing logistic regression analysis with ADO as independent variable and observed 2-year all-cause mortality as dependent variable.
Results: Complete data could be analyzed in 390 patients (70% male, mean age 68 years). 154 patients (40%) did not have COPD according to spirometric criteria (FEV1/FVC <70%). COPD GOLD stage I was found in 22 (9%) patients, GOLD stage II in 94 (40%), GOLD stage III in 90 (38%) and GOLD stage IV in 30 (13%) patients. Of the 236 patients with COPD (median ADO score of 4, IQR 3.5), 14 (6%) died during the 2-year follow up period. There was a significant association between predicted (ADO index) and observed risk of death in the cohort (p<0.01). The odds ratio for death per point increase in the ADO index was 1.9 with a 95% confidence interval (1.1-2.8). Conclusion: The ADO index seems to be a significant predictor of 2-year all-cause mortality in patients with COPD treated in primary-care settings.

P726
Subutilization of COPD guidelines in Mexico 
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Aim: To evaluate the reliability, accuracy and concordance of the lung function measured in a primary care setting using COPD6 in early detection of COPD patients in urban areas in Zambia.
Methods: A cross-sectional study was carried out in four clinics, representing different socioeconomic areas in Lusaka. A total of 1014 patients who attended the clinics for any reason were considered eligible for COPD screening. Of these, 946 patients (94%) were included in the study. A diagnosis of COPD was made according to COPD6 criteria. Reliability, accuracy and concordance of the lung function measured in a primary care setting using COPD6 in early detection of COPD patients in urban areas in Zambia were calculated. The reliability of the measurement of the forced expiratory volume in one second (FEV1) was assessed using the intraclass correlation coefficient (ICC).
Results: The mean age of the patients was 52.6 ± 20.0 years (range 16-86 years), 64.2% were female, 69.7% were living in high, 21.6% medium, and 8.5% low-density areas respectively. The educational attainment of participants was up to primary in 54.5% of the cases, up to secondary in 19.5% and higher than secondary in 24.0% of the cases. Self-reported asthma symptoms in the last year were: 48.0% cough, 25.7% night awakening, 19.7% shortness of breath, 15.8% wheezing and 7.7% asthma attack, while 6.3% reported using asthma medications currently. Medications used to alleviate asthma symptoms were mostly oral (antibiotics 40.0%, antihistamines 26.0%, SABA 24.0%, cough mixtures 16.0%, theophyllines 9.5%, and steroids 6.5%), while inhaled medications were seldom used (SABA 13.0%, steroids 7.5%, LABA none). Many misconceptions on asthma were identified, with 45% reporting that asthma cannot be symptom-free and 59.9% that asthmatics cannot exercise or engage in strenuous exercises, among others. Finally, on asthma perceptions only 47.1% reported that hospitalizations for asthma are preventable, although 68.9% thought asthma symptoms can be prevented with medications. Overall, 64.2% of participants agreed that asthma is a serious health problem in Zambia.
Conclusion: We conclude that knowledge on asthma and its management is poor. Awareness and medical education programmes would improve asthma patients quality of life.

P727
Relationship between quality of life and multidimensional assessment indices in patients with COPD 
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Aim: To evaluate the reliability, accuracy and concordance of the lung function measured in primary care setting using COPD6 in early diagnosis of COPD patients in urban areas in Croatia.
Methods: A cross-sectional study was carried out in four clinics, representing different socioeconomic areas in Lusaka. A total of 1014 patients who attended the clinics for any reason were considered eligible for COPD screening. Of these, 946 patients (94%) were included in the study. A diagnosis of COPD was made according to COPD6 criteria. Reliability, accuracy and concordance of the lung function measured in a primary care setting using COPD6 in early detection of COPD patients in urban areas in Croatia were calculated. The reliability of the measurement of the forced expiratory volume in one second (FEV1) was assessed using the intraclass correlation coefficient (ICC).
Results: The mean age of the patients was 52.6 ± 20.0 years (range 16-86 years), 64.2% were female, 69.7% were living in high, 21.6% medium, and 8.5% low-density areas respectively. The educational attainment of participants was up to primary in 54.5% of the cases, up to secondary in 19.5% and higher than secondary in 24.0% of the cases. Self-reported asthma symptoms in the last year were: 48.0% cough, 25.7% night awakening, 19.7% shortness of breath, 15.8% wheezing and 7.7% asthma attack, while 6.3% reported using asthma medications currently. Medications used to alleviate asthma symptoms were mostly oral (antibiotics 40.0%, antihistamines 26.0%, SABA 24.0%, cough mixtures 16.0%, theophyllines 9.5%, and steroids 6.5%), while inhaled medications were seldom used (SABA 13.0%, steroids 7.5%, LABA none). Many misconceptions on asthma were identified, with 45% reporting that asthma cannot be symptom-free and 59.9% that asthmatics cannot exercise or engage in strenuous exercises, among others. Finally, on asthma perceptions only 47.1% reported that hospitalizations for asthma are preventable, although 68.9% thought asthma symptoms can be prevented with medications. Overall, 64.2% of participants agreed that asthma is a serious health problem in Zambia.
Conclusion: We conclude that knowledge on asthma and its management is poor. Awareness and medical education programmes would improve asthma patients quality of life.

P728
Knowledge and perceptions of asthma in Zambia: A preliminary report 
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Aim: To explore the knowledge and perceptions of asthma in Zambia.
Methods: A cross-sectional study was carried out in four clinics, representing different socioeconomic areas in Lusaka. A total of 1014 patients who attended the clinics for any reason were considered eligible for COPD screening. Of these, 946 patients (94%) were included in the study.
Results: The mean age of the patients was 52.6 ± 20.0 years (range 16-86 years), 64.2% were female, 69.7% were living in high, 21.6% medium, and 8.5% low-density areas respectively. The educational attainment of participants was up to primary in 54.5% of the cases, up to secondary in 19.5% and higher than secondary in 24.0% of the cases. Self-reported asthma symptoms in the last year were: 48.0% cough, 25.7% night awakening, 19.7% shortness of breath, 15.8% wheezing and 7.7% asthma attack, while 6.3% reported using asthma medications currently. Medications used to alleviate asthma symptoms were mostly oral (antibiotics 40.0%, antihistamines 26.0%, SABA 24.0%, cough mixtures 16.0%, theophyllines 9.5%, and steroids 6.5%), while inhaled medications were seldom used (SABA 13.0%, steroids 7.5%, LABA none). Many misconceptions on asthma were identified, with 45% reporting that asthma cannot be symptom-free and 59.9% that asthmatics cannot exercise or engage in strenuous exercises, among others. Finally, on asthma perceptions only 47.1% reported that hospitalizations for asthma are preventable, although 68.9% thought asthma symptoms can be prevented with medications. Overall, 64.2% of participants agreed that asthma is a serious health problem in Zambia.
Conclusion: We conclude that knowledge on asthma and its management is poor. Awareness and medical education programmes would improve asthma patients quality of life.
P730
Subjective (CAT, MMRC) versus objective (PFT, 6MWD, SPO2) assessment in stable COPD patients
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Karim Beshakhabzade. Internal Medicine (Pulmonary Division), Ardabil University of Medical Sciences, Ardabil, Islamic Republic of Iran Internal Medicine (Pulmonary Division), Mashad University of Medical Sciences, Mashad, Islamic Republic of Iran for Patient with Asthma and for patient with asthma at P731
Background: Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disease that leads to morbidity and mortality in the world. The excess of investigation has shown that this illness is not confined only to the respiratory system, but it is a systemic inflammatory disease which affects different system of patients.

The aim of this study was to investigate the relationship between subjective tests such as COPD assessment test (CAT) and Modified Medical Research Council (MMRC) scale with objective tests in stable COPD patients.

Methods: We evaluated 60 stable COPD patients in a cross-sectional study; quantifying the following: dyspnea with MMRC scale, lung function parameters, exercise capacity with six-minute walk distance (6MWD), oxygen saturation (SpO2), BODE index and the number of exacerbation during the last year. Then, the CAT questionnaire was completed by all patients.

Results: There was a significant difference between the CAT score with BODE index (p<0.001). Significant correlation was observed between CAT score and MMRC scale (p<0.001, r=0.55). The negative association was found between CAT with FEV1% and SpO2 (p<0.005, r=−0.39 and p<0.01, r=−0.47 respectively). There was negative significant correlation between the CAT score and 6MWD (p<0.001, r=−0.49). Frequent exacerbation was found in patients with higher CAT scores.

Conclusion: The CAT score is a reliable indicator of airflow obstruction, dyspnea scale, exercise capacity and saturation of arterial oxygen in COPD patients and can be used as a predictor of exacerbation risk in stable COPD.

P731
Real current situation of management and for patient with asthma at community
Van Thanh Nguyen1, Respiratory Department, National General Hospital of Can Tho (NGH-CT), Can Tho, Viet Nam
Background and the objective: Despite now we have a remarkable improvement on knowledge of pathophysiology and management for Asthma (1) but the majority of patient do not have opportunities to get them (2). So to understand and to have the solutions for this situation we must know the real current situation of management and treatment for this illness in the community. This is also the objective of this study.

Study population and methods: This investigation is carried out on the patient with Asthma in the 8 communes of Can Tho city, wich were chosen randomly. With the physician’s guidance and explanation the patient complete a questionnaire.

The internal consistency will be validated by Cronbach’s coefficients with value > 0.6. Analysis will be carried out by descriptive statistics.

Results: From data on 197 patients there are 57.9% of them with ACT score < 20 and 57.6% with ACT score < 15. 42.4% of patients don’t know their own disease as asthma. The automedication is very common. Almost of patient do not know the asthma control concept and also think that they will go to the local setting for health care when it is necessary.

Conclusion: The situation of asthma control in the community is so not good.

From these data improving the quality of health care at local setting is suitable idea in this background.

ACT: Asthma control test

Reference:

P732
Validity of spirometry performed in the primary care setting
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Background: Spirometry is a valuable diagnostic tool in the identification of patients with Chronic Obstructive Pulmonary Disease (COPD) in the community. In the primary care setting, low acceptability of spirometric manoeuvres has been reported which may affect the interpretation of results and clinical decision making. T R Schermer et al had demonstrated in the Netherlands that spirometric indices performed by trained general practice staff were marginally but statistically significantly higher than those measured in pulmonary function laboratory. He concluded laboratory and general practice values should not be used interchangeably.

Aims: To evaluate the validity of spirometric testing performed in the community.

Methods: Retrospective study of 405 patients found to have abnormal screening spirometry performed in the community. Screening criteria included adults with a history of smoking. This was followed by repeat spirometry in the hospital pulmonary function laboratory. Data was analyses using SPSS.

Results: N=405, mean age 54 years (range 22 to 78), 46% (187) and 41% (165) were current and ex-smokers respectively. 78.5% (318) were using short-acting beta agonists 60% (242) were already on inhaled steroids. 0.7% (3) were on oral steroids. 82% (331) had obstructive spirometry. Majority (45%) of them had moderate COPD. 32% and 11% were found to have mild and severe COPD respectively. The Mean FEV1 in the community (1.52 liters) was slightly higher than the pulmonary function laboratory (1.49 liters). Paired t test study showed the results to be in concordance to the results demonstrated by T R Schermer et al.

Conclusions: This study validates the results published in the Netherlands by T R Schermer et al.

P733
Prevalence of the chronic obstructive pulmonary disease among smokers in Georgia
Mohammed Harris1,2,3, Shahrzad M. Lari, Nasrin Fouladi, 2,3
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Background: The prevalence of COPD in Georgia is suspected to be high due to high smoking rate, but the real data is unknown.

Aim: The aim of the study was to assess the prevalence of COPD among smokers more than 40 years of age attending primary healthcare (PHC) facilities in Georgia.

Methods: The World Health Organization proposed questionnaire were filled in patients who visited for any reasons PHC in 10 districts of Georgia. The patients were placed into one of four diagnostic categories (mild, moderate, severe, very severe stage).

Results: Out of 4275 patients 2268 (53.5%) were current and past-smokers, among them 2054 male (90.5%) and 214 female (9.5%). Out of those 2268 patients 360 subjects were eligible for data analysis (due to smoking cough, and sputum production). 351 patients performed spirometry and 9 patients were excluded because of poor spirometry manoeuvers. Of the 351 patients 92 (26.2%) showed airflow limitation.

Most of the subjects (42 patients, 45.6%) had moderate disease (stage II). Thirty patients (32.6%) had an FEV1 less than 50% predicted (stage III). The stage I of COPD were stated in 13 subjects (14.1%). Seven cases (7.6%) of very severe COPD (stage IV) were diagnosed. Airflow limitation was significantly related to male gender and cumulative pack-years.

Conclusion: It was shown that there are potentially a number of COPD cases that are undiagnosed by GP’s in Georgia. Use of spirometry as a routine test for smoker patients will help in early detection and correct diagnosis of COPD, which subsequently will help in implementation of preventive measures.

P734
Asthma control in Tunisia
Nadia Keskes Boudawara1, Leila Boussofara2, Mona Ben Khalifa1, Imen Toulou1, Mounira Sakka1, Ilyed Ksni2, Pneumology, Tahar Sfar Hospital, Mahdia, Tunisia
Introduction: Control of asthma is related to recent daily symptoms and exacerbations; it represents the ultimate goal of treatments according to current guidelines. The definition of asthma control was derived from the Global Initiative for Asthma (GINA) criteria of severity, etiology and treatment of substance was collected. Regarding control asthma, the questionnaire response of the Asthma Control Test has classified as controlled, well controlled, or uncontrolled.

Objectives: To evaluate the prevalence of asthma in Tunisia for adult patients identified by GPs in Tunisia. Use of spirometry as a routine test for smoker patients will help in early detection and correct diagnosis of COPD, which subsequently will help in implementation of preventive measures.

Aim: The aim of this study was to assess the prevalence of COPD among smokers more than 40 years of age attending primary healthcare (PHC) facilities in Georgia.

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Aim: The mean of age was 49.4±15.8years. Asthma was intermittent in 3.1%, persistent mild in 31.3%, persistent moderate in 51.5% and persistent severe in 14.1%. Treatment as recommended by GINA was applied in 63% of patients. 67.5% of patients were controlled, 26% were well controlled and 6.5% were totally controlled. Factors of uncontrolled asthma were the advanced age (p<0.001) and low Forced Expiratory Volume in one second (FEV1) (P<0.001).

Conclusion: Despite all efforts through international recommendations and despite the existence of effective therapies against asthma, a significant number of patients with asthma remain uncontrolled in this study. Asthma control in Tunisia is probably as poor as in other areas of the world.
P735
Quality of care of adult asthma patients in primary health care facilities in Saint-Petersburg, Russia: Trends between 1998 and 2011
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Background: This study was performed to assess the changes in diagnosis and treatment of asthma (1998-2011) in primary health care facilities in Saint-Petersburg, the second largest city in Russia.
Methods: Case record forms (CRF) of 1248 outpatients 18 to 89 years old with asthma were reviewed in 13 outpatient departments in 7 residential areas in Saint-Petersburg in 1998, 2002 and 2005 (253, 579 and 416 respectively) and telephone interviews with 205 asthma outpatients (aged 24 to 90 yrs) was conducted in 2011. Asthma control was assessed by using the Asthma Control TestTM (ACT) in 2011.
Results: During the past 12 month spirometry were performed in 81.3% of patients in 2002 and only 62.1%, 50.7% and 26.8% in 1998, 2005 and 2011 respectively (p<0.01). Inhaled corticosteroids were more often prescribed to persistent asthma patients in 2005 (87.8% vs 79.1%, 63.4% and 46% in 2002, 2005 and 1998, p<0.01), whereas oral steroids for maintenance therapy were more frequently used in 1998 and 2000 (32% and 28% vs 14.9% and 7.3% in 2005 and 2001, p<0.001). Fixed combination of budesonide/formoterol and fluticasone/salmeterol were not used in 1998 while their prescriptions were increased from 0.9% in 2002 to 32.4% and 45.4% in 2002 and 2011 (p<0.001). Asthma was uncontrolled for 72.2% of patients in 2011.
Conclusion: Quality of diagnostics and treatment of asthma in primary health care is not sufficient and should be improved. Asthma pharmacotherapy has been changed in the past 13 years according to evidence-based guidelines.

P736
Evaluation of a simplified new score of quality of life for the assessment of COPD patients in general medicine – A prospective study
Regina Szendregyecz1, Claire Andrejak2, Corinne Hybiak3, Florence Le Meunier3, Isabelle Rault3, Olivier Carre3, Dominique Proisy4, Houcine Bentayeb1, Emmanuelle Lecuyer1, Marie Boutrym1, Vincent Jouenneaux1, Yousouf Donaud1, Charles Dayen1. 1Pneumology Unit, Saint Quentin Hospital, Saint Quentin, France; 2Pneumologie Unit, Amiens Hospital, Amiens, France; 3Pneumologie Unit, Clinique de l’Europe, Amiens, France; 4Pneumologie Unit, Soissons, France
Introduction: Chronic obstructive pulmonary disease (COPD) is a common pathology in the general population and therefore in general medicine. However, it remains under-diagnosed and difficult to assess. There are some scores in the literature to scale COPD patients (Saint-Georges (SGRQ), VQ-11 and COPD Assessment Test (CAT)). We therefore wondered if a reliable and easy-to-use score could assist the practitioner in the assessment and adaptation of treatments.
Materials and method: We proposed a score called CED which measures Cough, Expectoration and Dyspnea, on a visual analogue scale. With the help of 13 general practitioners from Picardy between March and September 2011, we conducted a prospective pilot study of patients suspected of COPD (n = 31). We collected the CED, SGRQ, CAT and VQ-11 scores of our patients.
Results: The dyspnea criteria of the CED and the SGRQ, which is the gold standard of COPD quality-of-life score, were significantly correlated (r = 0.390; p<0.05). The CED was significantly correlated with the decrease in FEV1 (r = 0.534; p<0.01) and with other specific quality-of-life scores such as the SG (r = 0.484; p<0.01).
Conclusion: The CED score is significantly correlated to respiratory functional status and quality of life of the patient. CED score seems to be a good tool in general medicine for the assessment of COPD patients.

P737
A comparison of the RIQ-MON 10 and the SGRQ among patients with COPD in routine care
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The short 10-item Respiratory Illness Questionnaire monitoring 10 (RIQ-MON) has been developed for the estimation of health-related quality of life in routine primary care. A cross-sectional, observational study of 31 COPD patients (25 male, 6 female, mean age 64±10.8 years; mean FVC 85.1±19.7%, mean FEV1 57.8±21.0%) was undertaken. All patients completed 6-min walk test, the RIQ-MON 10, and the SGRQ. Relationships between parameters of the 6MWT (mean 363±46.9m), the RIQ-MON 10 (mean 18.7±6.75), the SGRQ (mean 51.8±20.8), spirometry, and patient characteristics were assessed with Spearman rank correlation coefficients. Twenty patients (64.5%) performed 6MWT ≤ 400m. The correlations between the SGRQ Total scores and the RIQ-MON 10 Total scores (ρ = 0.761), the 6 min walk distance and FVEI (ρ = 0.471), and the 6 min walk distance and FEVI (ρ = 0.573) were all significant at the level of 0.01. There was no correlation between the RIQ-MON 10 Limitations domain and the SGRQ Symptoms. We proved that RIQ-MON 10, although inferior to the SGRQ, can be useful in routine primary care practice because it provides enough information for just a few minutes.

P738
CURB-65 scoring utilization in predicting mortality of hospitalized patients with AE-COPD
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AE-COPD is a commonly encountered problem in COPD patients leading to expensive in patient treatment and ICU admissions. It is associated with significant mortality. Historically CURB-65 score is used to predict mortality in CAP and there is no scoring system to predict the mortality in hospitalized AE-COPD patients. The aim of this study is designed to evaluate the prediction of CURB-65 score in predicting mortality in AE-COPD hospitalized patients.
This is a retrospective study conducted at JPMC, Karachi, Pakistan. Charts reviewed from July 2010 to June 2011 of hospitalized patients; only AE-COPD included in the study. Patients with other respiratory diseases (asthma, bronchiectasis, I LD and consolidation on chest x-ray or incomplete charts were excluded). CURB-65 was defined as C=Altered level of consciousness (GCS <13), U = urea >7mmol/l, R = Respiratory rate >35breaths/min, B= Blood pressure (SBP <90mmHg or DBP <60mmHg) and age is >65 years. One point awarded for each. Chi- square test was used to see statistical significance of mortality difference in CURB-65 groups. 200 charts reviewed; 97 incomplete charts; 38 patients with ILD, bronchiectasis, asthma PNA. 65 patients met the inclusion criteria. A direct correlation was observed between mortality and CURB-65; highest mortality noted with CURB-65 ≥ 3. In hospital mortality in different CURB-65 groups were, low risk (score 0-1)10.0% (2/32), moderate risk score (2) 10.0% (2/12) and high risk (score 3-5) 80.0% (16/21). The CURB-65 scoring system is effective in predicting mortality in AE-COPD; can be used in AE-COPD to stratify patients into different management groups as our conclusion indicates CURB 65 is helpful in assessing severity in AE COPD.

P739
Is there any relationship between the duration to diagnosis of COPD and severity of the disease?
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The aim of this study was to investigate whether there is a relation between the duration from beginning of symptoms until diagnosis of chronic obstructive pulmonary disease (COPD) and severity of COPD.
Method: One hundred and fifty patients with COPD (140 males, 10 females) were included in the study. All the patients had a history of smoking at least 10 pack/years. None of the patient had reversibility.
Results: The CED score was significantly correlated with the decrease in FEV1 (r = 0.534; p<0.01) and with other specific quality-of-life scores such as the SG (r = 0.484; p<0.01).
Conclusion: The CED score is significantly correlated to respiratory functional status and quality of life of the patient. CED score seems to be a good tool in general medicine for the assessment of COPD patients.

121s
Background: GOLD currently recommends making treatment decisions based on a combined assessment of current symptoms and future risk. The modified MRC (mMRC) dyspnoea scale (grade 0–4) is recommended to assess the level of current symptoms, but data on the efficacy of different treatments in subgroups based on symptom-grading are lacking. Roflumilast (ROF) is a PDE4 inhibitor approved for maintenance treatment of severe COPD associated with chronic bronchitis, in adult patients with a history of frequent exacerbations. GOLD recommends ROF as an option for patients with mMRC grade ≥2, severe lung function impairment and/or frequent exacerbations (Group D).

Aims: To determine the effects of ROF on exacerbations and lung function when added to titroprocion (TIO) in patients with baseline mMRC grade ≥2.

Methods: Study M2-128 included symptomatic patients with moderate-to-severe lung function impairment. ROI 500 or placebo (PBO) was added to TIO for 24 weeks. A post-hoc subgroup analysis of patients with mMRC grade ≥2 at baseline was performed.

Results: This subgroup included 395 patients (ROI n=208, PBO n=187). ROI reduced the mean rate of moderate/severe exacerbations/patient/year by 45.5% (an-ti-trended exacerbation rate ROI:0.22, PBO:0.46; rate ratio 0.55, 95% CI 0.31, 0.96; p=0.034) vs PBO. The mean between-treatment difference in pre-bronchodilator FEV1 was 78 mL (95% CI 38, 119), p=0.0002, and in post-bronchodilator FEV1 79 mL, (95% CI 38, 118). p=0.0002.

Conclusions: ROI reduces moderate/severe exacerbations when added to TIO in COPD patients with moderate-to-severe lung function impairment and mMRC grade ≥2. These results support the GOLD recommendation for combined assessment of current symptoms and future risk.
Presently, no study has directly compared these two categories of prevention to usual care (UC) in a trial or economic evaluation.

Aim: To model the cost-effectiveness of prenatally-started unifaceted (UF) and multifaceted asthma (MF) primary prevention programmes with UC in a decision-analytic framework.

Methods: A decision-tree model was developed to compare (from a healthcare perspective) two UF and three MF programmes to UC (unstructured allergen-avoidance advice in the Netherlands). Analyses had a time horizon of 10 years. Costs and effects for each option were evaluated through incremental cost-effectiveness ratios (ICERs).

Results: UC and an MF were found to dominate the other options. UC turned out to be less effective but also less costly compared to the MF. To avoid one asthma case the costs will be €8,250 when choosing the MF over UC. Most of the uncertainty in the results was attributable to the cost estimates for low-risk children.

Conclusion: Although there is no point of reference for the amount society would be willing to pay to avoid a case of asthma, the threshold used for a QALY roughly ranges between €20,000 and €80,000. As a case of asthma prevented will certainly equal at least one QALY gained, this study gives support to the feasibility of multifaceted programmes as viable option to replace usual care in the primary prevention of asthma amongst children.

P745

Management of COPD in a primary care in Bahia, northeast of Brazil

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Introduction: Deficiencies in management of COPD is responsible for the disease exacerbations increased numbers.

Objective: To evaluate the current pharmacological treatment of the COPD in a primary health care center and to compare as recommended by GOLD 2010 guidelines.

Methods: A prospective cross-sectional survey was performed with COPD out-patients. The patients were recruited as a sequential sample from September 2010 until August 2011, in the primary center of Bahia State Health Department.

Results: In total, the sample was 363 outpatients (245 male, aged from 65.3±11.4 yrs) with moderate to very severe disease status (FEV1 40.6±14.4% pred). Of these, 263 (72.4%) patients were using any drug to treatment of COPD. The prescriptions according to GOLD stages are documented in the table below. Under-prescribing with bronchodilators long acting agents, particularly long-acting anticholinergic were recommended in 76% of the cases and 16.8% were using. Inhaled steroids were over-prescribed (recommended in 55%; taken by 77%). The overall analysis showed that only 97 (37.2%) patients were under treatment according with GOLD guidelines.

Table: Drug prescriptions stratified according GOLD stages and divided for drug classes

<table>
<thead>
<tr>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=61)</td>
<td>(n=130)</td>
<td>(n=72)</td>
<td>(n=263)</td>
</tr>
<tr>
<td>Short-acting β2-agonist</td>
<td>39.3</td>
<td>56.9</td>
<td>54.1</td>
</tr>
<tr>
<td>Short-acting anticholinergic</td>
<td>9.8</td>
<td>16.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Long-acting β2-agonist</td>
<td>75.4</td>
<td>70.0</td>
<td>63.8</td>
</tr>
<tr>
<td>Inhaled Steroids</td>
<td>85.2</td>
<td>77.6</td>
<td>70.8</td>
</tr>
<tr>
<td>Long-acting anticholinergic</td>
<td>11.4</td>
<td>12.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Methylxanthine</td>
<td>13.1</td>
<td>9.2</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Conclusion: Our study has demonstrated that COPD patients in the primary care in Bahia-Brazil did not receive the pharmacological treatment recommended.

P746

Home visits for improving asthma follow-up consultation attendance

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Background: Our Child Asthma Program provides care for around 500 patients. Every 6 months the population under control is reviewed. Since December 2010 non-attendance (missing appointments for more than 3 months) was recorded. 37.2% were non-attenders. Regular review is a marker of quality care and relates to better asthma control. Non-attendance is a frequent and concerning problem.

Aim: Improve attendance to asthma follow-up consultations and learn about the causes of non-attendance.

Methods: We implemented a home visit strategy. Every month the non-attenders were identified and a home visit was planned. Completed visits considered a visit. We measured at 6 and 12 months the non-attenders and if the home visit led to attendance or not.

Results: 147 home visits were done. 67 were completed, with a 65.7% of success (patient attends to appointment). 80 home visits failed and only 16.3% of those patients had spontaneous appointments. At 6 months 17% of patients were non-attenders, and 24% at 12 months. In one year the non-attendance rate was reduced in 35.5%.

Conclusions: Improving attendance is feasible. Looking for non-attenders is an important issue for managing asthmatic children. Causes of non-attendance are diverse and had to be explored. Feeling well despite of uncontrolled asthma and difficult to access appointments are worrisome causes. Home visits also provide the opportunity to reinforce prescriptions in patient’s natural environment.

P747

Quality of life in patients with COPD three years after a multidisciplinary program of pulmonary rehabilitation in primary care

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Background: COPD is an irreversible widespread disease which increases dramatically. According to previous research the quality of life in (QoL) patients with COPD is impaired but can be improved by pulmonary rehabilitation.

Aim: The aim of this study was to evaluate if a six week nurse-led multidisciplinary program for pulmonary rehabilitation in primary care had effect on quality of life in patients with COPD in a three-year period.

Method: Quasi experimental design was used to evaluate the program. The intervention group consisted of 40 patients who had participated in the program. The control group consisted of 24 patients who received traditional care. QoL was measured at baseline, after one year and after three years using Clinical COPD Questionnaire (CCQ). Statistical analysis of differences within the groups over the three years was performed by means of Friedman’s test. Mann-Whitney U test was used to analyze differences between the groups.

Results: There was no statistically significant difference between the groups at baseline. There was no statistically significant difference in improvement between the groups during a three year period for CCQ total. Neither was there any statistically significant difference within the control group. During a three year perspective there was a statistically significant difference of improvement within the intervention group for CCQ total (p=0.037) and CCQ functional state (p=0.026).

Conclusion: The rehabilitation program had an improving effect on QoL, in patients with COPD within the intervention-group during a three year perspective.

P748

Omalizumab improves asthma in long term therapy

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Introduction: X-TEND, a multi-center, non-interventional study on omalizumab (Xolair®), is a long-term follow-up examination on patients who participated in prior non-interventional omalizumab studies X-CLUSEIVE and X-PERTISE. Study objectives have been (i) examination of drug utilisation over several years, (ii) evaluation of changes in the course of disease, quality of life (QoL) and allergen sensitivity, (iii) assessment of long-term efficacy and tolerability of omalizumab therapy in real life.

Methods: Following data were collected during daily routine specialist care conditions.

- Mini AQLQ
- Number of asthma exacerbations in the past 12 months
- Frequency, application of dosage, therapy interruptions and discontinuation
- Tolerability assessment based on analysis of adverse events

Results: Data from 106 patients were analyzed. Mean observation period of omalizumab treatment was 5.0±0.54 years. At the visit of X-TEND, 50% were still on omalizumab. Mean treatment duration was 1253±618 days (3.4 years). Mean FEV1 improved from 1.9±0.7 L to 2.3±0.9 L (p<0.001). The median number of severe asthma exacerbations during the last 12 months was 0 per patient vs. 3 as assessed prior to initiation of omalizumab therapy. QoL scores improved in Mini AQLQ from 3.0±0.79 (at the beginning of X-PERTISE) to 4.9±1.52 (p<0.001) (at the visit of X-TEND). In patients still on treatment with omalizumab mean QoL was 4.4±1.28, whereas patients who discontinued reported 4.4±1.67 (p=0.037).

Conclusion: In this real-life observation in patients who were approximately 1253 days on omalizumab treatment, we observed an improvement in asthma exacerbations, quality of life and FEV1.
P749
Is a consultant supported community respiratory service an alternative to hospital based specialist care? – Experience of a local service improvement project
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Introduction: Better integration of primary and secondary care services and shifting the balance of care remain a major challenge with only few practical examples in respiratory care. Aims: The aim of a local service improvement project is to gain insight into an example of specialist supported, integrated respiratory care closer to the patient’s home. The objectives are to provide more flexible access, more patient centred care and develop general practitioners as partners in care. Method: Regular consultant respiratory clinics supported by a general practitioner with a specialist interest were set up in a local surgery. An interactive triage system, E-communication, meetings with primary care colleagues and consultant access to primary care patient data and radiology were implemented. Service user satisfaction, general practitioner satisfaction and number of patients seen by the general practitioner with a specialist interest were recorded for a period of 16 months. Results: 73 out of 116 service users completed the questionnaire and were all satisfied with the new service and felt well supported to manage their condition. 76 out of 77 found it easy to get a suitable appointment. All 7 general practitioners were highly satisfied. 73 of the 116 respiratory patients were seen by the general practitioner with a specialist interest.

Conclusion: Our consultant supported community respiratory service project demonstrates a model of integrated and flexible care in partnership closer to the service user’s home which could serve as a possible alternative to hospital based specialist care.

P750
The evaluation of a tele-monitoring model (Telehealth) as an aid in the case management of patients with COPD
Nasir Dar Bakti, Jane Roberts. Department of Respiratory Medicine, NHS Salford/Salford Royal NHS Foundation Trust, Salford, United Kingdom

Introduction: One of the many challenges for health care systems is to reduce the impact of chronic diseases like COPD on health care resources. Distant monitoring systems are increasingly being used for this purpose. Method: Potential COPD patients were identified through their Case Managers (CMs). Those who met the inclusion and exclusion criteria were invited to participate. Those consented received a telemonitoring device (Telehealth) with instructions and education and were remotely monitored by CMs as part of case management process. Data on hospital admissions and Health Care Utilisation (HCU) was collected for management process.

Results: Total of 16 patients were included in the analysis. Following the introduction of Telehealth, Hospital admissions halved from 20 to 10 with reduction in the number of bed-days from 134 to 96. Total cost of admissions had subsequently dropped by £20,000 (£23,400).

HCU data showed a drop in the number of home visits to patients (50 to 30) but a small increase in the number of telephone consultations (68-76).

SGRQ scores for QoL showed average of 3.3 points improvement which is below the clinically significance threshold.

HAD data is presented in table 1.

<table>
<thead>
<tr>
<th>HAD data</th>
<th>Baseline (n=16)</th>
<th>After 1 year (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Borderline 5 Abnormal 2</td>
<td>Borderline 5 Abnormal 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Borderline 3 Abnormal 6</td>
<td>Borderline 3 Abnormal 3</td>
</tr>
</tbody>
</table>

Conclusions: Telehealth appears to reduce admissions to hospital and some aspects of HCU in primary care. There is a need for more trials looking into the difficulties encountered during the implementation and evaluation of such complex technology.

P751
Assessing asthmatic patients’ satisfaction with inhalation devices
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Introduction: Patients’ satisfaction with their asthma medication devices is usually decided by using properly designed questionnaires. These questionnaires are to be used to evaluate patients’ opinion, which is considered important for the selection of a device.

Objectives: The aim of this study was to reliably estimate the ease of use and the satisfaction of asthmatic patients with different marketed dry powder inhalers (DPIs). Feeling of satisfaction with inhalers (FSI-10) questionnaire was selected as the appropriate measuring tool.

Methods: A four week, open, non-interventional, multicenter, parallel study, was performed. 560 asthmatic patients (355 women), aged 19 to 97 years, participated in three groups using different DPIs (Elpenhaler®, Turbuhaler® and Diskus®). Demographics of the groups were comparable. Patients had already achieved mastery of their inhalers, were receiving their asthma treatments exclusively via the investigated route and agreed to complete the questionnaire in the second visit. They were recruited in 79 private medical offices and hospital centers all over Greece.

Results: 523 participants completed the study and the questionnaire. Although consistent and satisfactory results were obtained with all DPIs tested, certain statistically significant differences in the ratings between the devices were observed (Elpenhaler® was rated first in 7 out of 10 questions, having also the highest mean total score). No significant differences in scores from patients of different ages were observed in any of the tested devices.

Conclusions: Certain statistically significant differences were found in ratings between the tested DPIs. Devices were similarly acceptable to adult patients of different ages.

P752
Effects of the gripe vaccination, smoking cessation, and short acting beta agonist in COPD subjects
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Objective: To compare the efficacy of the seasonal gripe vaccination, smoking cessation and use of salbutamol in COPD patients.

Material and methods: We performed a cross-sectional study including 147 patients with confirmed COPD according GOLD criteria. We evaluated the number of exacerbations and the number of hospitalisations. All were immunize against seasonal influenza, ex-tobacco users and received regular consultation.

An equal number of patients were evaluate like controls. They were also COPD patients, but didn’t receive gripe vaccination, active smokers and didn’t use salbutamol according doctors recommendation. Evaluation period was 12 months.

Results: In the examined subjects our results demonstrated 29.9% of exacerbations and 8.8% hospitalizations e.g. 41 versus 12 subjects. In the controls our article confirmed 74.5% exacerbations and 28.5 hospitalisations or 102 and 39 subjects were respectively.

Conclusion: The number of COPD exacerbations/hospitalisations were significantly higher (P < 0.05) in not immunized, smokers and patients who denied to receive regular therapy.

Conclusion: Our results confirm that gripe vaccination, smoking cessation and regular therapy use, significantly decrease the number of exacerbations and hospitalisations in COPD patients.

P753
Factors affecting attitude towards pneumococcal and influenza vaccination in patients admitting to a pulmonary diseases outpatient clinic
Elif Sen, Fuat Cicek, Nalan Demir, Oya Kayacan. Department of Pulmonary Diseases, Ankara University School of Medicine, Ankara, Turkey

Patient knowledge and attitude towards influenza and pneumococcal vaccines may affect administration rates. Our aim was to assess factors affecting attitudes. A questionnaire was applied to 1058 patients (514 female 544 male) between October 2011-January 2012. Ratio of patients with a vaccination indication was 73.2% (n=775). Ratio of influenza-vaccinated (IV) patients (n:222, %21) or pneumococcal-vaccinated (PV) patients (n:61, 6.5%) were determined. Of all patients, 64.5% (n:682) defined influenza and 68% (n:719) defined pneumococcal vaccine beneficial. Vaccination rate upon physician advice was 82.4% for influenza and 83.6% for pneumococcus. More IV patients considered vaccine protective (p<0.001), decreases hospitalization rate (p=0.002), decreases pneumonia and death (p<0.02), pneumococcal vaccine is beneficial, and they were informed by the physician (p=0.001). IV patients had more cardiopulmonary disease and a vaccination rate against pneumococcs (p<0.001). Influenza-novaccinated patients were unaware of the necessity of the vaccine (p=0.001). More PV patients considered the vaccine beneficial (p=0.001) and were more frequently informed by physician (p=0.039). Pneumococcus-novaccinated patients were unaware of its necessity (p=0.001). PV patients had higher incidence of cardiopulmonary diseases. Our study shows that vaccination rates in vaccine-indicated patients were low. Vaccinated patients were more frequently informed by physician. The thought of patients that vaccination is beneficial and decreases the rate of severe conditions was distinctive in being vaccinated. The nonvaccinated patients were unaware of the vaccine’s necessity.
**P754**
Enhanced care review for people with COPD in primary care addressing quality, cost-effectiveness and productivity

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Department of Respiratory Medicine, Wighton, Wigan & Leigh Foundation Trust, Wigan, Lancashire, United Kingdom

An enhanced care review, delivered by nurses working for a social enterprise within University Care and supported by a Respiratory Physician has proved to be a cost effective way of improving the quality of life with patients with COPD. The aim of the project was to improve the quality of care on a number of parameters such as accurate diagnosis, treatment of exacerbations, self management plans, referral to preventative services. This was delivered through a nurse led service supported by a respiratory consultant in primary care to reduce hospital admissions and outpatients referrals.

The 12 month pilot project was delivered to 23 GP practices within an urban, deprived setting in the North of England. Specialist Respiratory nurses and practice nurses delivered the service within GP practices following education and training identifying patients at risk of exacerbations or hospital admissions and post exacerbation assessment and prevention using specialist computer software which also provided a data collection template - data was collected through GP practice readad searches together with admission data from the Primary Care Trust. Hospital admissions were reduced amounting to savings of £90,000 in comparison to other parts of the borough. Medicines management savings amounted to £40,000 were achieved through treatment optimisation. Prevalence of COPD was increased by 12.3% and there was a 56% increase in pts being diagnosed between the ages of 35-50. There was a 63% increase in referral to pulmonary rehab and 20% increase in patients coded now as ex-smokers. There was a 58% increase in patients being given a self management plan.

**P755**
Management of community acquired pneumonia (CAP): Knowledge, attitude and current practice of general practitioners (GPs) in urban areas of Pakistan

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Background: CAP is a major burden with high prevalence and significant mortality and morbidity. Current evidences suggest that treatment of low risk patients in community is safe and reduce health costs by minimizing unnecessary hospital admissions and GPs can play an important role in primary care.

Objective: Our aim was to assess, at a community level, GPs knowledge about CAP, attitudes and prescription pattern.

Methodology: A multicentre cross sectional survey was done in 10 cities of Pakistan from November 2011 to January 2012. A total of 110 GPs were recruited, with minimum of 3 years experience, and were not engaged with University teaching or research. Convenient sampling was done and data was collected on structured questionnaire.

Results: 71% of GPs reported to work in high prevalence areas for respiratory ailments. Diagnosis of CAP was relied on physical examination in less than 5% cases. 58% of GPs used PSI and 38% CURB 65 for assessment of severity but it was alarming to note that only 58% intend to treat severe pneumonia with IV antibiotics and there was reluctance for referral to hospital.

The majority (70%) of GPs claimed awareness of recent guidelines of CAP but the antibiotic class most prevalently used was oral macrolide (54%) in mild oral quinolones (40%) in moderate and combinations of non antipseudomonal cephalosporin and Macrolide (55%) in severe cases.

Conclusion: The major problems encountered were late referral of patients to hospital, poor knowledge of recent guidelines and prescription of inadequate regimens that in turn can lead to high mortality and morbidity and emergence of resistant bacteria as cause of CAP.

**P756**
Practice patterns in the management of acute asthma and COPD in Turkey

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Introduction: The recognition and management of the asthma and COPD exacerbations is a cornerstone in the achievement of optimum control of these diseases.

Aims and objectives: The “ONDINE Study” aimed to evaluate practice patterns in the management of acute asthma and COPD in Turkey.

Methods: Patients with asthma or COPD were included in this national, multicenter, cross-sectional, non-interventional study. Patient demographics, control level, exacerbation severity and the exacerbation management of asthma and COPD were evaluated.

Results: A total of 596 patients included in the study having the diagnosis of asthma [n=401; mean (standard deviation; SD): age: 45 (13) years; 74% were females] or COPD [n=295; mean (SD) age: 62 (11) years; 86% males]. Disease control was evident in 38% of COPD patients while in 51% of asthma patients while severe COPD (31%) and intermittent asthma (51%) were the most common forms of disease severity. Hospital admission due to an acute exacerbation within the last 12 months was identified in 75% of asthma and 78% of COPD patients. Emergency and intensive care unit hospitalization rates were 40% and 1% in asthma patients and 53% and 2% in COPD patients, respectively. The most commonly performed tests in asthma and COPD patients were chest X-ray (98% and 99%) and spirometry (98% and 99%). Long acting beta-agonist and inhaled corticosteroid combination was the most common continuous prophylactic treatment (69%) in asthma and (71%) in COPD.

Conclusions: The study revealed that acute asthma exacerbations were managed better than COPD exacerbations and higher control rates were obtained in both diseases as exacerbation were managed more appropriately with respect to recommendations in the guidelines.

**P757**
Beliefs and attitudes of health care workers on influenza and pneumococcal vaccine

Fatma Ciftci, Elf Sen, Nalan Demir, Oya Kayacan. Department of Pulmonary Diseases, Ankara University School of Medicine, Ankara, Turkey

It is recommended to vaccinate health care workers against influenza and streptococci pneumonia if at risk group. This study is done to determine the vaccination rates and attitudes on vaccines of health care workers. A total of 192 health care workers (100 female, 92 males) consisting of 55 nurses, 42 health officers, 21 paramedics, 19 medical secretaries, 52 auxiliary staff, and 3 domestic health care workers were questioned between October 2011-January 2012. One-hundred and fifty-five (80.7%) health care workers were nonvaccinated against influenza. The reasons of this were fear of side effects (% 30.2) or 20% doubt on efficacy %27 (1), 26%, unawareness of the vaccine %23.5 (n:23), doubt on safety %19.8 (n:19), and lack of adequate data %16.8 (n:16). Sixty-eight (48.6%) of influenza nonvaccinated workers recommended patients vaccination whereas 23 (69.7%) of vaccinated workers recommended the vaccine. Vaccine recommendation rates of influenza-vaccinated workers were significantly higher in vaccinated than nonvaccinated workers (66% and 48%, respectively). The reasons for nonvaccination were fear of side effects (% 28.9 (n:33), doubt on efficacy %25.4 (n:29), unawareness of the vaccine %23.1 (n:27), doubt on safety %20.2 (n:23), and lack of adequate data (%16.8, n:19).

As a conclusion, health care workers have a low rate of vaccination and recommendation of vaccination against influenza and streptococcus pneumoniae.

**P758**
Assessment of satisfaction with inhalation devices in COPD patients

Eleftherios Zervas1, Mina Gaja1, Nikolaos Gerekas2, Katerina Papastasiou2, Katerina Athanassious2. 17th Respiratory Clinic, Sotiria Hospital, Athens, Greece; 2Clinical Research Department, Elpen Pharmaceutical Co Inc, Pikermi, Attica, Greece

Introduction: The choice of drug delivery system is one of the most important factors for COPD management. Health care professionals, taking also in mind the opinion of their patients, consider that ease of use and patient satisfaction for an inhalation device is a key element when choosing such a device.

Objectives: The aim of this non-interventional study was the reliable measure of the ease of use and patient satisfaction with different dry powder inhalers (DPIs).

Feeling of satisfaction with inhalers (FSI-10) questionnaire was used as measuring factors for COPD management. Health care professionals, taking also in mind the recommendations of vaccination against influenza and streptococcus pneumoniae. Vaccine recommendation rates for pneumococcal vaccine were significantly higher in vaccinated than nonvaccinated workers (66% and 48%, respectively). The reasons for nonvaccination were fear of side effects (% 28.9 (n:33), doubt on efficacy %25.4 (n:29), unawareness of the vaccine %23.1 (n:27), doubt on safety %20.2 (n:23), and lack of adequate data (%16.8, n:19).

Conclusions: Statistically significant differences were found in the scores among the tested devices. Patients in advanced stages of the disease generally express higher level of satisfaction with their devices.
and/or necrosis. Increased post-surgical plasma DNA concentration was due to the presence of patients with asthma have a PAAP despite national recommendations. Our pilot involved 6 GP practices and patient focus groups to develop and evaluate a PAAP.

Patient feedback from pilot

<table>
<thead>
<tr>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were instructions easy to follow</td>
<td>49</td>
</tr>
<tr>
<td>When to seek an appointment with GP</td>
<td>49</td>
</tr>
<tr>
<td>What to do if symptoms worsening</td>
<td>49</td>
</tr>
<tr>
<td>What to do in an emergency</td>
<td>49</td>
</tr>
</tbody>
</table>

Total number of patients = 49

Partnership working has enabled us to provide structured educational sessions to health care professionals across primary and secondary care. Currently 90 GP practices are using the PAAP’s in North Staffordshire. Encouragingly practice nurses are more confident in managing asthma. Within secondary care PAAPs are given to asthma patients attending A & E wards and respiratory clinics. One year after the launch feedback from patients and health care professionals is extremely positive. Future plans include evaluating the impact of the PAAP on A & E attendances, GP visits and quality of life.

94. New results in molecular pathology and functional genomics of neoplastic and non-neoplastic lung disease

P760 Plasma DNA concentration and integrity measurement for NSCLC diagnostics and radical therapy effectiveness monitoring

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Plasma DNA concentration and integrity index (DII) were measured by real-time PCR in 60 NSCLC patients (stage I-IIIA), 100 patients with chronic respiratory inflammation (COPD, sarcoidosis, asthma) and control groups comprising 10 orthopedic patients and 40 healthy volunteers. NSCLC patients (8.0 ng/ml) presented significantly higher plasma DNA levels than patients with chronic respiratory inflammation (3.4 ng/ml), orthopedic patients (3.0 ng/ml) and healthy controls (2.3 ng/ml; p<0.0001). The cut-off point was 2.8 ng/ml provided 96% sensitivity and 80.5% specificity in discriminating NSCLC from healthy individuals (AUROC=0.90), while 56% specificity and 90% sensitivity in distinguishing NSCLC from any non-NSCLC subjects (AUROC=0.80; p<0.0001). The plasma DII was significantly higher in resectable NSCLC (3.1) and chronic respiratory inflammation (3.7) than healthy controls (1.0; p=0.0000). Resected NSCLC (68.7 ng/ml; p<0.0000) and orthopedic patients (28.4 ng/ml; p<0.0015) presented comparable plasma DNA dynamics after the surgery. During 3-6 month follow-up plasma DNA level were significantly reduced in relapse-free NSCLC patients (2.8 ng/ml), while in relapsed subjects were higher than at baseline.

Biomarkers are advanced tools for diagnosis, prognosis and monitoring of treat-ment and disease progression. The validation of biomarkers is a cumbersome process involving many steps. Serum samples from lung cancer patients were collected in the framework of a larger Lung Cancer Screening project. During the analysis of some biomarkers, differences between marker values depending on the time of blood extraction were inconsistent. Biomarker concentration differed significantly if taken before or after the induction of anesthesia. From 13 patients blood samples were drawn 1-2 days prior to surgery, on the same day and after anesthesia was applied. Markers SCC (microtiter plate), and CEA (E lectys) were analyzed. SCC showed a very strong effect in relation to the sampling time. While the first two time points were well comparable (correlation r=0.883), patients showed a highly significant (p = 0.0017) increase in concentration when comparing the first two time points with the time point after anesthesia induction. The concentration of CEA had almost no variation (r=0.993 comparing time points as above). In this study we show the unexpectedly high influence of blood extraction timing in the concentration of the protein biomarker SCC but not in CEA. Whereas the possible causes for this alteration remains to be elucidated in further studies, these results are a caveat to make sure that biomarker sampling protocols are controlled for this type of effects.

P762 Hypoxic phenotype in pulmonary metastases of different primary tumors

Thomas Schneider1,2, Christoph Nikolovsky1,2, Lukas Lehmann1, Robert Wiebringhaus4, György Lang1, Peter Birrer5, Walter Klepetko6, Hendrik-Jan Ankersnol7, Konrad Hoetzenecker1,2, Department of Surgery - Division of Thoracic Surgery, Medical University of Vienna, Austria; 1Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis and Regeneration, Medical University of Vienna, Austria; 2Clinical Institute of Pathology, Medical University of Vienna, Austria

Tumor hypoxia has been shown to be a common feature in tumor growth and metastasis. It negatively affects the clinical outcome in patients with various ma-lignancies. Although hypoxia is described in many primary tumor types, data on pulmonary metastases is lacking. We determined the expression of hypoxia-related proteins in paraffin-embedded specimens of pulmonary metastases of different types of cancer (breast cancer n = 6, colon-rectal carcinoma n=29, renal cell carcinoma n=13, sarcoma n=10). All recruited patients underwent curative metastasectomy at the Department of Thoracic Surgery, MUV, between April 2009 and December 2011. Expression of carbonic anhydrase 9 (CA9), heat-shock protein 70 and HIF prolyl hydroxylase 2 was evaluated by immunohistochemistry. Metastasis free survival and estimated tumor size and overall survival was determined for all sub-groups. Hypoxia related proteins are expressed in 66.6%, 76.9%, 7.7% and 0.0% of pulmonary metastases of breast cancer, colon-rectal carcinoma, renal cell carci-noma and sarcoma, respectively. Furthermore, metastases with highly positive CA9-staining are associated with early tumor spreading to the lung (Disease free interval: 21.8±7.0 months vs. 46.1±26.6 months; p=0.008). This study provides first evidence for hypoxia marker expression in pulmonary metastases and its clinical relevance. These findings may be important for future therapeutic targets in the therapy of generalized malignant diseases.

P763
P764

Vitronectin expression in primary lung cancer

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Rationale: Vitronectin (Vn) plays a role in extracellular matrix (ECM) remodeling during tumorigenesis. Vn is present in human bronchial submucosal glands and it is secreted by A549 lung adenocarcinoma cell line. However, whether Vn is differentially expressed in tissues of primary lung cancer has not been explored.

Methods: Lung tissue from 22 primary lung carcinoma and 36 non-lung cancer subjects were obtained from fibrobronchoscopy. Sections were analyzed by histopathological and immunohistochemical methods. The total area occupied by ECM, surface and glandular epithelium, as well as the percentage area occupied by Vn at each of these localizations were measured. Chi-square, t-student, U-Mann Whitney and ANOVA tests were used in group comparisons. Statistical significance was tested at P<0.05.

Results: Vn expression was observed in bronchial glandular and surface epithelium, as well as in ECM (Figure 1). In total, the average area of ECM, surface or glandular epithelium was 0.289mm² (± 0.032), 0.043mm² (±0.009), 0.084mm² (±0.031), respectively. The percentage area occupied by Vn in ECM, surface or glandular epithelium, was 4.899 (±1.186), 2.729 (±1.623), 3.285 (±1.038), respectively; with not significant statistical differences between lung cancer and non-cancer subjects or within different types primary lung cancer.

Conclusion: There were no statistically significant differences in Vn expression between lung cancer and non-cancer subjects, or within primary lung carcinomas.

P766

Ki-67 in non-small cell lung cancer

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Uncontrolled proliferative activity is one of the determinants of malignant growth and known to be a prognostic factor in a variety of human tumors. Many works have been published on this topic in pulmonary neoplasms but most studies are underpowered or have no clinical data available.

To ultimately clarify the role of proliferation in non-small cell lung cancer (NSCLC) we investigated the proliferative activity of >1000 NSCLC by Ki-67 staining and correlated the data with clinicopathological characteristics including therapy response and survival.

The mean proliferative fraction in NSCLC was 40.7%. Adenocarcinomas (ADC) proliferated significantly less than all other types of NSCLC but proliferation was tightly linked to specific growth patterns. Overall, proliferative activity was not associated with overall, disease free and disease specific survival. However, when patients were stratified according to adjuvant therapy, those patients with high intratumoral proliferative activity and without adjuvant chemotherapy or radiation had significantly diminished survival times when compared to patients whose tumors were proliferating slowly. These associations were reverted in the group of patients who received radio-chemotherapy.

Our study comprehensively clarifies the impact of proliferative activity on outcome in NSCLC patients. Our data suggest that Ki-67 stains can be used as an adjunct in the selection of patients for adjuvant therapy.
Results: The median percentage tumour cells and quantity of DNA extracted was significantly higher in surgical vs bronchoscopic samples (80% vs 30% and 2.3±g vs 1.6±g, P<0.0001), no statistically significant difference was observed between EB11, TNBA and bronchial biopsies. Although 25% of bronchoscopic samples had <10% tumour cells, an amount of DNA extracted ≥200ng and poor DNA quality (Cp=35) were observed in 1%. Comparative results revealed high accuracy and ability to detect mutant alleles present in low fraction of tumor cells.

Highly-sensitive, robust and reliable diagnostic method is crucial for clinically useful detection of EGFR mutations in NSCLC. Due to low sensitivity, direct sequencing is restricted for samples containing at least 50% of tumor cells. PNA-LNA PCR clamp method represents allele-specific approach to gene analysis and demonstrates high accuracy and ability to detect mutant alleles present in low fraction of tumor cells.

Method: Mutated DNA was isolated from cell lines harboring endogenous exon 19 deletion or L858R mutation. Sensitivity of direct Sanger sequencing and PNA-LNA PCR clamp method was analyzed in serial dilutions of mutant allele intermixed with wild-type DNA.

Results: PNA-LNA PCR clamp method reliably detected both exon 19 deletion and L858R down to 1% DNAadmixture level. Direct sequencing presented considerably lower sensitivity detecting only down to 50% of mutated exon 19 allele in DNA mixture and down to 5% in samples with L858R mutant allele.

Conclusions: PNA-LNA PCR clamp method is the highly sensitive tool for detection of EGFR activating mutations. It might be particularly useful in heterogeneous samples with low content of mutant allele, like biopsy material. Direct sequencing presents lower sensitivity, limited by type of mutation.

P773
HOPE-BAL: A novel tool to expand the methodological capabilities in pulmonary research
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1Clin.&Exp. Pathology, Research Center, Borstel, Germany; 2Experimental Pneumology, Research Center, Borstel, Germany; 3Inflammation Discovery, Roche, Nutley, NJ, United States; 4Medical Clinic, Research Center, Borstel, Germany

Bronchial/vascular lavage cells are essential biomaterials for both, basic research and clinical applications. Easy to acquire with comparatively little risks for the patients, biomaterials even from non-malignant diseases like COPD or Asthma can be used to aid diagnostics or deliver samples from the alveolar space for basic research. However, these samples are transient materials which require timely read-out if used freshly. In case of formalin-fixed, paraffin-embedded cell blocks they are built to last but with the drawback of protein cross-linking and the severe side effects like degradation of nucleic acids. Since the rapid developments in molecular based techniques, archived samples increasingly need to meet more and more requirements for modern read-outs. Here we present a novel approach to BAL cells with all the possibilities of the omics-techniques. Human BAL cells were L858R fixed and paraffin-embedded to create cell blocks that are easy to store and convenient to handle. For routine diagnostic applications, standard marker molecules were targeted by means of immunochemistry without antigen retrieval. Furthermore we show that HOPE-fixed, paraffin-embedded BAL cells can be used for proteome analysis by application of 2D gel electrophoresis. In addition these BAL blocks contain enough RNA of sufficient quality for transcriptome analysis on Agilent Whole Genome arrays. Differential regulated genes showed distinct expression patterns between healthy donors and patients with Asthma or COPD. In summary, HOPE-BAL is a novel powerful tool for both diagnostics and translational research. Additionally biobanks of HOPE-BAL will ensure proper accessibility for unrestrained investigations.

P777
The predictive model for perinatal asphyxia risk evaluation in the neonates Natalia Gorovenko1, Svetlana Kryvyachenko2, Zoya Rososka2, 1Medical and Labortoratory Genetics, National Medical for Postgraduate Education named after P.L. Shupyk, Kiev, Ukraine; 2Laboratory of Molecular Genetics, Reference Centre for Molecular Diagnostics of Ministry of Public Health, Kiev, Ukraine

Background: Perinatal asphyxia (PA) is often associated with nonreversible adverse neurological outcome. Modern tests for PA diagnostic have low predictive values.

The aim of this study was to define the genetical based predictive model for early preventive diagnostic of PA.

Methods: We performed a case-control study of 201 neonates PA cases and 110 from control group. The markers were selected based on the results of association and differential expression analysis. We used five genetic markers: rs226953, rs1002395, rs12039714, rs1027037 and rs8110310. The results of association analysis were also correlated with the presence of maternal smoking, alcohol consumption and socio-economic factors. The statistical analysis was performed using GEM software.

Results: The frequency of all investigated genotypes with mutant allele was significantly higher among PA cases.
Asbestosis and silica exposures reveal similar and divergent gene expression patterns and pathways related to fibrosis in human bronchial epithelial cells

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Background: Asbestos and silicosis, two common forms of pneumoconioses are caused by excessive exposure to airborne minerals, leading to pulmonary fibrosis. However, both diseases have distinct pathological presentations, which are likely due to the physicochemical characteristics of the two minerals. The epithelium is an initial target cell to come in contact with inhaled materials. The early molecular events that therefore take place in epithelial cells have a strong influence on the molecular and cellular responses that promote inflammation, lesion formation, and fibrosis.

Methods: Primary human bronchial epithelial cells were exposed to non-lethal doses of crocidolite asbestos and cristobalite silica for 24 hours. Affymetrix/GeneSifter® analysis utilizing pairwise-comparison, hierarchical clustering and Ingenuity pathway analysis was used to reveal similar and unique gene expression patterns.

Results: Both minerals altered a number of genes related to inflammation, cell proliferation, apoptosis, cell-surface receptors, and transcription factors. Genes selectively altered by asbestos were related to evasion of apoptosis, MAPK signaling, and iron metabolism. Conversely, genes altered by silica were involved in TNF-signaling, TLR-signaling, and mitochondrial biogenesis. Similar and distinct pathways associated with inflammation and fibrosis were affected by both mineral exposures.

Conclusions: These studies exhibit initial changes in gene expression by asbestos and silica in target bronchial epithelial cells as early molecular events that may initiate the inflammatory and fibrotic responses leading to asbestosis and silicosis.

P773
The effect of cigarette smoking on BAL protein profile
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Background: BAL protein analysis gives a panorama of the complex network of proteins of different origin and function and their modifications at alveolar level, simultaneously providing new information about events in the alveolar microenvironment and insights into lung physiology and pathology. In this study we applied the proteomic approach to the study of BAL in order to evaluate the effect of smoking exposure to BAL protein composition.

Aim: Aim of this study was to investigate qualitative and quantitative differences in BAL protein profiles from cigarette smoker and non-smoker healthy subjects.

Methods: BAL samples were obtained by 10 healthy never-smoker and 8 asymptomatic smoker subjects. After centrifugation, dialysis and denaturation of samples, BAL samples were analyzed by two-dimensional electrophoresis and proteins differentially expressed were identified by mass spectrometry.

Results: 20 BAL proteins were differently expressed: 15 were up-regulated in smokers and 5 proteins were up-regulated in never-smokers. Among these proteins some were involved in immune-regulation, host defense (i.e.Pulmonary surfactant-associated protein A2), apoptosis and inflammatory responses (e.g. antichymotrypsin) and oxidant/antioxidant balance (i.e. Glutathione S transferase P and Annexin A5).

Conclusion: In healthy subjects smoking exposure modifies the expression of several BAL proteins implicated in the regulation of crucial biological activities (such as oxidant/antioxidant balance, inflammation and tissue matrix turnover) potentially involved in the pathogenesis of several smoke-induced lung diseases.
activity of allergic inflammation. Polymorphism can predict the occurrence of fatigue in sarcoidosis patients. Based on these results, we concluded that proinflammatory gene and was absent in non-fatigue group, and we found weak significant difference frequency (29.58% vs. 19.30%, p = 0.01). After subdividing according to genotypes, the number of annexin V positive cells did not differ between patients carrying TT genotype (50.0%, 23.3–7.8% and 8.8%) with CC genotype (54.5%; 41.7–71.7%; p = 0.05). Genotyping and investigations on association between apoptosis and genotypes in larger patient-control groups are under progress. In conclusion, PBMC obtained from sarcoidosis patients showed more apoptosis resistant phenotype than cells from control subjects. In our pilot cohort, wild type ANXA11 gene and its R230C variant did not differ in terms of sensitivity to apoptosis. Further studies in a larger patient cohort are ongoing. Grant support: IGA MZ CR NS/11171, IGA PU-EL 2012_07, CZ.1.05/2.1.00/00003.

P77 Proinflammatory gene polymorphism and fatigue in sarcoidosis

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Introduction: Fatigue is one of the most prominent symptoms in sarcoidosis patients. Cause of fatigue in sarcoidosis is still unknown. No relationship was found between fatigue and disease activity marker in sarcoidosis. Fatigue can persist many years after disease remission. Proinflammatory cytokines, TNF-α and IL-1β are involved in asthma pathogenesis (e.g. STAT6 signaling). Therefore, we evaluated the diagnostic and prognostic role of procalcitonin in sarcoidosis. Patients and methods: A total of 50 patients with AECOPD and 10 of apparently healthy individuals (control group) were studied. On presentation, serum PCT concentrations were measured, and quantitative sputum culture was performed for AECOPD. The patients were reevaluated when they had returned to their stable clinical state. The patients were classified into two subgroups: group A included patients with bacterial AECOPD (n = 20), group B included patients with nonbacterial AECOPD (n = 30).

Results: On presentation, the levels of PCT for patients of group A (2.69 ± 0.62 ng/ml) were significantly higher than in group B (0.07 ± 0.02 ng/ml) and control group (0.05 ± 0.02 ng/ml) (p < 0.001). When they had returned to their stable state, the levels of PCT for patients of group A decreased to (0.06 ± 0.03 ng/ml), which was significantly lower than in exacerbation (2.69 ± 0.62 ng/ml) (p < 0.001). But in patients of group B compared with exacerbation the levels of PCT did not change (0.06 ± 0.02 ng/ml) (p > 0.05). Asymptotic correlation was recorded between PCT levels in group A and temperature (r = 0.898, p < 0.05), leucocytic count (r = 0.889, p < 0.05), FEV1% of predicted (r = 0.898, p < 0.05).

Conclusions: Procalcitonin is a good marker for differentiation between bacterial and nonbacterial AECOPD and could be used to guide antibiotic therapy and reduce antibiotic overuse in hospitalized patients with AECOPD.

P78 Transforming growth factor-beta1 (TGF-β1) expression is related to reticular basement membrane (Rbm) hypervascularity in smokers and COPD

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Introduction: TGF-β1 is likely to play an important role in COPD airway pathology, including angiogenesis and epithelial mesenchymal transition (EMT), but it is relatively under-investigated in this context. We have previously published that the Rbm is fragmented as a likely marker of active EMT and hyper-vascular in the airways of current smokers either with or without COPD.

Objective: This study evaluated the status of TGF-β1 in endobronchial biopsies (ebb) from smokers with or without COPD.

Methods: Ebb sections from 15 smokers with normal lung function (S-NLF), 19 current (CS) and 14 ex-smokers (ES) with COPD were immunostained for TGF-β1 and compared to 17 normal controls (NC). The percentage of area of tissue and the number and area of vessels and the percentage of vessels staining positively for TGF-β1 were compared between groups.

Results: There were no differences between groups in epithelial TGF-β1 staining of TGF-β1 stained vessels in the Rbm were increased in S-NLF, CS-COPD and ES-COPD compared to NC, but especially so in CS-COPD (median (range) for number of vessels/mm Rbm 2.5 (0.0-12.7), 3.4 (0.0-8.1) and 1.0 (0.0-7.0), p = 0.051). Percentage of vessels stained was also increased in these clinical groups compared to NC (median (range) for S-NLF 31% (0-121), for CS-COPD 40% (0-123) and for ES-COPD 22% (0-114) vs. H-N 0% (0-26), p < 0.05).

Conclusions: Vessel-associated TGF-β1 was increased in smokers and COPD, especially in CS-COPD. This is likely to be related to the pathogenesis of COPD; EMT, structural remodelling, angiogenesis and tumorigenesis.

95. Inflammatory mechanisms in COPD

P780 Procalcitonin as a diagnostic marker in acute exacerbation of COPD

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Background: Rational prescription of antibiotics in acute exacerbations of COPD (AECOPD) requires predictive markers. Recently, measurement of procalcitonin (PCT) levels appears to be useful in order to minimize this problem. We aimed to evaluate the diagnostic and prognostic role of procalcitonin in COPD patients and methods: A total of 50 patients with AECOPD and 10 of apparently healthy individuals (control group) were studied. On presentation, serum PCT concentrations were measured, and quantitative sputum culture was performed for AECOPD. The patients were reevaluated when they had returned to their stable clinical state. The patients were classified into two subgroups: group A included patients with bacterial AECOPD (n = 20), group B included patients with nonbacterial AECOPD (n = 30).

Results: On presentation, the levels of PCT for patients of group A (2.69 ± 0.62 ng/ml) were significantly higher than in group B (0.07 ± 0.02 ng/ml) and control group (0.05 ± 0.02 ng/ml) (P < 0.001). When they had returned to their stable state, the levels of PCT for patients of group A decreased to (0.06 ± 0.03 ng/ml), which was significantly lower than in exacerbation (2.69 ± 0.62 ng/ml) (P < 0.001). But in patients of group B compared with exacerbation the levels of PCT did not change (0.06 ± 0.02 ng/ml) (P > 0.05). Asymptotic correlation was recorded between PCT levels in group A and temperature (r = 0.898, p < 0.05), leucocytic count (r = 0.889, p < 0.05), FEV1% of predicted (r = 0.898, p < 0.05).

Conclusions: Procalcitonin is a good marker for differentiation between bacterial and nonbacterial AECOPD and could be used to guide antibiotic therapy and reduce antibiotic overuse in hospitalized patients with AECOPD.
Blood outgrowth endothelial cells are senescent and dysfunctional in COPD due to increased DNA damage; implications for endothelial dysfunction

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Introduction: Cardiovascular disease (CVD) is a major cause of death in COPD. The molecular pathways that lead to endothelial dysfunction and CVD in COPD remain unclear. DNA damage has been recognized as an important contributor in aging disorders. Blood outgrowth endothelial cells (BOEC) - alternately named Late endothelial progenitor cells- could serve as a research tool to investigate endothelial defects in COPD patients.

Aim and objectives: To examine whether BOEC exhibit increased DNA damage linked to dysfunctional characteristics, illustrating the underlying molecular process of endothelial dysfunction in COPD.

Methods: BOEC were isolated from peripheral blood samples received from 16 healthy non-smokers (age ± SD, 57.6±2.7yr; 5 males), 10 healthy smokers (57.6±2.6yr; 5 males) and 16 COPD patients (67.1±1.6yr, 11 males). DNA damage was assessed by measuring two markers of double-strand break formation, 53BP1 and γH2AX, by immunostaining. Endothelial senescence was measured by senescence-associated β-galactosidase (SA-β-Gal) activity, and sirtuin (SIRT)1 protein levels by Western blotting.

Results: BOEC from smokers and COPD patients showed marked increases of marked DNA damage and displayed significantly reduced SIRT1 protein levels and increased senescence compared to healthy non-smokers.

Conclusions: Our results confirm that BOEC from smokers and COPD patients display increased DNA damage linked to epigenetic molecular dysfunction and increased senescence. These defects may contribute to endothelial dysfunction and cardiovascular events in smokers and patients with COPD.

P784

Increased levels of soluble intercellular adhesion molecule 1 in active smokers

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Objectives: Serum intercellular adhesion molecule-1 (sICAM-1) is known to be a smoking-associated inflammatory marker but data on the relationship between active smoking and sICAM-1 are lacking for COPD. In the present study we collected a group of COPD patients and non-COPD smokers and measured the sICAM-1 in order to provide information on its expression related to active smoking.

Methods: This report is based on a cross sectional analysis of a case-control study, in which 141 COPD cases and 56 controls (non-COPD smokers) were consecutively recruited. Clinical information from all subjects was registered and participants were consecutively recruited. A smoking questionnaire that included direct questions on co-morbid conditions, respiratory symptoms and tobacco history. Peripheral blood concentration of sICAM-1, together with interleukin-8 (CXCL8), C-reactive protein (CRP), and serum amyloid A (SAA) were determined in all cases.

Results: There were 89 ex-smokers and 108 active smokers of them in the sample. CRP and SAA (log-scale) were elevated in patients with COPD as compared to control subjects (p = 0.005 for CRP and p = 0.024 for SAA). SAA and sICAM-1 were associated with active smoking in the bivariate analysis. ICAM-1 retained this association when corrected by age, gender, the presence of COPD, inhaled corticosteroids use, body mass index, and FEV1 as covariates.

Conclusion: The present study confirms an association between sICAM-1 levels and active smoking in a group of COPD and non-COPD smokers. This association is specific of ICAM-1, not affecting other COPD-related biomarkers.

P785

Correlation between immunohistochemical CuZn-SOD expression and the histopathological features in small airways of patients with severe COPD

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The central causative factor of COPD is cumulative oxidative stress as result of long-term tobacco smoking and an extensive inflammatory response. Superoxide dismutases (SODs) are the primary superoxide-scavenging enzymes in mammalian tissues. This study investigate the relationship between inflammatory and SODs profiles in different small airways compartments according to the severity of COPD and local destructive index (DI).

The localizations of macrophages (M0), mast cells, neutrophils, CuZn-SOD, Mn-SOD, and EC-SOD were investigated by immunohistochemistry using paraffin embedded sections from 15 controls (non-smokers+s+smokers), and 25 subjects with mild-to-severe COPD. Histological/immunohistochemical analyses were performed using the same Region-of-Interest within each small airway. Significant (p<0.05) up-regulation of CuZn-SOD was observed in bronchial epithelium, pulmonary vessels, and alveolar parenchyma in very severe COPD, whereas epithelial Mn-SOD and EC-SOD expressions were less affected. The percentage of CuZn-SOD was higher in alveolar parenchyma than in severe COPD but this did not reach statistical significance. Higher Mq and neutrophils densities were found in the interstitium in very severe COPD. Statistically significant correlation was found between SOD expression in the small airways and Mq/Mn-SOD in the alveolar parenchyma.

In the small airways of patients with very severe COPD there is up-regulation of CuZn-SOD and correlates with the lower DI. The SODs had a patchy distribution in all compartments, where the intensity varied between micro-localization in small airways and alveolar parenchyma.

P786

The impact of long-term tobacco smoking on circulating IL-16+ NK cells

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Natural killer (NK) cells constitute a first line of anti-viral host defence and tobacco smoke may cause reduced cytotoxicity. Among the cytokines expressed in NK cells, interleukin-16 (IL-16) is of interest since it is known that the extracellular concentrations of this CD4 cell chemoattractant are increased in the airways of long-term smokers. Here, we investigated whether long-term smoking alters the number and IL-16 content of circulating NK cells.

Never-smokers (NS) and asymptomatic smokers (AS) with a normal ventilatory capacity plus a normal diffusion capacity for carbon monoxide (DLCO) were included. We also examined smokers who were smoked-related or never-smokers with severe DLCO (<2SD of the predicted mean). In each subject, a peripheral venous blood sample was taken during clinically stable conditions for flow cytometry analysis of intracellular IL-16 in NK cells (HL and CD8 CD36 CD16 CD56+). The relative and absolute number of NK cells (CD3 CD16 CD56) was determined. Smokers (AS and COPD) exhibited a lower relative number of IL-16+ NK cells compared to NS (Mann-Whitney U test, p<0.05). In line with this, the absolute number of IL-16+ NK cells tended to be lower in smokers as well, although this trend was not statistically significant. Among smokers, there was a negative and statistically significant correlation for both the absolute and relative numbers of NK cells, on the one hand, and tobacco load (e. pack-years; Spearmann Rank Corr. test; p<0.05; rho=0.056 for both correlations) on the other. Our study indicates that long-term smoking exerts a negative impact on circulating NK cells, in terms of number and IL-16 content. Hypothetically, this impact may impair anti-viral host defence.

P787

The dynamics of IV-type collagen contents in BALF of patients with COPD

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Background: Chronic obstructive pulmonary diseases are diagnosed in 4-6% of men and 1-3% of women above 40 years old. The persistent inflammatory process in bronchi, the development of microcirculation disorders, the increasing of hypoxia processes result in the activation of fibroblasts and their production of IV-type collagen, which is manifested by the formation of peribronchial pneumosclerosis. Purpose of the study: The evaluation of the IV-type collagen level dynamics in BALF of patients with COPD. Materials and methods: The contents of IV-type collagen in BALF has been evaluated by the Enzyme-linked immunosorben assay method in 28 patients with 2nd stage of COPD in a relapse phase, and then in the same patients again in 6,4±1,2 years during the transformation of the disease into 3rd stage of COPD. Results of the study: The contents of IV-type collagen in BALF with II stage COPD in the relapse phase was (38,6±1,21) ng/ml, which is 3,99 times higher than in almost healthy people whose level was (9,6±1,24) ng/ml. The average FEV1 magnitude was 57,4±4,2%. During the progressing of COPD and its transformation into 3rd stage, the average magnitude of the FEV1 indicator was 43,4±4,6%; the IV-type collagen level in BALF rose up to 35% in comparison with previous data and it was equal (9,6±1,24) ng/ml. Conclusions: The progressing of COPD is accompanied by the increase of the remodulation of bronchial tree due to peribronchial pneumosclerosis, which is manifested by the IV-type collagen levels rise.
P788
Senescence marker protein-30 decreases oxidative stress in human lungs of smokers with chronic obstructive pulmonary disease
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Introduction: Senescence marker protein-30 (SMP30) reportedly protects mice lung from oxidative stress associated with smoking. Little is known about the presence of SMP-30 in lungs of chronic obstructive pulmonary disease (COPD).

Methods: Lung tissue was examined from 47 subjects undergoing resection for peripheral lung tumors as follows: current smokers with (n=9) and without COPD (n=7), ex-smokers with (n=8) and without COPD (n=8), nonsmokers with (n=7) and without COPD (n=6). SMP-30 was investigated by immunohistochemistry in lung tissue specimens and Western analysis, qRT-PCR in total lung homogenates. Morphologic evaluations of the lungs, glutathione, malondialdehyde (MDA), interleukin-8 (IL-8) and tumor necrosis factor-a in the lung tissues were determined.

Results: Weak SMP-30 protein was localized predominantly in the cytoplasm of bronchial epithelial cells. A notable decline of SMP-30 mRNA and protein was found in lung tissue of patients with COPD compared to healthy subjects (P<0.05), also in smokers and ex-smokers with or without COPD when compared with spiroemphy matched nonsmokers. Inverse correlation was observed between SMP-30, MDA, IL-8 and alveolar destructive index (P<0.05).

Conclusions: SMP-30 decreases oxidative stress from smoking and pulmonary inflammation, which may contribute to protecting smokers from susceptibility to the development of COPD.

P794
Relation of inflammatory process with COPD phenotype
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Aim: Chronic obstructive lung disease (COPD) does not have a uniform clinical and morphological nature. The aim of the study was to characterize the inflammatory process in two distinct forms of COPD (chronic bronchitis or emphysema).

Methods: 33 COPD patients were investigated. They were divided into two groups: emphysema (n=15) and chronic bronchitis patients (n=18). The distinguishing criteria were the presence of emphysema in HRCT and hyperinflation in pulmonary function test.

Results: The concentration of inflammatory mediators in BAL (IL-8, TNFα, MPO, myeloperoxidase (MPO), and neutrophil elastase (NE)) and blood (IL-8, TNFα, CRP, and fibrinogen) were measured.

Data expressed as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>IL-6 (pg/ml)</th>
<th>sIL-6 (pg/ml)</th>
<th>sTNFα (pg/ml)</th>
<th>CCL2 (pg/ml)</th>
<th>CCL3 (pg/ml)</th>
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<tbody>
<tr>
<td>COPD</td>
<td>136.2(103.3)</td>
<td>136.2(103.3)</td>
<td>136.2(103.3)</td>
<td>136.2(103.3)</td>
<td>136.2(103.3)</td>
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<tr>
<td>HS</td>
<td>116.8(84.5)</td>
<td>116.8(84.5)</td>
<td>116.8(84.5)</td>
<td>116.8(84.5)</td>
<td>116.8(84.5)</td>
</tr>
<tr>
<td>HNS</td>
<td>125.6(256.9)</td>
<td>125.6(256.9)</td>
<td>125.6(256.9)</td>
<td>125.6(256.9)</td>
<td>125.6(256.9)</td>
</tr>
</tbody>
</table>

Conclusions: We report evidence of enhanced IL-6 signaling and CCL3 activity in COPD sputum. We have observed that there is reduced CCL2 activity and enhanced CCL3 activity in COPD sputum. IL-6 may therefore promote neutrophilic inflammation in COPD through up-regulation of CCL3 expression.

P795
MMP-9 expression and activity is increased in the BAL of patients with acute exacerbation of COPD
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Background: Exacerbations of COPD are associated with accelerated deterioration of respiratory symptoms and pulmonary function. Matrix metalloproteinases (MMP) are a family of endopeptidases involved in extracellular matrix clevage. We hypothesize that there is a difference in the expression and the enzymatic activity of MMP in bronchoalveolar lavage fluid (BALF) of COPD patients with and without exacerbation.

Methods: Seventy patients with COPD diagnosed according to the GOLD guidelines with either stable disease or exacerbation and undergoing diagnostic bronchoscopy were included in this prospective cohort study. BAL was performed by installation of 3 x 50 ml of pyrogen-free sterile NaCl 0.9% solution over the working channel of the bronchoscope according to standard guidelines. Enzymatic activity of MMP was assessed by gelatin zymography and protein levels of MMP-2, MMP-9 and of tissue inhibitors of MMP (TIMP) were measured by ELISA.

Results: Data of 40 patients with COPD (stable COPD n=20, exacerbation n=20) have been analyzed so far. Mean age was 68.9 years ±(9.5), mean FEV1%pred 49.9% ±(16.9). Mean DLCO %pred 43.1% ±(18.8). As compared to patients with COPD at stable state, the MMP-9 enzymatic activity and protein expression were increased by 73% and 62%, respectively (p<0.001) in the BALF of patients with COPD at exacerbation. In contrast, there was no significant alteration in TIMP expression, indicating a net increase of collagenase activity associated with exacerbation.

Conclusion: Increased activity of MMP-9 during acute exacerbation might contribute to tissue destruction and development of emphysema in patients with recurrent exacerbations of COPD.

Rationale: IL-6 is a pleiotropic cytokine that is involved in the regulation of inflammation. Increased serum IL-6 levels are associated with reduced FEV1 in COPD patients independent of age or smoking status. Elevated levels of plasma IL-6 in COPD patients have been associated with increased exacerbation frequency. The mechanism by which IL-6 may mediate inflammation in COPD is uncertain. We sought to determine levels of IL-6 and its soluble receptor (sIL-6R) in COPD sputum. IL-6 signaling can alter the levels of the neutrophil chemotactant CCL3 and the monocyte chemotactant CCL2; we also investigated the levels of these chemokines.

Results: Healthy smokers had the highest levels of plasma IL-6. COPD patients expressed the highest levels of sIL-6R. COPD patients also expressed the highest levels of plasma CCL3. In contrast, CCL2 expression was significantly reduced in COPD patients.

P793
Enhanced IL-6 and CCL3 activity in COPD
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Introduction: IL-6 is a pleiotropic cytokine that is involved in the regulation of inflammation. Increased serum IL-6 levels are associated with reduced FEV1 in COPD patients independent of age or smoking status. Elevated levels of plasma IL-6 in COPD patients have been associated with increased exacerbation frequency. The mechanism by which IL-6 may mediate inflammation in COPD is uncertain. We sought to determine levels of IL-6 and its soluble receptor (sIL-6R) in COPD sputum. IL-6 signaling can alter the levels of the neutrophil chemotactant CCL3 and the monocyte chemotactant CCL2; we also investigated the levels of these chemokines.

Methods: 70 patients with GOLD stage IV COPD and 30 healthy controls comprising of 15 healthy smokers (HS) and 15 healthy non-smokers (HNS) underwent sputum sampling with PBS processing. Levels of IL-6, sIL-6R, CCL2, CCL3 were determined by multiplex analysis (MDx) platform of sputum supernatant.

Results: Healthy smokers had the highest levels of plasma IL-6. COPD patients expressed the highest levels of sIL-6R. COPD patients also expressed the highest levels of plasma CCL3. In contrast, CCL2 expression was significantly reduced in COPD patients.

Conclusion: We report evidence of enhanced IL-6 signaling and CCL3 activity in COPD sputum. We have observed that there is reduced CCL2 activity and enhanced CCL3 activity in COPD sputum. IL-6 may therefore promote neutrophilic inflammation in COPD through up-regulation of CCL3 expression.

P792
Differences in cellular expression of C-reactive protein and serum amyloid A in lung tissue in patients with chronic obstructive pulmonary disease
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Introduction and objectives: The lung bronchial and parenchyma tissues are a potential source of acute phase reactants in Chronic Obstructive Pulmonary Disease (COPD) patients as compared with resistant smokers. The aim of this study was to determine the expression of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) in epithelial cells, macrophages and lung fibroblasts between COPD and resistant smokers. This expression was also studied according to the different grades of COPD.

Method: This report is based on a cross sectional analysis of a case-control study. These patients included were consecutively recruited, in elective lung surgery. Epithelial cells, macrophages and fibroblasts were obtained by magnetic separation microbeads and CRP and SAA1, 2 and 4 expression was analysed by real time PCR.

Results: The sample was formed by 19 COPD and 27 resistant smokers. Although all cell types were able to synthesize the biomarkers, fibroblasts of COPD patients had a significantly higher expression (5 folds, p=0.015) of SAA1 than resistant smokers. Our results also showed significant differences in the expression of SAA between macrophages from COPD in different stage of the disease, being higher in patients in GOLD II (25 folds higher for SAA1, p=0.015) and 30 for SAA4, p=0.014).

Conclusions: There are differences in the synthesis of SAA-1 in fibroblasts of COPD and controls. The pattern of expression in macrophages is different for SAA according to stage of disease. These findings could be useful to elucidate the contribution of each cellular compartment in the inflammatory component of the disease.
Elevated sputum complement factor H levels in COPD: Relationship with stimulation with PMA and S. aureus was more intensive during AECOPD ROS production in sputum and peripheral blood neutrophils after (p < 0.05). The most significant increase of ROS production was documented after neutrophil stimulation with 30 nM of PMA (in sputum neutrophils – during AECOPD 45±28-fold; in SCOPD 18±19-fold, HI 80±11-fold, respectively, (p=0.01); in PBN - during AECOPD 98±41-fold, in SCOPD 162±24-fold, HI 118±18-fold, respectively, (p=0.005)). The intensive ROS production in neutrophils after stimulation with S. aureus was found in AECOPD group compared with SCOPD and HI (p=0.01).

Conclusions: ROS production in sputum and peripheral blood neutrophils after stimulation with PMA and S. aureus was more intensive during AECOPD compared with SCOPD. Sputum neutrophils produce higher levels of ROS compared with PBN.

P794
Elevated sputum complement factor H levels in COPD: Relationship with disease severity
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Background: Inflammatory processes in COPD are not fully clarified yet. Complement activation products C3a and C5a are elevated in COPD spuha, but complement regulatory proteins, such as factor H, have been not investigated in this disorder.

Objective: Our primary goal was to determine airway complement factor H levels in stable and exacerbated COPD in order to gain information about the relationship between factor H level, complement activation and clinical characteristics of disease groups.

Methods: We examined complement factor H levels and SC5b-9, a marker of complement activation in plasma and spuha of 15 healthy, 15 stable and 17 exacerbated COPD subjects by ELISA.

Results: Factor H and SC5b-9 levels were both higher in spuha of stable COPD patients compared to healthy controls (Factor H: p=0.001, SC5b-9: p=0.003), which further increased in acute exacerbation (Factor H: p<0.0001, SC5b-9: p=0.02), and returned to stable level after 5-7 days of systemic corticosteroid treatment. Plasma concentrations showed similar tendencies, but with much smaller differences. There was a significant positive relationship between sputum factor H levels and FVC (%: r=0.71, p<0.01) as well as FEV1 (%: r=0.57, p=0.04) values in stable patients. Sputum SC5b-9 concentrations correlated with FEV1/FVC (%: r=0.55, p=0.04) in stable COPD.

Conclusions: Increased sputum factor H level is associated with milder airway obstruction in stable COPD, which may be connected to early inflammatory processes preceding extensive alveolar destruction.

This work was supported by the Hungarian Scientific Research Fund (OTKA 68808).

P795
Stage-dependent regulation of brain-derived neurotrophic factor and transforming growth factor-β1 in patients with COPD
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Chronic Obstructive Pulmonary Disease (COPD) is characterised by complex inflammatory, neural and fibrotic changes. Brain-derived Neurotrophic Factor (BDNF) and Transforming Growth Factor-β1 (TGF-β1) are stored in alpha-granules of platelets. Serum BDNF and TGF-β1 are predominantly platelet-derived (released from platelets during serum preparation). BDNF is a key regulator of neuronal plasticity, whereas TGF-β1 is involved in tissue repair and emphysema pathogenesis. We have previously shown that serum BDNF but not TGF-β1 levels were found in GOLD stage 4 in contrast to asthma. This work appears to be characterised by increased concentrations of both BDNF and TGF-β1. Very severe COPD is associated with highest TGF-β1 concentrations, but relatively lower BDNF concentrations. We thus speculate that these findings might reflect a maximum of neuronal and inflammatory activity in GOLD stage 2 and 3, and a predominant activity of tissue remodeling factors in GOLD stage 4.

Gastroesophageal reflux disease (GERD) is tightly linked to bronchial asthma and COPD. In our study we evaluated serum of 54 patients. Diagnoses was as follows: asthma (n=14), COPD (n=12), GERD (n=20), asthma and GERD (n=8). Serum of 17 volunteers was studied as a control group. IL-4, IFN-gamma and TNF-alpha levels were detected by ELISA. All patients underwent upper gastrointestinal endoscopy and spirometry. For statistics nonparametric method of Kruskal-Wallis and Spearman’s correlation were used.

Results: The IL-4 and IFN-gamma levels in all groups of patients were significantly higher than control (p=2.5E-09 and 1.7E-09 respectively). Meanwhile TNF-alpha values in patients cohorts was lower than in control group (p=0.007).

Conclusions: Our results suggest that there is a significant contribution of inflammation processes in the pathogenesis of gastroesophageal reflux disease (GERD) in patients with different pulmonary diseases. Further investigations are necessary to determine the role of other cytokines in GERD in different clinical settings.

P796
IL-4, IFN-gamma and TNF-alpha levels in serum of patients with COPD, bronchial asthma and GERD
Nikolay Novy, Central Laboratory for Molecular Medicine, I.P.Pavlov State Medical University, St. Petersburg, Russian Federation

Stage-dependent regulation of brain-derived neurotrophic factor and transforming growth factor-β1 in patients with COPD

P797
C-reactive protein and serum amyloid A overexpression in lung tissues of chronic obstructive pulmonary disease patients
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Background: Although researchers have consistently demonstrated systemic inflammation in chronic obstructive pulmonary disease (COPD), its origin is yet unknown. We aimed to compare the lung bronchial and parenchymal tissues as potential sources of major acute-phase reactants in COPD patients and resistant smokers.

Material and methods: Consecutive patients undergoing elective pneumectomy or lobectomy for suspected primary lung cancer were considered for the study. Patients were categorized as COPD or resistant smokers according to their spirometric results. Lung parenchyma and bronchus sections were obtained and C-reactive protein (CRP) and serum amyloid A (SAA1, SAA2, and SAA4) expressions in COPD patients were 1.89-fold, 3.46-fold, 3.65-fold, and 3.9-fold the control values, respectively. In the parenchyma, CRP, SAA1, and SAA2 gene expressions were 2.41-, 1.97-, and 1.76-fold the control values, respectively. SAA4 was not overexpressed in the parenchyma. The expressions were higher in the parenchymal tissue than in bronchial tissue for both COPD and controls. The protein analysis supported the results obtained in the PCR.

Conclusions: These results indicate an overexpression of CRP and SAA genes in both bronchial and parenchymal tissue in COPD. This expression differs between the parenchyma and bronchial tissue, indicating tissue/cell type specificity of these markers.

P798
T cell chemokine receptor expression in COPD
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Background: COPD is characterized by accumulation of T cells in the lung.
Recruitment is regulated by chemokines binding to receptors on the cell surface. We studied the expression of chemokine receptors on T cells from never-smokers, smokers with normal lung function and COPD patients.

**Methods:** Thirteen never-smokers, 38 smokers with normal lung function and 32 COPD patients, GOLD stage I-II (23 smokers and 9 ex-smokers) underwent BAL (5±0.5 ml). BAL and blood T cells were analysed for CD3, CD4 and CD8 in combination with the activity marker CD69 and the chemokine receptors CXCR3, CCR4 and CCR5 using multicolor flow cytometry. **Results:** The percentage of CD4+CD69+ (non-activated) T cells expressing CXCR3 was significantly lower in BAL from “normal” smokers and from COPD smokers compared to neversmokers (p<0.001 and p<0.05). CD4+ T cells from “normal” smokers had significantly higher median fluorescence intensity (MFI) of CCR5 compared to neversmokers (p<0.05). An increase, albeit not significant, was also observed in COPD patients who were current smokers. The expression of CXCR3, CCR4 and CCR5 on CD8+ T cells in BAL did not differ. In blood from COPD patients (both current and ex-smokers), we observed a higher percentage of activated (CD69+CD4+) T cells expressing CXCR3 compared to “normal” smokers (p<0.05 for both).

**Conclusions:** The lower percentage of CD4+CD69+CXCX3+ T cells and the higher MFI of CCR5 on CD4+ T cells in BAL from both smoking groups were related to smoke exposure per se, rather than the degree of airway obstruction. This was not observed in COPD exsmokers, indicating that both smoking history and current smoke exposure affect the expression. Analysis of soluble ligands for CXCR3, CCR4 and CCR5 is in progress.

96. Cell biology and inflammatory gene expression in chronic lung disease

**P800**

*Human alveolar macrophages express mucin5B*

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**Introduction:** This study investigated whether alveolar macrophages (AM), in addition to epithelial cells, express mucin5B (MUC5B) in human lung environment influenced by long-term cigarette smoke.

**Methods:** We analysed MUC5B expression at the level of a polymic and mRNA in human BALF cells from fifty subjects (20 non-smokers, 17 patients with chronic bronchitis (CB) and 13 patients with chronic obstructive pulmonary disease (COPD)).

**Results:** Apomucin5B was observed in BALF mononuclear cells in 60% of all subjects whereas significantly higher frequency of apomucin5B+ cells was found in CB (95% CI 4.5-24.9) and COPD (95% CI 6.2-39.6) subjects than in non-smokers (CB: 0.1-2.5; COPD: 0.1-5.2). Apomucin5B+ mononuclear cells showed strong expression of CD163, confirming their identity as AM. MUC5B mRNA expression was detected in AM of subjects investigated by sit analysis. qPCR showed MUC5B mRNA expression in purified AM of subjects investigated. An inverse correlation between apomUC5B+ AM levels and FEV1 was found (r = 0.46, p = 0.002 in whole study group). The correlation between apomUC5B+ AM levels and smoking pack-years was positive in whole study group (r = 0.65, p < 0.001).

**Conclusion:** The level of circulating cigarette smoking human alveolar macrophages can change their expression profile in the lung.

**P801**

*Molecular mechanisms of plasminogen activator inhibitor-1 elevation in COPD sputum*

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**Background:** Plasminogen activator inhibitor-1 (PAI-1) is an important regulator of fibrinolytic at sites of vascular injury and thrombus formation. Oxidative stress is known to involve in PAI-1 expression. We previously reported that mean PAI-1 levels in sputum of COPD was significantly higher than that of age-matched controls and significantly correlated with both sputum malondialdehyde (a oxidative stress marker) and NF-KB DNA binding activity in sputum macrophages. However, the precise mechanisms of PAI-1 elevation in COPD were not clarified. We hypothesised that HDAC2 reduction in COPD involves in PAI-1 elevation. The aim of this study was to investigate the association between HDAC2 reduction and elevated PAI-1 expression.

**Methods and results:** A549 cells were transfected with siRNA of HDAC2 to knockdown HDAC2 and followed by treatment with TGF-β (1 ng/ml). HDAC2 knockdown (KD) significantly upregulated PAI-1 release (Wild type (WT) vs HDAC2 KD: 2.9±0.2 vs 4.1±0.3 mg/ml with 0.1ng/mlTGF-β, 7.4±1.04 vs 8.4±1.5 ng/ml with 0.1ng/ml TGF-β). To investigate the association between NF-kB DNA binding activity and HDAC2 KD cells, we stimulated by 10 ng/ml TNFα for 2hrs, and NF-kB DNA binding activity and p65 acetylation were evaluated with TransAM NF-kB p65 Activation Assay Kit and Western blot, respectively. NF-kB DNA binding activity was significantly increased in HDAC2 KD cells (activity(OD)/protein: WT vs HDAC2 KD: 76±4 vs 98±14). Acetylation of p65 was also significantly upregulated in HDAC2 KD cells (acetyl-p65/65: WT vs HDAC2 KD: 2.3±0.1 vs 3.1±0.1).

**Conclusion:** HDAC2 reduction in COPD seems to cause PAI-1 elevation in COPD via activation of NF-kB DNA binding by p65 acetylation.
Background: Patients with refractory asthma are more susceptible to allergen- and infection-induced exacerbations. This susceptibility is poorly understood, but it may be related to an inefficient activation of innate host defence pathways. Interleukin-stimulated genes (ISGs), such as myxovirus resistance (MX1), 25'-oligoadenylate synthetase (OAS) and viperin are associated to biological activities, including antiviral, antiproliferative, and proapoptotic effects.

Objective: The aim of the study was to investigate the expression of antiviral genes in patients with refractory compared with moderate and mild asthma.

Methods: The mRNA expression of the ISGs (MX1, OAS and viperin), interferon (IFN) type 1 (I) and type III (IL-28 and IL-29) were measured by RT-qPCR in cells of induced sputum from 19 healthy subjects, 19 mild, 22 moderate and 22 refractory asthmatics. 

Results: The mRNA expression of MX1 and viperin were significantly reduced in refractory asthmatics (p<0.04 and p<0.03, respectively), while the mRNA expression of OAS, IFNIFN IL-28 and IL-29 was not different between groups.

Conclusion: The results point to a deficient innate immune response in refractory asthma demonstrated by a decreased expression of some interferon stimulated genes.

P804 Corticosteroid treatment selectively decreases mast cells in the smooth muscle and epithelium of asthmatic bronchi

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Objective: The aim is to reveal the disorders of apoptosis in bronchial epithelium based on the estimation of expression of Bcl2, Bax, caspase-3 activity in bronchial asthma (BA) based on the estimation of expression of BA, and caspase-3 activity.

Methods: In 21 patients a fibropenic bronchoscopy was performed (patients have signed the ICF). Expression of Bcl2, Bax, CPP32 (caspase-3 activity) in bronchial epithelium was performed by immunohistochemical analysis of bronchus biopsies taken in fibrobronchoscopy using DAKO kits.

Results: In allergic BA elevation of Bcl2 expression and decrease of Bax expression compared to nonallergic BA and oral glucocorticoids taking patients were found. Activity of Bax expression was significant decreased in allergic BA compared to that in other groups. The same data were revealed on analysis of Bcl2/Bax index. Expression level of caspase-3 was high in both groups.

Conclusion: Features of apoptosis in bronchial epithelium in different variants of BA could indicate to different pathogenic mechanisms of apoptosis in allergic inflammation persistence.

P806 Role of altered level of oxidant-antioxidant in disease prognosis of asthma

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Background: Asthma is a chronic airway disorder which is associated to airway obstruction. Inflammatory and immune cells generate more reactive oxygen species in asthma and lead to contribute in tissue injury. Aims and objectives: The aim of this study was to investigate the role of oxidant-antioxidant imbalance with disease severity in asthmatic patients.

Methods: In this study 140 asthmatic patients and 70 healthy controls were documented. Malondialdehyde level, total protein carbonyls and sulphydrols were measured as the indicator of oxidative stress in plasma. Antioxidants were evaluated by the activity of catalase, glutathione peroxidase, total blood glutathione and total antioxidant capacity.

Results: The present work showed that the levels of malondialdehyde (4.5±1.02 mmol/mL) and protein carbonyls (1.30±0.02 mmol/mg) were found to be significantly higher in asthmatic patients while protein sulphydrols (0.54±0.01 mmol/L) decreased as compared to controls (2.8±0.12 mmol/mL, p<0.001, 0.79±0.02 mmol/mg, p<0.01 and 0.6±0.01 mmol/L, p<0.01 respectively). We also observed increased total blood glutathione (9.8±0.02 mmol/L), decreased glutathione peroxidase (41.2±1.10 U/g Hb) and catalase activity (465±81.36 U/g Hb) in erythrocytes compared with control (0.84±0.04 mmol/mL, p<0.01, 48.3±2.47 U/g Hb, p<0.01 and 494±6.99 U/g Hb, p<0.05 respectively). The level of total antioxidant status (714.70±23.75 μmol/L) in plasma was also decreased as compared to control (840.46±28.39, p<0.001).

Conclusions: These results support the hypothesis that an imbalance in oxidant-antioxidant is associated to the oxidative stress which plays a significant role in severity of the disease.
**P808**

Tobacco smoking alters the relationship between airway inflammation and airway hyperresponsiveness in asthma

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**Background:** Smoking in asthma patients constitutes a major health problem, due to impaired steroid responsiveness, poor symptom control and an accelerated loss of bronchial reactivity. This may relate to alterations in the airway inflammation. The aim of the present study was to evaluate the effect of smoking on the relationships between airway inflammation and airway hyperresponsiveness in asthma patients not on steroid treatment.

**Material and methods:** A group of smoking asthma patients (n=27) was compared to a group of non smoking asthma patients (n=34) with induced sputum, exhaled nitric oxide (eNO) and airway hyperresponsiveness with a bronchial challenge with mannitol. Airway eosinophilia was defined as a sputum % eosinophils >2.

**Results:** A significantly higher proportion of patients with non-eosinophilic asthma was observed in the smoking group than in the non-smoking group (44% and 18%, p=0.025). The mean eNO was lower in the smoker group compared to the non-smoker group (11.7 ppb vs 38.2 ppb (p=0.001)). The proportion of subjects with a positive mannitol test was comparable among smokers (68%), and non-smokers (50%) (p=0.19). Smokers with a positive mannitol test had lower LI and lipase levels (mean difference of 26 units (p=0.03) and 9 U/L (0.001), respectively). Also, patients taking proton pump inhibitors (PPIs) had not lower LI and lipase levels (mean difference of 26 units (p=0.03) and 9 U/L (0.001), respectively). A lower LI was observed in smoking group than in the non-smoking group (587 ml, p=0.019) and an inverse relationship between LI and lung function when adjusted for the presence of asthma that is not controlled (50%) (p=0.19). Smokers with a positive mannitol test had a lower mean difference of 307 ml, p=0.019).

**Conclusion:** Our data showed that despite of a lower proportion of eosinophilic phenotype amongst the smoking asthma patients than amongst the non-smokers, no reduced degree of airway hyperresponsiveness to mannitol in the smoker group was observed, indicating that pathogenetic mechanisms other than eosinophilic airway inflammation are responsible for the tendency to airway narrowing in smoking asthma patients.

**P809**

Lipid laden macrophages and lipase as markers of aspiration in patients with chronic cough

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**Introduction:** Gastroesophageal reflux disease (GERD) causes chronic cough by increasing the risk of regurgitation of stomach contents into the airways. GERD could be confirmed for the lipase.

**Results:** A significantly higher proportion of patients with non-eosinophilic asthma was observed in the smoking group than in the non-smoking group (44% and 18%, p=0.025). The mean eNO was lower in the smoker group compared to the non-smoker group (11.7 ppb vs 38.2 ppb (p=0.001)). The proportion of subjects with a positive mannitol test was comparable among smokers (68%), and non-smokers (50%) (p=0.19). Smokers with a positive mannitol test had lower LI and lipase levels (mean difference of 26 units (p=0.03) and 9 U/L (0.001), respectively). Also, patients taking proton pump inhibitors (PPIs) had not lower LI and lipase levels (mean difference of 26 units (p=0.03) and 9 U/L (0.001), respectively). A lower LI was observed in smoking group than in the non-smoking group (587 ml, p=0.019) and an inverse relationship between LI and lung function when adjusted for the presence of asthma that is not controlled (50%) (p=0.19). Smokers with a positive mannitol test had a lower mean difference of 307 ml, p=0.019).

**Conclusion:** Our data showed that despite of a lower proportion of eosinophilic phenotype amongst the smoking asthma patients than amongst the non-smokers, no reduced degree of airway hyperresponsiveness to mannitol in the smoker group was observed, indicating that pathogenetic mechanisms other than eosinophilic airway inflammation are responsible for the tendency to airway narrowing in smoking asthma patients.

**P811**

Change of phenotype and phenotypic plasticity of alveolar macrophages in COPD

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Development of chronic obstructive pulmonary disease (COPD) is due to imbalance of Th1/Th2 immune responses which shift disorder in M1 and M2 macrophages phenotypes.

**Objective:** Assessment of macrophages phenotype and phenotypic plasticity of alveolar macrophages (AM) in COPD.

**Methods:** In vitro experiments were carried out on AM cultures of COPD patients (n=18, 59.7±3.56 y.o.). AM phenotype was assessed by flow cytometry (Beckman Coulter, FC500) by surface macrophages markers CD80, CD25 and CD163, CD206, typical for M1 and M2 phenotype, respectively. Phenotypic plasticity of AM was measured as percentage change of markers during 36 hours of AM reprogramming in the presence of standard serum (FBS) in concentrations 0%, 10%, 40%.

**Results:** In COPD patients AM of M1 phenotype prevaled, thus AM population was not monophenotypical. AM from NA donors yields 72.3±6.1% CD80, 16.3±2.1% CD25 and 9.9±1.2% CD163. Increase of FBS concentrations from 0% to 10% significantly increased M2 markers expression CD163 and CD206. After 36 hours of culturing with 10% FBS only CD80 pointed to M1 phenotype prevalence in AM of COPD patients.

**Conclusions:** In changing environment the previous condition of macrophages phenotype is longer fixed by M1 marker CD80, and CD206 can be used for phenotypic plasticity definition. Phenotypic plasticity should be assessed specific to certain factors so that different markers show different picture of phenotypic plasticity in COPD.

**P812**

Phenotypic plasticity of fibrocytes upon culture with airway smooth muscle

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Asthma is a major cause of morbidity and mortality worldwide and its prevalence is increasing. Increased airway smooth muscle (ASM) mass is a hallmark of asthma, which increases with disease severity and is associated with decline in lung function. Fibrocytes (FCs) are elevated in the peripheral blood and ASM in asthma and ASM has the potential to mediate FC recruitment (Saunders et al, J Allergy Clin Immunol, 2009;123:376-84). We hypothesised that once recruited to certain factors so that different markers show different picture of phenotypic plasticity in COPD.

**Objective:** To assess the possibility of immune response plasticity management in pulmonary diseases with inflammatory component.

**Methods:** A group of patients with chronic obstructive pulmonary disease (n=18), bronchial asthma (n=17), sarcoidosis (n=23) were cultured with various concentrations of standard serum FBS containing TGF-β and surfactant protein D (SP-D) to assess macrophages plasticity. Quality of macrophages bioprogramming was measured by morphological characteristic (light microscopy), cytokine production and surface macrophages markers expression (flow cytometry, Beckman Coulter, FC500).

**Results:** Changing of macrophages microenvironment with FBS concentration and the level of TGF-β and SP-D, respectively, purposefully programmed macrophages phenotype on M1 proinflammatory, or M2 antiinflammatory, shifting the immune response to Th1 or Th2, respectively. Decreasing FBS concentration to 0% programmed macrophages to M1 phenotype which was confirmed by morphological characteristic, cytokine production and macrophages markers expression. The consecutive increasing of FBS concentration from 20% to 40% led to bioprogramming of macrophages on M2 phenotype and Th2 response development with close relationship to concentration.

**Conclusions:** Serum model of reprogramming was effective in regulation of immunomodulation strategy for COPD patients. Our results show that FCS have the capability to undergo phenotypic plasticity, depending on culture conditions. Further work is required to understand the factors affecting FCs differentiation upon localisation to the ASM in asthma and the resultant contribution of FCs to ASM dysfunction.

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<td>Cells (%) positive</td>
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<td>p&lt;0.05 compared to *24h after isolation, *paired FC data, *FC+ASM, t-tests, n=4-7.</td>
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Disorder of the immune response plasticity is the basis of pathogenesis of pulmonary diseases with inflammatory component.

**Objective:** To assess the possibility of immune response plasticity management in pulmonary diseases with inflammatory component by means of microenvironment components of alveolar macrophages (AM).

**Methods:** A group of patients with chronic obstructive pulmonary disease (n=18), bronchial asthma (n=17), sarcoidosis (n=23) were cultured with various concentrations of standard serum FBS containing TGF-β and surfactant protein D (SP-D) to assess macrophages plasticity. Quality of macrophages bioprogramming was measured by morphological characteristic (light microscopy), cytokine production and surface macrophages markers expression (flow cytometry, Beckman Coulter, FC500).

**Results:** Changing of macrophages microenvironment with FBS concentration and the level of TGF-β and SP-D, respectively, purposefully programmed macrophages phenotype on M1 proinflammatory, or M2 antiinflammatory, shifting the immune response to Th1 or Th2, respectively. Decreasing FBS concentration to 0% programmed macrophages to M1 phenotype which was confirmed by morphological characteristic, cytokine production and macrophages markers expression. The consecutive increasing of FBS concentration from 20% to 40% led to bioprogramming of macrophages on M2 phenotype and Th2 response development with close relationship to concentration.

**Conclusions:** Serum model of reprogramming was effective in regulation of immunomodulation strategy for COPD patients. Our results show that FCS have the capability to undergo phenotypic plasticity, depending on culture conditions. Further work is required to understand the factors affecting FCs differentiation upon localisation to the ASM in asthma and the resultant contribution of FCs to ASM dysfunction.
Erika Cagnoni

mature dendritic cells in fatal asthma

expression of factor XIIIa+ cells, CD207+ Langerhans cells and CD83+ subsets.

Figure 1

Fien Verhamme

subsets (IRF8) gene impair differentiation of mononuclear phagocytes into dendritic cells (DC) and confer susceptibility to mycobacterial disease. In autosomal recessive interferon regulatory factor 8 (IRF8) gene impairment, CD14+ DC in the skin is very low, whereas numbers of Langerhans cells are normal, implicating important heterogeneity in dermal DC (Hamblyton et al., N Engl J Med 2011). Since infection with Mycobacterium tuberculosis occurs via inhalation, we investigated the expression of IRF2, IRF4 and IRF8 in the 3 major resident pulmonary DC populations: Langerhans-type myeloid DC (LDC), interstitial-type myeloid DC (intDC) and plasmacytoid DC (pDC).

Lung tissue was obtained from 4 subjects who underwent pneumectomy. DC were isolated by FACS from mononuclear cell suspensions of lung digestes to obtain highly purified (≥95%) DC subsets. LDC, intDC and pDC were identified as respectively langerin+, DC-SIGN+ and BDCA2+ cells in the low autofluorescent, CD3 and CD19 fraction. RNA was extracted and expression of IRF2, IRF4, IRF8 and housekeeping genes GAPDH, HPRT1 and PPIA was analyzed by RT-PCR.

Expression of IRF8 was significantly higher in pDC compared with both LDC and intDC. LDC had the lowest IRF8 expression (Figure 1). Expression of IRF2 and IRF4 did not differ between the DC subsets.

These results suggest distinct roles of IRF8 in the development of human lung DC subsets.

P814

Expression of factor XIIa+ cells, CD207+ Langerhans cells and CD83+ mature dendritic cells in fatal asthma

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Rationale: Dendritic cells (DCs) are a heterogeneous class of antigen presenting cells that initiate immune responses in the lung. Little information is known about the expression of different DCs in the airways and lymph nodes (LNs) of asthmatics. The aim was to study the expression of CD83+ mature DCs, CD207+, Langerhans cells, and factor XIIa+ reticular DCs in mediastinal LNs and airways of patients that died of asthma.

Methods: We studied 10 non-smoker fatal asthma patients (FA) and 8 non-smoker individuals that died of non-pulmonary causes (controls, CTLRs). Immunohistochemistry was performed with antibodies against CD83, CD207 and factor XIIa. The total area stained with anti-CD83/CD207 antibodies was measured on the cortical area of the LNs and on the internal, airway smooth muscle and external layers of the cartilaginous airways. Factor XIIa was analyzed only on LNs.

Results: CD83 and CD207 stained cells in the airways and all antibodies stained cells in the LNs of FA and CTLRs. No differences were found in the areas stained with CD83, CD207 and factor XIIa between FA and CTLRs. In fatal asthma CD83+ stained area in LNs correlated with CD207+ stained area in LNs (r = 0.65; p = 0.01) and CD207+ stained area in LNs correlated with CD83+ stained area in the internal (r = 0.79, p = 0.006), muscle (r = 0.78, p = 0.008) and external (r = 0.73, p = 0.02) layers of the airways. A fatal asthma episode is not associated with an increased expression of Langerhans cells, factor XIIa+ reticular cells and mature CD83+ DCs in cartilaginous airways or thoracic LNs. In asthma however, some DC cell trafficking between airway mucosa and LNs seems to occur.

P815

TCR V-beta usage in patients with sarcoidosis

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Sarcoidosis is a granulomatous disease of unknown aetiology, mainly affecting the lungs. Elevated numbers of activated T cells are found in bronchoalveolar lavage (BAL) fluid. HLA-DRB1*0301 (DR3)+ patients, who typically have Löfgren’s syndrome, are characterized by good prognosis and an accumulation of lung CD4+ T cells using the T cell receptor (TCR) gene segment Valpha2.3 (AV2S3). However, the corresponding β-chains that are part of the TCR have been poorly characterized, and there is only limited knowledge about the TCR usage in non-acute patients.

We used antibody staining and flow cytometry to characterize TCR Vbeta usage in CD4+ and CD8+ T cell subsets in blood and BAL fluid samples from different sarcoidosis patient groups as well as from healthy controls. Overall, the TCR Vbeta usage of Valpha2.3 + CD4+ T cells was quite diverse, indicating a predominant role in antigen recognition only for the alpha chain in these T-cell expansions. However, a preference for selective use of Vbeta 22 was noted in one patient.

A higher degree of selective Vbeta expression in both BAL and blood of non-acute patients may be due to epitope spreading over time, with more antigenic epitopes available to trigger distinct T cells. The higher non-random TCR Vbeta usage in the lung compared to blood could be related to antigenic triggering at the site of active disease, although more BAL samples of healthy individuals should be analyzed to estimate the normal differences between lung and blood in this respect.

P816

CD4+/CD8+ T-cells ratio in patients with pulmonary tuberculosis

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Introduction: A wide range of immune components are involved in an effective immune response against M. tuberculosis. CD4+ and CD8+ T-cells are central for protection against active tuberculosis.

The purpose of this research was studying CD4+/CD8+ T-cells ratio and parameters of spirometry in 34 patients with pulmonary tuberculosis.

Material and methods: Parameters of spirometry, CD4+/CD8+ T-cells ratio were analyzed. Depending on CD4+/CD8+ T-cells ratio patients with pulmonary tuberculosis have been shared into 2 groups: 1 group - 18 patients CD4+/CD8+ ratio < 1.3; 2 group - 16 patients CD4+/CD8+ ratio ≥ 1.3.

There was no difference in age between groups. Student’s t-test was used in the statistical analysis. Significance level was set at 0.05.

Results: Mean values of parameters spirometry in each group are submitted on the diagram.
potential mechanisms for increased mass by migration, proliferation and survival assays. 

Contraction of collagen gels impregnated with ASM cultured with FCs for 3-4d vs ASM alone increased significantly (i.e. reduction in area under curve of gel size as a percentage of the original size plotted over 30 min (AUC50). Table 1). ASM wound healing (WH) increased significantly in the presence of supernatants (SNs) from FCs/ASM 7d cultures vs control media, but no additional WH was seen in the presence of FC or FC+ASM SNs vs ASM SNs alone (Table 1). ASM proliferation and survival was unaffected by culture with FCs/FC SNs for 7d.

<table>
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<th>Table 1</th>
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<tr>
<td>Control</td>
</tr>
<tr>
<td>Contraction (AUC50)</td>
</tr>
<tr>
<td>WH (cells moved into wound at 6h)</td>
</tr>
<tr>
<td>p&lt;0.05 vs control, *FC, **ASM; t-tests, n=3-5.</td>
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</table>

Localisation of FCs to the ASM-bundle could contribute to the hypercontractility of ASM in asthma, which is integral to the pathophysiology of asthma. The mechanism by which this occurs requires further investigation, but has the potential to provide future therapeutic targets.

P818

Airway wall responses to tidal breathing and deep inspiration

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Introduction: Mechanical stretch attenuates airway smooth muscle (ASM) force production, which may explain the reversal of bronchoconstriction (i.e. bronchodilation) following a deep inspiration (DI) in vivo. We measured the effect of simulated DI on both narrowing and ASM force in isolated bronchi.

Methods: Bronchial segments were dissected from pig lungs and maintained in organ bath chambers. Airway narrowing (% volume) to acetylcholine (ACh, 10$^{-7}$M - 3x10$^{-3}$M) was measured under static transmural pressure (Ptm) conditions and during fixed P0 oscillations simulating tidal breathing (3.5cmH2O) with interdial DI (25cmH2O). In a separate group of experiments, the above protocols were repeated using fixed volume oscillations to simulate tidal and DI breathing whilst measuring the increase in P0 produced by ASM contraction. Under each condition, airway wall stiffness was measured from the change in P0 and volume during tidal oscillations.

Results: Under static conditions, maximal response to ACh was 92.3m4.3% narrowing (ACh) and 73.5±9.2cmH2O P0 (ACh). DI to 25cmH2O reversed ~60% narrowing at low doses of ACh but had no affect at moderate or high doses, whereas fixed volume DI attenuated ASM force to 12.7±5.6% (ACh) conditions and during fixed P0 oscillations simulating tidal breathing (3.5cmH2O) with interdial DI (25cmH2O). In a separate group of experiments, the above protocols were repeated using fixed volume oscillations to simulate tidal and DI breathing whilst measuring the increase in P0 produced by ASM contraction. Under each condition, airway wall stiffness was measured from the change in P0 and volume during tidal oscillations.

Conclusions: The mechanical loading conditions present during tidal breathing and DI influence the airway response to mechanical stretch. Inhibition of bronchoconstriction to mechanical stretch is minimal during fixed P0m oscillations particularly at high levels of ASM activation.

P819

PI3K signalling may explain differential response of lung cells to mechanical stretch

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Alveolar epithelial cells may be subjected to increased mechanical stretch (MS) during ventilation although low tidal volume is applied. High amplitude MS impairs PI3K activity and leads to apoptosis in alveolar type II (ATII) cells. The response of human pulmonary microvascular endothelial cells (HPMEC), fibroblasts (HPF), human AS49 cells and rat ATII cells to MS is compared in this study.

Stretching patterns (frequency/strain) in culture media, but no additional data was chosen to mimic physiological breathing (P) and the effects of high frequency (fH), high amplitude (aH) and both (HFA). MS was compared with static cultures at 24h. Supernatant LDH, cell necrosis/apoptosis (Annexin V binding/propridium iodide-staining) and cellular PI3K activity (measured as phosphorylated Akt-kinase, pAkt) were analyzed. MS increased the release of LDH in all cell types. This effect increased with the Hf, aH and HFA stretching patterns. Viable HPMEC and ATII cells decreased significantly in response to MS with a minimum in the HfA and HfA group; predominately due to apoptosis. AS49 cells showed only a small decrease

in viable cells with little change in necrotic and apoptotic cells. HPE, however, did not undergo apoptosis in response to MS. Cellular PI3K content was reduced in response to MS in HPMEC and ATII cells, unchanged in AS49 cells and increased in HFA. PI3K stimulation increases the percentage of apoptotic cells. In contradiction with endothelial and epithelial cells, pulmonary fibroblasts do not undergo apoptosis and show increased PI3K in response to MS. In lung injury both may remain as a scaffold for the pulmonary structure leading the way for repair.

P820

Remodelling of cytoskeleton towards a softer cell by latrunculin prevents stretch-induced apoptosis in alveolar type II cells

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Background: Cyclic stretching of alveolar type II (ATII) cells is associated with alterations of the actin cytoskeleton that has been shown to induce apoptosis.

Objectives: We hypothesize that the cytoskeleton of ATII cells and its viscoelastic properties are involved in the mediation of high amplitude mechanical stretch-induced apoptosis. Therefore we investigated the influence of the actin-modulating drug Latrunculin D on viscoelastic properties and stretch-induced apoptosis of ATII cells.

Methods: Alveolar type II (ATII) cells from Sprague Dawley rats were exposed to cyclic stretching using a pattern characterized by frequency of 40 [min-1] and an amplitude of 30 [%]. During stretching cells were treated with Latrunculin D. After stretching we determined apoptosis and cell injury using an Annexin V-FITC Apoptosis Detection Kit and the CytoToxity Detection Kit. Further, elasticity measurements of Latrunculin treated cells were performed with the atomic force microscope (AFM) and the optical stretcher.

Results: Determination of elastic modulus using the AFM showed that Latrunculin reduced stiffness of ATII cells (83.5%). Using the optical stretcher ATII cells treated with Latrunculin showed a higher deformation than controls (25.3%). Treatment of overstretched cells with Latrunculin reduced significant the number of apoptotic cells (control 30.0%, Latrunculin 19.1%) and decrease the level of LDH (control 0.21 U/ml; Latrunculin 0.13 U/ml).

Conclusions: We conclude that the remodelling of cytoskeleton towards a softer cell is a protective mechanism against stretch-induced apoptosis in ATII cells.

P821

Surfactant release into the alveolar space protects the lung from ventilation-induced injury

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Objective: The aim of this study was to investigate mechanisms involved in resistance to ventilation-induced lung injury.

Methods: Sprague-Dawley rats were randomly exposed to an injurious low-stretch ventilation (V T =9 ml/kg, PEEP=5 cm H2O) (n=12) and an injurious high-stretch ventilation (V T =25 ml/kg, PEEP=0 cm H2O) (n=29). Animals were continuously monitored for a maximum period of 2.5 h. The high-stretch ventilation group (HV60) was subdivided in two groups: 1) animals showing a substantial P0 reduction and peak airway pressure (Paw) increase, sacrificed at 60 min (HV60=n=11); and 2) animals with insignificant Paw and Paw changes at 60 min (n=18), sacrificed at 150 min (HV150). Lung tissue, plasma, and bronchoalveolar fluid (BAL) were analyzed in the three groups. BAL provided native cytometric, inflammatory marker, and surfactant data.

Results: The HV60 group was characterized by leakage of plasma proteins into the alveoli, presence of hyaline membranes, high increase of inflammatory markers in BAL (TNF-α, MIP-2, MIP-1, C-reactive protein, and acidic sphingomyelinase), pronounced decrease of alveolar macrophages, and an accelerated conversion of freshly secreted active surfactant to inactive surfactant. In contrast, the HV150 group was characterized by high amount of active surfactant, absence of edema, and normal P0. These animals exhibited a slight decrease of alveolar macrophages and increase of some BAL inflammatory markers (IL6, TNF-α, MIP-2, and MIP-1).

Conclusions: These results suggest that increased surfactant release into the alveolar space safeguards the lung from ventilation-induced injury and that surfactant alteration might directly contribute to lung dysfunction.

97. The many roads to lung injury
Effects of PEEP-like cyclic stretch on the IL-6 protein production in normal human pulmonary artery endothelial cells in vitro

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Background and aim: Excessive cyclic stretch is one of the main causes of ventilator-induced lung injury. However, the molecular injury of the stretch injury has not yet been fully understood. The aim of the present study was to examine the effects of PEEP-like cyclic stretch on the IL-6 protein production in normal human pulmonary artery endothelial cells (HPAECS) in vitro.

Methods: Normal HPAECS were stretched by a Flexcell® FX-4000™ Tension System (Flexcell International). The stretching rate was 15 cycles/minute, and the cells were cyclically stretched from 0 to 5%, 0 to 10%, 0 to 20%, 3 to 20%, and 5 to 20%. Stretch from 3 to 20% and from 5 to 20% simulated excessive stretch during mechanical ventilation with PEEP. The cells were stretched for various durations (0, 1, 3, 6 and 12 hours). During the experiments, culture medium was sampled 0, 3, and 6 hours after stretch started. The IL-6 concentration of the samples was determined by ELISA.

Results: Excessive stretch (0 to 20%) significantly increased the IL-6 production of the cells stretched for more than 3 hours compared to the unstretched cells (n=5, P<0.05). Moderate stretch (0 to 5% and 0 to 10%) did not yet significantly increase the IL-6 protein production of the cells at any sampling points.

Conclusions: The IL-6 protein was produced by excessive cyclic stretch (0 to 20%). Excessive stretch production was suppressed by PEEP-like cyclic stretch (3 to 20% and 5 to 20%). This result suggests that HPAECS would be protected by PEEP during mechanical ventilation even if the cells are excessively stretched.

P823
LSC 2012 Abstract – Repair of the very immature lung following brief, injurious mechanical ventilation commences within 24 hours

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Background: Very preterm infants often require mechanical ventilation (MV). This intervention can cause lung injury that contributes to bronchopulmonary dysplasia. To investigate mechanisms of injury and repair in newborns we developed a novel method of ventilating the lungs of fetal sheep. Using this model MV-induced injury resolves within 15d, but it is not known when repair starts.

Methods: Pregnant sheep at 110d and 125d gestational age (GA; term=147dGA) were exposed to a continuous positive airway pressure (CPPAP) of 10cmH2O, at 12 breaths/minute with a PEEP of 5cmH2O. After stretching we determined PKC-expression by Western blot. Next, we treated Mike cells with PMA during stretching reduced the number of apoptotic cells (control 32.8%; PMA 16.1%). Inhibition of PKC using staurosporin increased the number of apoptotic cells (control 32.8%; PMA 22.7%; Staurosporin 36.1%).

Conclusions: We conclude that activation of PKC is able to promote apoptosis in stretched cells. Remodeling of cytoskeleton to a softer cell by PKC seems to be a possible mechanism for it.

Kallistatin protects against LPS-induced mouse lung injury

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Acute lung injury (ALI) is caused by overwhelming lung inflammation, resulting in diffuse alveolar damage, edema, and subsequently respiratory dysfunction. The mortality remains high, and the treatments are exclusively supportive because of lacking selective and efficacious pharmaceutical agents targeting on the pathogenesis of ALI. Kallistatin is a serine protease inhibitor that exhibits pleiotropic functions in vasodilation, anti-angiogenesis, anti-inflammation, and anti-apoptosis, which may contribute to its therapeutic effects in a variety of human diseases. Kallistatin is also found in the lungs, implicating its involvement in the regulation of lung functions. However, the role of kallistatin in the pathophysiology of ALI is still unclear. Herein, we hypothesized that kallistatin plays a role in protection against lung injury. Using kallistatin gene-transfered mice by delivering plasmid DNA encoding human kallistatin into the lungs, we examined the protective effect of kallistatin against LPS-induced lung injury. We found that the severity of lung injury was attenuated in kallistatin gene-transfered mice compared with untreated mice, indicated by decreasing cell counts, LDH and protein levels of bronchoalveolar lavage fluids (BALF). BALF levels of TNF-α, IL-1β, IL-6, and IL-8 were also lower in human kallistatin gene-transfered mice than untreated mice, suggesting a decline in inflammatory response after LPS treatment. In addition, the kallistatin gene-transfered mice showed less extent of epithelial cell apoptosis shown by TUNEL staining. Our data demonstrate for the first time that kallistatin protects against LPS-induced lung injury through attenuation of inflammation and epithelial cell apoptosis.

P826
Plant proteasome from Bauhinia bauhinioideis Kallikrein inhibitor (BbKk) attenuates mechanics, inflammation and remodelling induced by elastase in mice

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Proteasome plays a key role on emphysema development. This study evaluated the capacity of the plant proteasome inhibitor BbKk in the inactivation of elastase and its response modulator.

Methods: C57Bl6 mice received elastase intratracheal or saline (Ve group). After one month mice were treated with BbKk (2mg/kg) on days 1, 4, 12 after elastase instillation (E-group) or saline instilation. On day 30 mice were anesthetized and mechanically ventilated and we analyzed respiratory system resistance (Rrs), elastance (Ers), tissue elastance (Hts), tissue damping (Gms), airway resistance (Raw) and exhaled nitric oxide (ENO). Afterwards, bronchoalveolar lavage fluid (BALF) was performed and lungs were removed. By morphometry, we quantified the mean linear intercept (Lm), and the amount of collagen and elastic fibers in distal lung parenchyma.

Results: In elastase group there was a significant increase in the Ers, Rrs, Raw, Hts, Lm, ENO, total and, macrophages, neutrophils and lymphocytes in BALF, and elastic and collagen fibres compared to controls (p<0.05). The BbKk treatment of elastase group decreased the Lm (59.3±4.7 μm), Raw (0.33±0.05 cmH2O/ml/s), Ers (36.8±5.73 cmH2O/L), Rrs (0.84±0.19 cmH2O/ml/s), Hts (37.3±6.2 cmH2O/L), cells/mLs), neutrophils (19.3±9.1±106 cells/mls), lymphocytes (19.5±1±2±104 cells/mls) in the BALF, ENO (19.6±8.33 μm), and elastic fibers content (30%±0.1%) compared to E-group (p<0.05).

Conclusions: This proteasome inhibitor (BbKk) reduced elastase-induced pulmonary inflammatory and extracellular matrix remodeling alterations. Financial Support: FAPESP, CNPq, LIM-20 HCFMUSP.
A single dose of a specific serpin inhibitor attenuated the protease-antiprotease imbalance in an experimental model of emphysema. Claire R. Oliveira1, Juliana D. Lourenço1, Luciana Neves1, Francine Almeida1, Carla M. Prado1, Iolanda C.L. Tibério1, Aparecida Tanaka2, Sergio Saaksi2, Milton A. Martins1, Fernanda D.T.Q. Lopes1, 1Medicine, School of Medicine of University of Sao Paulo, SP, Brazil; 2Biological Science, Universidade Federal de Sao Paulo, SP, Brazil; 3Medical Chemistry, Universidade Federal de Sao Paulo, SP, Brazil; 4Human and Natural Science, Universidade Federal do ABC, Sao Paulo, SP, Brazil

We showed that a single dose of specific serpin inhibitor in mice attenuated parenchymal destruction with an improvement in lung function in emphysema.

Objectives: To study the possible effects of this inhibitor in pathological mechanisms that contribute to emphysema.

Methods: Mice were submitted to either a nasal instillation of porcine pancreatic elastase (PPE) or saline (S) and 1h after, animals received a second nasal instillation of either a protease inhibitor (r-BMIA, 35.54mol) or vehicle (VE). After 21 days, we evaluated the number of macrophages (MAC) and cells expressing metalloproteinase 12 (MMP-12). We measured the protease-antiprotease imbalance. We quantified caspase-3 to evaluate apoptosis and expression of 8-iso-prostanate as a marker of oxidative stress.

Results: We observed an increase in MAC in groups that received PPE and only PPE-VE group showed higher values of MMP-12. There were no differences between groups when we analyzed caspase-3 and 8-iso-prostanate.

<table>
<thead>
<tr>
<th>SAL-VE</th>
<th>SAL-BMIA</th>
<th>ELA-VE</th>
<th>ELA-BMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC-2 (cells/mm³)</td>
<td>1.59±0.406</td>
<td>1.85±0.287</td>
<td>2.60±0.367*</td>
</tr>
<tr>
<td>MMP-12 (cells/mm³)</td>
<td>1.47±0.254</td>
<td>1.69±0.180</td>
<td>2.79±0.235**</td>
</tr>
<tr>
<td>Caspase-3 (cells/mm³)</td>
<td>1.30±0.218</td>
<td>1.47±0.154</td>
<td>1.46±0.202</td>
</tr>
<tr>
<td>8-iso-prostanate (%)</td>
<td>2.65±0.477</td>
<td>4.05±0.477</td>
<td>2.92±0.624</td>
</tr>
</tbody>
</table>

*Compared to control groups; **compared to other groups.

Conclusions: Although this inhibitor treatment has not diminished the macrophages in animals that received PPE, it reduced MMP-12 positive cells, suggesting that the improvement in parenchyma destruction and in lung function occurred due to attenuation in protease-antiprotease imbalance. Supported by FAPESP, LIMHC-FMUSP, Brazil.

P828

Plant proteinase inhibitor from Enterolobium contortisiliquum (EcTI) attenuates elastase-induced pulmonary inflammatory, remodeling and mechanical alterations in mice

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Aims: To evaluate if a plant Kumit; proteinase inhibitor EcTI contributes to inactivation of elastase-induced mechanical, inflammatory and remodelling alterations.

Methods: C57Bl/6 mice received elastase (E-group). Control group received saline (VE-group). Mice were treated with EcTI (2mg/kg) on days 1, 14 and 21 after elastase instillation (IE-group). On day 30, mice were anesthetized, mechanically ventilated and we analyzed respiratory system resistance (Rrs) and elastance (Ers), tissue damping (Gtis), airway resistance (Raw) and exhaled nitric oxide (ENO).

Results: In-8 group there was a significant increase in the Ers, Raw, Hts, Lm, ENO, total cells and macrophages, neutrophils and lymphocytes in BALE, elastic and collagen fibers compared to controls (p < 0.05). In IE-group there was a decrease in Lm (57.63±5.5μm), Raw (0.29±0.05cmH2O/ml/s), Hts (39.47±0.02%), total cells (1.17±0.104 cells/ml) and ENO (0.00±0.01 104 cells/ml) in BALE compared to ELA group (p < 0.05).

Conclusions: This proteinase inhibitor (EcTI) reduced elastase-induced pulmonary inflammatory, remodeling and mechanical alterations induced by elastase. Although more studies need to be performed, this inhibitor may contribute as potential therapeutic tool for COPD management.

P829

Treatment with proteinase inhibitor, BbCI, modulates inflammatory response, mechanic alterations, and remodeling on elastase-induced emphysema in mice

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Bubiha bauhinioiides Z Crucipain Inhibitor (BbCI) is a proteinase inhibitor that neutralizes neutrophil elastase and cathepsin G. The present study evaluated the capacity of BbCI in the treatment of elastase-induced emphysema.

Methods: Mice received elastase intratracheally (EAL group) or saline (SAL group). Afterwards, mice were treated with BbCI (2 mg/kg) at days 1, 15 and 21 after elastase (EALBI group) or saline instillation (SALBI group). At day 28, mice were ventilated and respiratory resistance (Rrs), elastance (Ers), tissue elastance (Hts), tissue damping (Gtis), airway resistance (Raw), and exhaled nitric oxide (ENO) were analyzed, and BALF was obtained. We also quantified, mean linear intercept (Lm), elastic and collagen fibers.

Results: In ELA group, there was a significant increase in the Ers, Rrs, Hts, ENO, total cells, macrophages, neutrophils and lymphocytes in BALE, elastic and collagen fibers compared to controls (p < 0.05). In ELA group, we observed a decrease in Ers (37.08±1.6 cmH2O·L⁻¹·s⁻¹), Hts (39.47±1.7 cmH2O·L⁻¹·s⁻¹), Lm (58.2±7.5) μm, elastic content (0.34±0.03%); total cells (11.7±0.1 104 cells/ml) and neutrophils (0.00±0.01 104 cells/ml) in BALE compared to ELA group (p < 0.05).

Conclusions: The treatment with BbCI reduced inflammatory, mechanics and extracellular matrix remodeling alterations induced by elastase. Although more studies need to be performed to elucidate the mechanisms involved in this process, we may consider BbCI as a therapeutic tool for COPD management.

Supported by: FAPESP, CNPq, LIM-20 HCFMUSP.
anti-inflammatory system in several diseases and ACh release depends on neu-
rotransmitter storage in synaptic vesicles mediated by the vesicular acetylcholine transporters (VACHT).

Aim: To investigate the role of the cholinergic system on emphysema in mice with reduced levels of ACh release.

Methods: Mice with decreased expression of VACHT (VACHT KDHOm 70%) (HOM) and littermate wild-type mice (WT) received intranasal elastase or saline on day 0. On day 28, pulmonary mechanics, bronchoalveolar lavage fluid (BALF), mean linear intercept (Lm), elastic and collagen fibers in alveolar septa were evaluated.

Results: WT-treated elastase animals presented a reduction in tissue elastance (Hiss) and an increase in Lm, total cells and macrophages in BALF, and colla-
gen and elastic fibers in lung parenchyma compared to saline groups (p<0.05). The HOM-treated elastase animals presented high values of total cells, macro-
phages, lymphocytes and neutrophils in BALF compared to WT-treated elastase group (p<0.05). There were no differences between WT-treated elastase and HOM-treated elastase groups. Lm, collagen and elastic fibers contents between.

Conclusions: Reduction of endogenous ACh worsens pulmonary inflammation in mice with emphysema without changing pulmonary function and remodeling, suggesting that the major determinant of pulmonary inflammation in this model. Our results suggest however a major role of the cholinergic anti-inflammatory system in the control of inflammatory response induced by elastase.

P832 Activation of the coagulation system following exposure of mice to chlorine Nadiya Monogarova1, Inna Vasilenko2, Olena Semendyayeva3, Natalia Surgay2, Chair of Pathomorphology, Donetsk National Medical University named after M. Gorky, Donetsk, Ukraine; 2Chair of Pulmonology, Donetsk National Medical University named after M. Gorky, Donetsk, Ukraine

Chlorine (Cl2) is a highly irritant and reactive gas produced in large quantities throughout the world. The accidental release of large amounts of Cl2 in 30 large cities has caused significant injury to humans and animals. Our previous findings show that exposure of rodent to Cl2 causes both pulmonary and systemic injury (Zorziannis et al. J Respir Cell Mol Biol, 2011; 15(2):386-92). Honwar et al Am J Respir Cell Mol Biol, 2001; 145(2):419-25). Herein we tested the hypothesis that exposure to Cl2 activates intraalveolar and systemic coagulation cascades which in turn may contribute to the development of lung and other end-organ injury. Male C57B16 mice (6-8 weeks) were exposed to either Cl2 (600 ppm for 45 minutes in environmental chambers) or air (0 ppm). Mice were returned to room air and sacrificed immediately or at 1 h post-exposure and their lungs were lavaged. Mice exposed to Cl2 had much higher levels of Thrombin/antithrombin (TAT) antigen (measured by ELISA) as compared to those exposed to air both in the BAL (10±2 ng/ml vs. 0.5 ± 0.1; mean ± SE; n=6; p<0.01) and plasma (25±1 ng/ml vs. 0.1±0.05; mean ± SE; n=6; p<0.05) at 1 h post exposure. In addition, clotting time in the blood (measured by thromboplastin time) was significantly prolonged in Cl2 exposed mice as compared with air controls (275±25 sec. vs. 150 ±10; mean ± SE; n=6; p<0.01). In contrast, there was no significant change in the clotting time blood taken from mice immediately after Cl2. Taken together, these data demonstrates a strong activation of the coagulation with the airspace as well as development of a systemic disseminated intravascular coagulation after Cl2 exposure in mice.

P833 Novel swine model of transfusion-related acute lung injury (TRALI) Fatima Telavarys Ceric1,1, Karl Otto Larsen1, Oystein Sandanger2, Else Marit Laberg3, Geir Arve Christensen1, OleHenningSkjønsberg1, 1Department of Pulmonary Medicine, Oslo University Hospital Ulleval, Oslo, Norway; 2Institute for Experimental Medical Research and Center for Heart Failure Research, Oslo University Hospital Ulleval, University of Oslo, Oslo, Norway; 3Research Institute for Internal Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway; 4Department of Pathology, Oslo University Hospital Ulleval, Oslo, Norway

Aim: To study circulating levels of IL-18 during one week of hypoxia exposure in mice, and to investigate whether induction of IL-18 correlates with inflammatory changes in lung parenchyma.

Methods: IL-18 levels in blood was determined in C57Bl/6j mice (n=4 at each time point) exposed to hypoxic conditions at 6 hours (h) and 1-7 days. Lungs were harvested at each time point for histological analyses. Concentration of MIP-2 in blood was determined at 6h, 12h, 1-3 days.

Results: The levels of circulating IL-18 were significantly increased at all time points peaking at day 1 (Figure 1A) compared to normocitic controls. Histology revealed perivascular infiltration of neutrophil granulocytes increasing from day 1 to
to day 3. At day 7 neutrophils were still present, but to a lesser extent than at day 3. The concentration of MIP-2 was significantly increased at day 1 (Figure 1B).

Conclusions: The increase in IL-18 induced by alveolar hypoxia may promote the subsequent influx of neutrophils in lung parenchyma, possibly mediated through the neutrophil chemoattractant MIP-2.

P836
Combined treatment with EPO and MSC can reduce acute lung the atrophy of the corresponding zones in the other groups. LPS + EPO group were found in the lymphoid tissue - considerable hyperplasia infiltration and kidney tubular necrosis. The most significant differences in the group 5 we observed significantly less leukocyte lung interalveolar septal injury and kidney damage, cause hyperplasia of lymphoid tissue and enhance the injury and kidney damage, cause hyperplasia of lymphoid tissue and enhance the

P837
Mesenchymal stem cells and recombinant erythropoietin treatment in an experimental sepsis model
Alexander Averyanov1, Anatoly Konoplyannikov2, Fedor Zaborzlaev3, Dmitry Akulishn1, Oleg Kozlov1, Anastasia Sorokina1, Biomedical Technologies Dept., Federal Research Clinical Center of the Specialized Types of Health Care and Medical Technologies FMBA of Russia, Moscow; 2Cell Technologies Dept., Medical Radiology Research Center, Obninsk, Russian Federation

As recently found the surface of mesenchymal stem cells (MSCs) have receptors for erythropoietin (EPO), we hypothesized that the introduction of EPO together with MSCs may enhance their effect and improve efficiency of sepsis treatment.

Aim: To evaluate effects of combined treatment with EPO and MSC in an experimental LPS sepsis model.

Methods: 50 Wistar rats were randomized into 5 groups: Group 1 - the healthy controls, Groups 2-5 were intraperitoneally introduced bacterial LPS 20 mg/kg. Two hours later LPS injection animals received the following intravenous treatments: Group 3: 4 x 10^6 allogeneic MSCs, Group 4: 8.5 μg of recombinant EPO-beta, Group 5: MSCs and EPO in the same doses. Surviving animals were euthanased on the 4th day.

Results: The highest white blood cells count was determined in group 5 (8.15 x 10^9 cells/ml) compared with controls (2.15 x 10^9 cells/ml) and LPS controls (6.52 x 10^9 cells/ml). Serum IL-1β level in groups 2 and 4 was significantly higher than in healthy and treated with MSCs and EPO + EPO animals. Histologically in the group 5 we observed significantly less leukocyte lung interalveolar septal infiltration and kidney tubular necrosis. The most significant differences in the LPS + EPO group were found in the lymphoid tissue - considerable hyperplasia of spleen white pulp up to 64.9% and thymus cortex up to 69.7% in contrast to the atrophy of the corresponding zones in the other groups.

Conclusions: Combined treatment with EPO and MSCs can reduce acute lung injury and kidney damage, cause hyperplasia of lymphoid tissue and enhance the immune response more than separate treatment in an experimental model of sepsis in rats.

P838
Derivation and characterization of young and aged stem cell populations in an interleukin 1 receptor antagonist mouse model system
Daniel Pelaz1, Robert Jackson1, Qingzhou Li1,2, Roy Levin1,4,5, Herman Cheung1,6,7,8, 1Geriatric Research Education and Clinical Center, Miami Veterans Affairs Medical Center, Miami, FL, United States; 2Research Service, Miami Veterans Affairs Healthcare System, Miami, FL, United States; 3Department of Anesthesiology, University of Miami Miller School of Medicine, Miami, FL, United States; 4Anesthesiology, Miami Veterans Affairs Medical Center, Miami, FL, United States; 5Hussman Institute of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, United States; 6Department of Biomedical Engineering, University of Miami, Coral Gables, FL, United States

Recent evidence suggests that the IL1 receptor antagonist (IL1RN) assumes an important role in regulating stem cell senescence, and a deficiency of IL1RN may contribute to impaired lung tissue repair associated with COPD pathogenesis. Here we isolated stem cells from the teeth of transgenic mice and compared them to bone marrow (BM) derived stem cells from control B6C3 F1 mice. B6 IL1RN overexpressing transgenic mice (T16); and B6 IL1RN knockout mice (IL1RN KO) and tested the hypothesis that the IL1 pathway would also regulate stem cell functions in this unique dental stem cell pool. BM cells were obtained by flushing the medullar space of both femurs and establishing adherent cultures. Dental cells were obtained by digesting excised teeth and mandibular pocket overnight, followed by plating single cell suspensions for culture. Cells were then analyzed by immunohistochemistry for stem cell associated as well as for endothelial pro- genitor and pluripotency-associated markers. A viable stem cell population was obtained and established from the BM and the dental tissues of all mice strains. BM stem cell populations displayed CD105 and KDR surface markers and contained populations expressing the VEGER2 endothelial progenitor marker, indicating a possible population of circulating endothelial progenitors. Dental cells from both young (8 wks) and old (10 mo) animals contained the pluripotency associated markers OCT4, Sox2, and NANOG, as well as the CD105 and Connexin43 surface markers. These results demonstrate that dental tissue derived precursor cells may be obtained from transgenic mice and tested in experimental emphysema models.

P839
Factors predicting exercise-induced oxygen desaturation in stable COPD
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Background and objective: Some resting pulmonary function and blood gas parameters might predict exercise-induced oxygen desaturation in patients with stable COPD. We aimed at studying these factors.

Patients and methods: We tested 55 patients with stable COPD (FEV1/FVC%: 45.31). Resting pulmonary function, arteriolar blood gases, echocardiography, and incremental cardiopulmonary exercise testing were done for all patients. We classified exercise caused desaturation as significant (FEV1% predicted <90%) and non-significant (FEV1% predicted ≥90%). We compared desaturated (DS) with non-desaturated (NDS) patients.

Results: Exercise induced oxygen desaturation (DS) occurred in 28 subjects while 27 were non-desaturated (NDS). FEV1% of predicted was significantly lower in DS (33.75±10.28) than NDS patients (49.4±19.86, P<0.001). Diffusing capacity DLCO % predicted was significantly lower in DS (47.54±20.25) than NDS patients (67.35±19.62, P<0.001). Resting O2 saturation SaO2% was significantly lower in DS (91.9±2.88) than NDS patients (95.94±2.9, P<0.001). Resting PaCO2 mmHg was significantly higher in DS (63.46±11.58) than NDS patients (38.97±6.38, P<0.001). Pulmonary artery systolic pressure mmHg was significantly higher in DS (42.21±11.90) than NDS (34.15±12.14, P<0.01). Medical Research Council MRC dyspnea score was significantly lower in DS (3.5±0.69) than NDS patients (2.4±0.97, P<0.001). On the other hand, there were no statistically significant differences in FEV1/FVC%, total lung capacity, residual volume, and resting heart rate between the DS and NDS patients.

Conclusion: FEV1 %, DLCO, resting SaO2, resting PaCO2, pulmonary artery sys- tolic pressure and MRC dyspnea score can predict exercise-induced desaturation in stable COPD.

P840
A 4-min, self-paced step test to assess exercise impairment in COPD patients
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Background: There is a long-standing interest in developing “field” exercise tests for patients with chronic obstructive pulmonary disease (COPD) which can be easily performed in the consulting room with a minimum of technical support.

Objectives: To investigate whether a 4-min, self-paced step test (4MST) would be useful to assess exercise tolerance and oxygen/hemoglobin desaturation by pulse oximetry (SpO2) in a large group of outpatients with COPD.

Methods: 191 patients (GOLD stages: I= 16, II= 63, III= 79, IV= 33) prospectively underwent the 4MST. Patients were allowed to stop the test as needed and re-start it within the allowed 4-min.

Results: There were no significant test-related complications. There was a large variability in the steps climbed (ranging from low 20’s to more than 100). Based on the number of steps climbed, patients were separated into sub-groups of progressive impairment (Group A, N≥ 62; Group B, N= 61; Group C, N= 68). Group

98. Exercise capacity: from elite athletes to severe impairment
A patients were significantly younger than those of Group B and C (p < 0.05).

The number of interruptions during the tests increased from Group A to B (p

addition, this variable and the steps climbed were significantly correlated (r=

The number of interruptions during the tests increased from Group A to B; in

Factors associated with aerobic fitness in adolescents with asthma

Sveinnja Birna Mennhag1, Karin C. Ludvig Carlsen2,3, Sigurd Alfred Anderssen4,5,6, Peter Mowinckel1,7, Kai-Håkon Calrsen3,4,1, Department of Public Health, Sport and Nutrition, University of Agder, Kristiansand, Norway; 2Department of Paediatrics, Oslo University Hospital, Oslo, Norway; 3Faculty of Medicine, University of Oslo, Norway; 4Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway.

Background: In adolescents with asthma, information on factors associated with aerobic fitness levels is limited. The present study aimed to determine if physical activity as well as skin fold thickness, asthma exacerbations, use of inhaled corticosteroids or lung function influences direct measurements of peak oxygen uptake (VO2peak) in adolescents with asthma.

Methods: From the general population based birth cohort, Environment and Child-

hood Asthma study in Oslo, Norway, in a nested case-control study 86 13 years-old adolescents with and 76 without asthma performed maximal running on a treadmill with VO2peak measured. The sum of four skin fold thicknesses was recorded, fol-

lowed by wearing an activity monitor for four consecutive days. Lung function was measured by maximum forced expiratory flow-volume curves and body plethys-

mography. Asthma exacerbations and use of medication were registered by parental

structured interview. Data were analyzed using multiple regression analysis.

Results: Vigorous physical activity (coefficients with 95% confidence intervals; 1.73 (0.32 - 3.14) and body fat -0.35 (-0.41, -0.28)) were significantly associated with VO2peak in adolescents with asthma. Neither use of inhaled corticosteroids, lung function nor number of asthma exacerbations was associated with VO2peak when taking physical activity and skin fold thickness into account. In the adolescents without asthma only skin fold thickness was associated with VO2peak.

Conclusions: VO2peak appears to be determined by vigorous physical activity level and skin fold thickness in Norwegian adolescents with asthma and not by asthma related factors such as use of inhaled corticosteroids, lung function nor number of asthma exacerbations.

P842 Predicting VO2max in elderly: Could equations established in younger

P843 Reference values for cardiorespiratory fitness in a 20 – 85 year old population

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Background: Existing reference values used during clinical exercise testing have been obtained with rather small none randomly sample sizes, lack of women and elderly or poor maximal end-criteria. The aim was to establish reference values during maximal exercise in a representative sample of men and women.

Methods: 904 randomly sampled healthy men and women (20 – 85 yr old) measured in a modified Bakle protocol to exhaustion.

Results: 759 participants met the criteria for an acceptable VO2max, based on RER>1.10 or BOR≥17. In the age group 20-29, the VO2max (ml/kg·min−1) was 40.3 (SD 7.1) and 48.6 (SD 9.6) in women and men, respectively. A linear decline (6% per decade) was observed after age 30 in both genders.

Physiological responses at maximal exercise, mean (SD)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>192.2 (7.7)</td>
<td>187.8 (8.8)</td>
<td>181.1 (11.2)</td>
<td>171.3 (13.0)</td>
<td>164.4 (13.6)</td>
<td>155.4 (14.0)</td>
</tr>
<tr>
<td>VO2peak (L/min)</td>
<td>0.43 (0.42)</td>
<td>0.72 (0.43)</td>
<td>1.26 (0.45)</td>
<td>1.55 (0.44)</td>
<td>1.46 (0.36)</td>
<td>1.21 (0.37)</td>
</tr>
<tr>
<td>Minute ventilation (L/min)</td>
<td>119 (28)</td>
<td>118 (30)</td>
<td>106 (31)</td>
<td>96 (27)</td>
<td>88 (23)</td>
<td>68 (23)</td>
</tr>
<tr>
<td>Breathing reserve (%)</td>
<td>28 (12)</td>
<td>24 (13)</td>
<td>25 (15)</td>
<td>27 (13)</td>
<td>26 (14)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>RER</td>
<td>1.22 (0.09)</td>
<td>1.23 (0.10)</td>
<td>1.21 (0.10)</td>
<td>1.19 (0.11)</td>
<td>1.17 (0.11)</td>
<td>1.13 (0.11)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>169 (25)</td>
<td>174 (23)</td>
<td>182 (24)</td>
<td>186 (25)</td>
<td>193 (27)</td>
<td>197 (28)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74 (15)</td>
<td>76 (18)</td>
<td>81 (18)</td>
<td>81 (19)</td>
<td>81 (20)</td>
<td>81 (20)</td>
</tr>
<tr>
<td>Blood lactate (mmol/L)</td>
<td>10.9 (2.6)</td>
<td>11.5 (2.8)</td>
<td>13.0 (2.9)</td>
<td>8.6 (2.8)</td>
<td>7.4 (2.5)</td>
<td>5.9 (2.2)</td>
</tr>
<tr>
<td>BORG scale (6-20)</td>
<td>17.9 (3.1)</td>
<td>17.9 (1.2)</td>
<td>17.4 (1.5)</td>
<td>17.3 (1.5)</td>
<td>17.2 (1.3)</td>
<td>17.6 (1.9)</td>
</tr>
</tbody>
</table>

Conclusions: The present study establishes VO2max, and other typical cardiorespiratory variables during maximal exercise and may be used as reference values.

P844 Exercise in patients with lymphangioleiomyomatosis: Performance and the prevalence of dynamic hyperinflation

André Albuquerque, Bruno Baldi, Suzana Pimenta, Joao Marcos Salge, Ronaldo Katulski Carlos Carvalho. Respiratory Department, Heart Institute (Incor) - University of Sao Paulo Medical School, Sao Paulo, Brazil.

Introduction: Previous studies suggested multiple factors for exercise cessation in LAM. Although airflow limitation is frequent in LAM, the dynamic hyperinflation (DH) and its repercussions during exercise have not been evaluated yet.

Objectives: To evaluate the prevalence and repercussions of DH in LAM and also the dynamic responses during maximal exercise, in comparison to controls.

Methods: 42 patients performed pulmonary function tests (PFT) and symptom-

limited incremental cycle exercise, in comparison to ten age-matched healthy women.

Dyspnea intensity, inspiratory capacity, oxygen saturation (SpO2), car-

diac, metabolic and respiratory variables were obtained during exercise. 6MWT was performed by LAM patients indeed.

Results: Compared to controls, LAM had higher baseline dyspnea, obstructive pattern, air trapping and lower DLCO in PFT. In LAM, maximal exercise perfor-

mance was reduced, associated with ventilatory limitation, greater desaturation and dyspnea. DH occurrence was higher in LAM than controls (55 vs. 0%), with a significant correlation to airflow obstruction, air trapping and DLCO. Patients who developed DH had not only a ventilatory contribution to exercise cessation on cycling, but also greater desaturation and dyspnea intensity during 6MWT, compared with non-DH subgroup.

Conclusions: Ventilatory limitation is an important reason for exercise cessation in LAM, compared with controls. DH was prevalent and had association with severity of disease, higher dyspnea and lower SpO2. On 6MWT, desaturation and increased dyspnea were greater in DH subgroup. Future interventions to reduce DH might contribute to improve dyspnea and exercise tolerance in LAM.
Exercise respiratory cycle time components in patients with emphysema

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Background: We have recently demonstrated that in patients with COPD the severity of emphysema (E) measured by high resolution computed tomography (HRCT) correlated with: ratio VTepeak/FEV1; VE/VCO2 slope and PETCO2 values at peak exercise. The aim of this study was to further investigate if exercise respiratory cycle time components correlated with % of E measured by HRCT.

Method: Twelve patients (age = 65.1±8 yrs; FEV1 = 55±17%pred) with moderate to severe E (quantified by lung HRCT as % voxels < -910 HU) were evaluated with incremental cardiopulmonary exercise testing (CPET). Mean inspiratory time (TiM), mean total respiratory cycle time (TotM), mean expiratory time during exercise (TeM-end) and mean expiratory time during the last third of exercise (TeM-end) has been calculated.

Results: Both TeM and TeM-end had a good linear correlation with % of E (r = 0.61, p = 0.004 and r = 0.63, p = 0.003).

Conclusions: VO2 is highly influenced by oxygen utilization in exercising muscles, as well as by blood oxygenation levels and cardiac function. However, the impact of skeletal muscle utilization during exercise on VO2peak varied greatly among the patients.

P847

Inspiratory muscle constraint during exercise in patients with pulmonary arterial hypertension

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We examined the impact of potential inspiratory muscle constraint on dynamic operating lung volumes response during symptom-limited incremental cardiopulmonary cycle exercise testing (CPET) in patients with pulmonary arterial hypertension (PAH).

Thirty-three young non-smoking PAH patients (idiopathic=26; heritable=7) with normal body mass index and no spirometric evidence of obstructive ventilatory defect (FEV1/FVC=115±10% predicted) performed a CPET to limit of tolerance. Ventilatory profile, operating lung volumes [derived from inspiratory capacity (IC) measurements] and inspiratory flow reserve (IFR), an indirect index of inspiratory muscle constraint/fatigue, were assessed throughout CPET.

Twenty-two patients (67%) decreased IC (i.e., dynamic hyperinflation) throughout exercise by 0.5L (PAH-H), whereas the remaining patients (33%) increased IC by 0.36L (PAH-NH). V̇E and V̇O2 at peak exercise were considerably different among the two groups. Despite these differences in operating lung volumes response, IFR at peak exercise was not statistically different between PAH-H and PAH-NH (1.9±1.0 vs 2.0±0.8L/s, p=0.7).

Both PAH-H and PAH-NH achieved inspiratory tidal flows that approached a similar percentage of the maximal available inspiratory flows (i.e., similar IFR), suggesting that the inspiratory flow-generating reserve of the inspiratory muscles at peak exercise was similar (but occurred at different operating lung volumes). The presence of inspiratory muscle constraint/fatigue and its contribution in modulating the dynamic operating lung volumes response to CPET is unlikely.

Support: 1) International Re-integration Grants (IRG), FP7-PEOPLE-2010-IRG; 2) PFIZER Investigator-Initiated Research (IR).

P848

A metabolic evaluation of a group of obese children: Oxygen consumption (VO2) and power

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Obesity, which has been considerably increasing in the last decades, is related to significant metabolic alterations.

The aim of this study was to evaluate whether this condition can also alter the VO2 (considered as the best assessment of cardiorespiratory form in healthy children) and the power in a group of obese children compared to a group of control children.

We tested 98 children; 42 controls and 56 obese children. Each child underwent a metabolic test on the cycle ergometer according to a protocol of increasing effort. VO2 values were 207.6 ± 24.8 ml/min for the group of controls and 207.8 ± 24.7 ml/min for the obese children (p=0.05). The higher value of power was obtained in the group of control children (140 watt) and lower in the obese children (120 watt) (p=0.05). This parameter normalized for the mass was higher in the group of controls (2.7 watt/kg) compared to obese children (1.9 watt/kg) (p=0.01).

Given the greater body mass of obese due to an increased fat component, it is not surprising that the VO2 is higher. These subjects must in fact move a large mass, with a considerable consumption of energy, to the detriment of their ability to work. The VO2/kg values are lower in the obese children 32.3 ml/kg compared to the group of controls 38.7 ml/kg/min (p=0.01).

Support: 1) International Re-integration Grants (IRG), FP7-PEOPLE-2010-IRG; 2) PFIZER Investigator-Initiated Research (IR).
PS49
Determinants of exercise capacity in patients with COPD without other comorbidities
Gloria Samperiz, Laura Madre, Pablo Cubero, Marta Forner, Elena Forcen, Santiago Carrizo, Jose M. Martin, Miguel Servet, Zaragoza, Spain

Introduction: The 6 min walking test (6MWT) is frequently used to assess exercise limitation and exertional dyspnoea in COPD. Age, sex, metabolic, cardiovascular, neuromuscular and respiratory variables can contribute to determine the final individual value of the 6MWT.

Aims: To evaluate exercise performance with the 6MWT in COPD patients free of other co-morbidities.

Methods: From the Bode International Cohort Study we selected 148 men with COPD and no other cardiovascular, cerebrovascular, metabolic or neuromuscular disorder. In addition, patients who were taking beta-blockers or anti-hypertensives were also excluded. A pre-specified protocol including two standardized 6MWT was applied to all patients.

Results: The mean ± SD of the post bronchodilator FEV1% predicted and 6MWT was 62.8±21 and 398±99 meters respectively. Walked distance correlated significantly with age, height, weight, baseline dyspnoea (as assessed by the MRC scale) and respiratory rate (RR) pre and post rehabilitation programme (RP) measuring oxygen uptake (V'O₂), carbon dioxide output (V'CO₂ ) and ventilation (V'E). The ventilatory efficiency was evaluated using the VE/CO₂ slope. Breathing patients was evaluated using iso-ventilation, i.e. maximal V'E, tidal volume (VT) and respiratory rate (RR) pre RP compared to the same parameters during iso-V'O₂ post RP. Exercise training in the RP consisted of endurance and strength training 5 days a week for six weeks.

Results: Exercise endurance increased and ventilatory requirements reduced post RP. Breathing pattern was improved in COPD pts but ventilatory efficiency was unchanged in both groups (Table 1).

<table>
<thead>
<tr>
<th></th>
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<th>CHF patients</th>
</tr>
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<tbody>
<tr>
<td>V'O₂max (ml/kg/min)</td>
<td>9.8±4.5</td>
<td>14.4±6.9</td>
</tr>
<tr>
<td>% iso-V'E</td>
<td>12.3±7.4</td>
<td>17.3±6.1</td>
</tr>
<tr>
<td>% iso-VT (L)</td>
<td>29.1±5.1</td>
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Data are presented as mean ± SD. *p<0.05 post RP vs pre; **p<0.05 CHF vs COPD.

Conclusion: Exercise training did not improve ventilatory efficiency but reduced ventilatory requirements during heavy exercise giving prospect of less dyspnoea during effort in these pts.

PS52
Effect of exercise training on ventilation in patients with COPD or chronic heart failure
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1Department of Physiology, University of Iceland, Reykjavik, Iceland; 2Department of Heart and Lung Rehabilitation, Reykjavik, Rehabilitation Centre, Mosfellbaer, Iceland

Ventilatory efficiency to evaluate the effect of exercise training on ventilation in these pts.

Methods: 25 COPD pts (11 males; 64±9 yrs old, GOLD 3-4) and 25 CHF pts (12 males; 65±10 yrs old; NYHA class II-III, ejection fraction <35%) underwent a standardized 6MWT and an isometric endurance test of the M. deltoideus voluntary contraction, followed by an isometric endurance test of m. deltoideus (10 s) against baseline and post bronchodilator. Ventilation, oxygen uptake (V'O₂), carbon dioxide output (V'CO₂ ) and ventilation (V'E). The ventilatory efficiency was evaluated using the VE/CO₂ slope. Breathing patients was evaluated using iso-ventilation, i.e. maximal V'E, tidal volume (VT) and respiratory rate (RR) pre RP compared to the same parameters during iso-V'O₂ post RP. Exercise training in the RP consisted of endurance and strength training 5 days a week for six weeks.

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Data are presented as mean ± SD. *p<0.05 post RP vs pre; **p<0.05 CHF vs COPD.

Conclusion: Exercise training did not improve ventilatory efficiency but reduced ventilatory requirements during heavy exercise giving prospect of less dyspnoea during effort in these pts.

PS53
Short-term ingestion of salbutamol increases isometric muscle power in endurance athletes
Anders Kalse1, 2, Morten Hestrup2, Jens Bangsbø2, Vibke Backer2
1Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark; 2Department of Exercise and Sport Sciences, University of Copenhagen, Denmark

Rationale: Salbutamol is on WADA’s prohibited but is allowed by athletes in therapeutic doses. Positive effects of oral salbutamol have been shown in active males and females. Yet, studies are needed examining the effects in athletes. Furthermore, no studies have examined whether oral salbutamol improves isometric muscle power and endurance. We examined whether acute and short-term intake of oral salbutamol improved isometric muscle power and endurance, and submaximal exercise performance in endurance athletes.

Method: Twenty non-asthmatic endurance athletes (M), aged 25.8±4.4 yrs, weight 74.9±11.2 kg, height 178.4±6.1 cm, were enrolled in a randomized double-blind parallel study, into either oral salbutamol 8 mg (SAL) or placebo (PLA). The protocol consisted of three tests. Isometric muscle power of m. quadriceps was measured by maximal voluntary contraction, followed by an isometric endurance test of m. deltoideus to exhaustion and a submaximal cycling test to exhaustion at 90% of VO₂max (TTE@90%). The protocol was performed at baseline, after acute ingestion, and after 14 days of ingestion.

Results: Short-term intake of salbutamol significantly increased isometric muscle power, 709.6±115.2 vs 662.8±100.8 at baseline (p<0.05). Furthermore, there was a significant linear trend of increased isometric muscle power with SAL throughout the intervention (p<0.05). No differences were found in the PLA-group. Neither SAL nor PLA had any impact on isometric endurance or TTE@90%.

Conclusion: Short-term intake of salbutamol might augment training response and increase isometric muscle power in endurance athletes. Salbutamol had no effect on submaximal exercise at 90% of VO₂max or on isometric endurance.
PS84
Effects of acute and two week intake of salbutamol on anaerobic power and capacity during repeated bouts of exercise in elite cyclists.

Morten Hostrup1,2, Anders Kalsen3,2, Jens Bangsbo2, Viveke Backer1.

1Respiratory Research Unit, Bispebjerg University Hospital, 2Department of Exercise and Sport Sciences, University of Copenhagen, Denmark

Rationale: Salbutamol was of 2011 relieved from WADA’s prohibited list needing a strict diagnosis of asthma, and can now be used more freely among athletes. Some studies have showed enhancing effects of oral salbutamol on anaerobic power in recreational men and women. However, no studies have investigated this in elite athletes. The aim of this study was to examine whether oral salbutamol, taken acutely and over a period of two weeks, increases anaerobic power during repeated Wingate tests in elite cyclists.

Method: We enrolled 20 non-asthmatic elite cyclists (M), aged 25.8±0.4 yrs, VO2peak 68.6±5.8 mln/min/kg, and a training volume of 14.4±3.6 h/wk. The cyclists were randomized into either oral salbutamol 8 mg (SAL) or placebo (PLA) in a double-blinded parallel study. The protocol consisted of three 30-s Wingate tests separated by two minutes of recovery. The intervention consisted of study visits at baseline, after acute ingestion, and after two week ingestion taken two-three hours prior to the cyclists’ regular training.

Results: Two week ingestion of salbutamol significantly increased peak power in the first (p<0.05) and second (p<0.001) Wingate, 894±64 W and 885±51 W versus 861±53 W and 848±54 W at baseline. Furthermore, the SAL-group had a significant higher mean peak power over 5s at both the first (p<0.05) and the second (p=0.05) Wingate, with 861±42 W and 829±56 W versus 809±58 W and 795±50 W at baseline. Acute ingestion of salbutamol didn’t increase any parameter in the SAL-group. No differences were found in the PLA-group.

Conclusions: Two week daily intake of salbutamol taken prior to training improves anaerobic power in elite cyclists.

PS85
Inspiratory muscle warm-up does not improve cycling time trial performance

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Combining an inspiratory muscle warm-up (IMW) with a sport specific warm-up improved intermittent running (Tong and Fu: Eur J Appl Physiol 2006: 97:637-680) and 6 min rowing time trial (Volaniut et al. Med Sci Sports Exerc 2001; 33:1189-1193) performances more than a sport specific warm-up alone. This study tested the hypothesis that inspiratory muscle warm-up would also improve cycling time trial performance.

Ten competitive cyclists (VO2max 64.7±3.9 ml/min/kg) performed three 10 km cycling time trials preceded by either no warm-up (CONT), a cycling specific warm-up (CYC) comprising three consecutive 5 min bouts at powers corresponding to 30, 70, and 90% of the aerobic gas exchange threshold, or a cycling specific warm-up preceded by an IMW (CYC+IMW) comprising two sets of 30 inspiratory efforts against a pressure-threshold load of 40% maximal inspiratory pressure (MIP). During CYC and CYC+IMW the cycling was performed after a 2 min rest period before the start of the time trial.

Performances during CYC (14.7±0.75 min) and CYC+IMW (14.7±0.75 min) were not different, although both were faster than CONT (14.9±0.90 min) (P<0.05). At 2.5 km intervals heart rate, rating of perceived exertion for leg and breathing, blood lactate concentration and pH, were not different between CYC and CYC+IMW. Baseline MIP during CONT and CYC were 151±31 and 156±39 cmH2O, respectively, and these were unchanged following the time trial. IMW increased MIP from 152±27 to 164±27 cmH2O and no further change was observed following the time trial.

In conclusion, improvements in 10 km cycling time trial performance following a specific cycling warm-up were not magnified by the addition of a specific inspiratory muscle warm-up.

PS86
Minute ventilation (Ve) and heart rate (HR) relationship during exercise in chronic cardiac and pulmonary diseases

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We have demonstrated in healthy subjects that the rate of increase in minute ventilation over heart rate (ΔVe/ΔHR), during incremental exercise, is described by a bilinear response, with a slope’s change at the ventilatory compensation point (VCP) (Onorati P. Eur J Appl Physiol. 2008;104:87-94).Med Sci Sports Exerc 2012 in press). We aimed at analyzing the exercise ΔVe/ΔHR response in patients with chronic cardiopulmonary diseases.

Method: Patients with chronic obstructive pulmonary disease (COPD) (n=10) and cardiovascular diseases (CVD) (Pulmonary Arterial Hypertension, PAH, n=9; and Chronic Heart Failure, CHF, n=10) underwent one-minute incremental cycling exercise. Gas exchange, Ve, HR were measured breath-by-breath. ΔVe/ΔHR response, before (S1) and after the VCP (S2) were computed by linear regression analysis.

Results: In all patients we observed a linear response of the ΔVe/ΔHR relationship; in COPD patients S2 was steeper vs PAH and CHF and approached the maximal voluntary ventilation (MVV). S2 slope was observed mainly in CVD patients and approached the maximal predicted HR.

A good agreement (Bland-Altman test) for VCP detection was observed between ΔVe/ΔHR vs the ventilatory equivalent for CO2 (Ve/VECO2) methods.

Conclusions: In patients with COPD, PAH and CVD, the ΔVe/ΔHR response during cycling incremental exercise can be utilized to discriminate between ventilatory and circulatory limitation.

PS87
Influence of ventilatory inefficiency in to limit exercise capacity in COPD patients

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Background: We recently demonstrated an influence of Ventilatory efficiency (VE/VO2) over exercise capacity in COPD (Respi Care 2012 in press). Purpose: to demonstrate increase of ventilatory inefficiency depending on the severity of COPD, and its influence into reduce exercise capacity.

Methods: 58 Gold I-III patients, mean age 61, mean FEV1: 98, 68.5 and 44.3%, mean DCO: 68, 59.5 and 45%.

A cardiopulmonary stress test measuring Power (Wmax), Oxygen consumption (VO2max), VE/VO2, expiratory flow limitation (EFL) and dynamic end expiratory volume (DEELV) was performed. In patients with hypertension correlations and multiple regressions between BMI, EFL, DEELV and VE/VO2 were analyzed. Patients were divided in 3 groups: GOLD I, GOLD II and GOLD III

Results: Patients ended the test due to dyspnea with increased VE/VO2 (mean 34). Depending on the severity of COPD, VE/VO2 was higher. 36 patients presented hyperinflation (mean DEELV 0.5 L), with a reduction in Wmax and in VO2max (mean: 63 and 76%). Significative correlation was demonstrated between VE/VO2 over VO2max and Wmax (r=0.5 and 0.5). In multiple regression the relation between VE/VO2, Wmax and VO2max was significative (p<0.05 and <0.05), but not to BMI, EFL and DEELV.

Conclusions: In COPD patients ventilatory inefficiency increases depending on the severity and is related with a reduction in the exercise capacity. Ventilatory inefficiency is an independent factor to reduce exercise capacity in COPD.

PS88
Respiratory muscle endurance training (RMET) with normocapnic hyperpnea (NH) improves ventilatory function and exercise performance in triathletes

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Recent studies show that RMET reduces dyspnea perception, improves exercise performance and decreases VE during exercise in healthy subjects. Aim: To evaluate the effect of 5 weeks of RMET with NH by means of Spiret® on respiratory function, cycling and running performance in triathletes.

Methods: 15M triathletes (aged 21-43) were allocated in 2 groups: RMET (10M) and Control (5M) group.

At baseline (T0) athletes underwent: pulmonary function tests (FEV1, FVC, MIP, MVV) and exercise tests (maximal incremental and endurance cardiopulmonary tests performed with both cycle ergometer and treadmill) and repeated the same tests after 5 weeks (T1). RMET group trained at home for 5 weeks: 20 min daily at the same ventilation level measured at the RC point during incremental test. Between T0 and T1 all subjects maintained the same training program.

Results are reported in Table 1. The trend of VO2, VE and RR showed lower values after RMET (p<0.05; ANOVA test). No change was found in control group.

Table 1

<table>
<thead>
<tr>
<th>FEV1</th>
<th>FVC</th>
<th>MIP (cmH2O)</th>
<th>MVV (l/min)</th>
<th>Max Watt</th>
<th>Max Speed (k/h)</th>
<th>Borg dyspnea</th>
<th>Difference test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>114±9</td>
<td>120±10</td>
<td>93±29</td>
<td>213±17</td>
<td>389±106</td>
<td>18±2</td>
<td>7/10±0,7</td>
</tr>
<tr>
<td>T1</td>
<td>115±11</td>
<td>120±10</td>
<td>97±25</td>
<td>231±18*</td>
<td>429±119*</td>
<td>19±2*</td>
<td>6/10±0,5*</td>
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</table>

Mean±SD; *p<0.05; T test.
Conclusion: RMET significantly improves MIP and MVV in triathletes and increases exercise performance. Furthermore the VE becomes more efficient as shown by the reduction of VE, RR and by the lower dyspnea Borg score; the new data is the lower trend of VO2 during incremental test.

99. New issues in pulmonary function

P859 Patterns of lung function abnormalities in smokers as possible manifestation of "early" COPD phenotypes

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The notion that the earliest manifestation of COPD is an increase in gas trapping, with a decreasing VC that forces the FEV1 to decline with it, has been recently re-evaluated [1]. To assess the prevalent patterns of lung function abnormalities in smokers at the onset of COPD, we evaluate cross-sectional data of a longitudinal study on 321 non-outpatient smokers (mean age 55±10 years; 60% males) belonging in part to a smoking cessation program and in part to a lung cancer screening study. Smoking history and chronic respiratory symptoms were collected, and spirometry and lung volumes were determined, according to standardized protocols. Mean pack-years were 38±22 and 38% of the smokers reported chronic cough and/or phlegm and/or dyspnea; they were significantly older and smoked more pack-years than those without symptoms (for both p<0.0001). Mean value of all lung function parameters was within the normal range, however lung function abnormalities were observed in 43% of smokers: 15% had FEV1/VC lower limit of normal and FRC >115% predicted, 19% had only airflow obstruction and 9% had an isolated increase in FRC without airflow obstruction. A similar pattern of increase in gas volume was found regardless the presence of respiratory symptoms or by considering either RV or RV/TLC. In conclusion, air trapping is not the prevalent pattern of lung function abnormalities in these two groups of smokers, isolated airflow obstruction or isolated increase in air trapping could be an "early" expression of two different phenotypes of COPD.

Reference:

P860 Airway distensibility with lung inflation following allogeneic haematopoietic stem-cell transplantation (HSCT)

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Aims: To study whether this effect may be due to increased airway distensibility.
Methods: 23 subjects were studied before and 1-3 and 3-6 mo after HSCT. Resistance (Rrs) and reactance (Xrs) of the respiratory system were measured by FOT (5, 11 and 19 Hz) at FRC and TLC. The ratio of changes in respiratory conductance (Grs) from FRC to TLC to changes in lung volume (ΔGrs/ΔVl) was used to estimate airway distensibility. Results: Grs at FRC was larger at all frequencies whereas Xrs at 5 Hz was less negative after than before HSCT (Figure 1). TLC was decreased by 5±2% whereas FRC was not changed. ΔGrs/ΔVl was steeper after than before HSCT (P<0.001), without differences after salbutamol (Figure 2, interrupted lines).

Conclusion: In uncomplicated HSCT, absolute lung volume is reduced but is the ability to reverse induced bronchoconstriction by deep-breath is enhanced.

Background: In uncomplicated HSCT, absolute lung volume is reduced but the drive and effectiveness of respiratory muscles contraction. They are useful in the diagnosis of advanced chronic lung diseases that accompany CO2 retention.

Results: TVs at 5 Hz was less negative after than before HSCT (Figure 1). TLC was decreased by 5±2% whereas FRC was not changed. ΔGrs/ΔVl was steeper after than before HSCT (P<0.001), without differences after salbutamol (Figure 2, interrupted lines).

Reference:

P861 Study on mouth occlusion pressure in normal subjects and patients with obstructive or restrictive lung diseases

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Mouth occlusion pressure (P0.1) is the mouth pressure developed against a complete occlusion at 0.1 second after beginning of inspiration from FRC. Consciousness, autogenous reflexes and various lung mechanics do not affect it. We did this study in sequence of arterial blood gas examination, flow-volume curve, body plethysmography, diffusion capacity and measurement of P0.1. We divided the subjects into 4 groups such as normal control groups below 35 and above 50 years old, and the patient groups of obstructive and restrictive lung diseases. We measured P0.1 during breathing of the ambient air and, again during 6% CO2 rebreathing with simultaneous measurement of ventilatory parameters such as MV (minute ventilatory volume)/P0.1, TTV/Ti (inspiratory time/total respiratory time), TV/Ti, and P0.1/TV/Ti. During breathing of the ambient air, and, again during 6% CO2 rebreathing, there was a characteristic change of P0.1 in the hypercapnic patient group compared with the normocapnic patient group. As a result, P0.1 and P0.1/TV/Ti are the valid indices of central inspiratory neuromuscular drive and effectiveness of respiratory muscles contraction. They are useful in the diagnosis of advanced chronic lung diseases that accompany CO2 retention.
P864
Expiratory capnography in brown Norwegian rat: Feasibility and effect of acute bronchoconstriction
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Rationale: The phase III slope of the expiratory volumetric capnogram (S3v) has been shown to increase with bronchoconstriction in asthmatics (ERJ 1994;7:318-323), however, the mechanisms involved remain speculative. We assessed the feasibility of expiratory capnographic slope analysis during acute bronchoconstriction in an experimental model in rat.
Methods: Rats underwent a separate study were divided into 2 groups: sensitized to ovalbumin (OVA) and exposed either to air or to NO2, 10 ppm, 6d/wk for 4 weeks. 24h after exposure, animals were anesthetized and mechanically ventilated. Respiratory mechanics were measured using multiple linear regression analysis of capnogram and after infusion of methacholine at 15 μg/kg/min (vs). Exhaled capnograms were recorded during tidal breathing using a rapid CO2 analyzer. The S3v was computed and averaged in a minimum of 10 respiratory cycles in each condition.
Results: Respiratory system resistance (Rs) and elastance (Es) significantly increased in response to MCH. Similarly, S3v increased during MCH infusion. This increase was significantly larger in NO2-exposed animals.
Table 1

<table>
<thead>
<tr>
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<th>Air-OVA (n=4)</th>
<th>NO2-OVA (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rs (cmH2O/ml)</td>
<td>0.89±0.05</td>
<td>1.47±0.49</td>
</tr>
<tr>
<td>Es (cmH2O/ml)</td>
<td>3.81±0.35</td>
<td>6.65±0.98*</td>
</tr>
<tr>
<td>S3v (mmHg/ml)</td>
<td>2.45±0.07</td>
<td>3.32±0.46</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline, within a group; *p<0.05 vs. Air-OVA, within a condition, by Kruskall- Wallis ANOVA on ranks.

Conclusions: Measurement of S3v is feasible in rat, and significantly increases following bronchoconstriction. This new experimental model will allow further study of the mechanisms associated with the increase in S3v.

P865
Effects of thoracic gas compression on airway responsiveness in asthma
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Background: The response to a bronchial challenge is usually assessed from the changes in the forced expiratory in 1 s (FEV1). Yet this measurement is negatively affected by the thoracic gas compression. Aim: To examine the effects of thoracic gas compression on the dose-response curve to methacholine (MCh) in asthmatics. Methods: 28 male and 25 female asthmatic patients participated in the study. Methacholine challenge was performed in a flow-type body plethysmograph to compute simultaneously FEV1 and compression-free FEV1 (FEV1/PLETH). The doses of MCh that caused a decrease in FEV1 and FEV1/PLETH by 20% of control were calculated by linear interpolation of the dose-response curve and transformed into natural logarithm. Results: On average, lnPd20FEV1 was significantly less that lnPd20FEV1/PLETH (5.49±0.94 vs. 5.74±1.00, p<0.001). The difference between lnPd20FEV1 and lnPd20FEV1/PLETH was positively correlated with absolute TLC (r=0.40; p<0.05 vs. baseline, within a group; *p<0.05 vs. baseline, within a condition, by Kruskall-Wallis ANOVA on ranks.

Conclusions: Thoracic gas compression has a significant effect on airway responsiveness, which depends on absolute lung volume and, thus, anthropometric characteristics.

P866
Change of CP location during bronchodilatation
Ole Pedersen, Riccardo Pellegrino, Pasquale Pompilio, Institute of Public Health, University of Aarhus, Denmark
Background: The wave-speed concept of flow limitation predicts a unique relationship between the MFSR-curve and the tube laws of the airways containing the choke points (CP). If the frictional loss pressure (Pfr) cannot be neglected J = Pel – Pfr must be substituted for Pel.
Aim: 1) To analyse data from Lambert et al. (JAP 52:44–46) in terms of motion pressure during expiration. 2) To measure upstream viscous pressure losses (Pfr) and J = Pel – Pfr. Meth: Physiological Volume 1, 2011: 1861-1881. The relationship between cross-sectional area (A) and transmural pressure (Ptm) – the tube laws were calculated from the relationship between Vmax and J.

P862
An integrative and comprehensive approach to evaluate lung mechanics in seated and upright positions
Andre Albuquerque, Pedro Caruso, Renata Pletsch, Pauliane Santana, Leticia Cardenas, Andre Apanavicius, Gabriel Rozin, Marcelo Macchione, Joao Marcos Salge, Carlos Carvalho. Respiratory Department, Heart Institute (Incor) - University of Sao Paulo Medical School, Sao Paulo, Brazil
Ventilatory and sensorial differences have been found between treadmill and cycle in respiratory diseases. However, there are still many doubts about lung mechanics in these two body positions.
Methods: 5 male healthy were evaluated at quite breathing (QB) and voluntary hyperventilation (VH) in seated (ST) and upright (UR) with transdiaphragmatic pressure (Pdi) - oesophageal and gastric sensors, electromyography (RMS) of sternocleidomastoid, Intercostal, Rectus abdominis and External Abdominal Oblique (OmEGM), ribcage (RC) and abdominal (Ab) bi-dimensional movement by inductance (V0.5) and flow measurement (V0.1).
Results: At QB in ST with similar flows, we found: the chest wall movement was mainly the Ab, with similar Pdi than UR (20.9 vs 28.1 cmH2O) but with a lower gastric pressure (11.2 vs 21.9cmH2O, NS). Inspiratory muscles accessory were poorly recruited in both positions, but UR lead to higher activity of abdominal muscles (p<0.08).
During (VH): the chest wall increase was mainly dependent of RC in ST, while in UR the contribution of RC and Ab was the same. The increase of Pdi was equivalent (30% vs 29%) in both positions during VH, gastric pressure augmented more in ST than UR (169 vs 109%, NS). Finally, VH in ST resulted in similar recruitment of inspiratory muscles but superior of exp muscle (incOmEGM 118% vs 83% NS) than UR.
Conclusion: Seated is characterized by greater contribution of Ab to chest wall movement than UR. The lower gastric pressure and also lower exp muscle recruitment than UR. During hyperventilation, the increase of Ab contribution was also greater in ST. Ab compartment is more recruited and less contributing to chest wall mechanics in UR.
Results: Bronchial dilatation increases maximal flow in all cases, but Pfr increases in two cases and decreases in two. Pfr increases when density dependence DD decreases, and increases when DD decreases. The A-Pun curves show an irregular appearance reflecting the elastic properties of the more and more peripheral airways containing the CP during the expiration. Central and peripheral airways could be detected in each case. In three of four subjects CP at 50%FVC moved to more central airways after bronchodilatation.

Conclusion: The magnitude of Pfr is small, and the study is inconclusive. However, the study indicates that CP moves centrally in 3 of the 4 subjects with bronchodilatation. More experiments are needed.

P867 Lung-packing and stretching increases vital capacity in recreational freedivers
Otto Johansson, Erika Schagaty. Department of Engineering and Sustainable Development, Mid Sweden University, Östersund, Sweden

Introduction: Lung volume is as an important factor for apneic diving performance, with a driver's ratio volume 50% larger than in matched controls. Some of this effect is likely due to predisposition, but elite divers often use stretching and “lung packing” in their training to improve lung capacity. Our aim was to study the effects on vital capacity of a training program involving a series of maneuvers typical of freedivers training.

Methods: Subjects were 13 recreational freedivers with a mean (SD) height; 197cm (8.4), weight; 73kg (13.8), age; 23 years (9.7), training apneic diving in average 1-2 h per week, and 6 matched control non divers. The diver’s lung training involved a set of 5 different lung exercises with yoga and lung packing maneuvers 5 times a week for 11 weeks. Subjects VC was determined before and after the training program using 3 maximal expirations for low VC, with the largest volume used.

Results: Mean (SD) VC had increased across the training period, from 5.9 (1.4) to 6.4 (1.1) L (P < 0.01). An increase in VC was observed in all but 1 subject. In the control group mean (SD) VC was 4.6 (0.7) L in test 1 and 4.7 (0.8) L in test 2 (NS), showing that the effect in divers was likely not due to retesting.

Discussion: The training used by elite divers, involving lung packing and stretching, may improve VC in recreational divers, despite previous dive training. The increase is more than twice as great as that previously obtained with only lung packing (Lindholm et al 2007). The main mechanism responsible could most likely be reduced chest recoil after stretching.

Conclusions: We conclude that vital capacity can be improved by training.

P868 Low-density lipoprotein cholesterol is associated with inspiratory capacity to total lung capacity ratio in AECPD patients
Xiaoming Bi, Li Zhao. Respiratory Department, Beijing institute of Respiratory Medicine, Beijing, China

Introduction: Air trapping leads to a reduction in inspiratory capacity/total lung capacity (IC/TLC) ratio in patients with chronic obstructive pulmonary disease (COPD). Knowledge of the effects of low IC/TLC ratio (IC/TLC <0.25) on nutritional status and respiratory impairment during acute exacerbations of COPD (AECOPD) is limited.

Material/Methods: In 108 patients admitted to the hospital due to an AECOPD (75% median age 72 years [interquartile range 60-85 to 70 years], FEV1 75% of predicted, BMI 24.4±4.5 kg/m2, FEV1/FVC ratio 0.35±0.21), the following data were collected: smoking status, sex, age, BMI, presence of comorbidities (diabetes, hypertension, COPD, asthma), smoking status, obesity, comorbidities, and respiratory symptoms. The results were compared with those of 108 healthy controls (age and sex-matched).

Results: In IC/TLC <0.25, BMI was significantly lower than in IC/TLC ≥0.25 (24.4±4.5 vs 25.5±4.0 kg/m2, p=0.042) and there was a significant difference in smoking status (22% in IC/TLC <0.25 vs 11% in IC/TLC ≥0.25, p=0.042). There was a significant difference in BMI between IC/TLC <0.25 and IC/TLC ≥0.25 (24.4±4.5 vs 25.5±4.0 kg/m2, p=0.042).

Discussion: The results of this study indicate that low IC/TLC ratio is associated with lower BMI, increased smoking status, and more severe disease. These findings suggest that low IC/TLC ratio may be an indicator of more severe disease in COPD patients. Further studies are needed to confirm these findings.

Conclusions: The results of this study suggest that low IC/TLC ratio may be an indicator of more severe disease in COPD patients. Further studies are needed to confirm these findings.
Conclusion: In mild-to-moderate asthmatics, 30min of high-intensity intermittent and continuous NH with humid and warm air resulted in no clinically relevant changes in lung function, airway resistance and reactance. Thus NH by partial rebreathing might be a promising strategy to specifically train the respiratory system of asthmatics.

### P872

**The relationship between long-term correlations (self-similarity) in PEF and FEV1 in COPD**

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**Conclusion:** Detrended fluctuation analysis (DFA) quantifies the rate of decay in self-correlation in a time series with an exponent “alpha” that is related to COPD exacerbation frequency. The relationship between α of different spirometric parameters in the same individual on the same days is not known.

**Methods:** We examined data from the London COPD cohort on 28 COPD patients who had recorded both FEV1 and FVC and PEF on daily diary cards for 300 days. Measurements were made after medication in the morning. At recruitment, these patients had a mean age (SD): 65.3 (9.3) years; FEV1, 1.08 (0.36) L; FEV1/FVC % predicted 37.3 (14.1); FEV1/FVC ratio 0.43 (12.8). DFA has been described (Frey et al Nature. 438: 667-70, 2005). The analysis was also repeated with data collected during exacerbations removed.

**Results:** The patients had an α of 0.97 (SD 0.22) for PEF, 0.93 (0.22) for FEV1, and 0.95 (0.23) for FVC. No differences was seen in any of the estimates (p>0.24). Figure 1 illustrates the relationship between alpha for FEV1 and PEF (r=0.69; p<0.001). There was no significant difference if data collected during exacerbation data were excluded. PEF α was 0.95 (SD 0.19); FEV1 α = 0.95 (19) and FVC α = 0.97 (SD 0.20).

**Conclusion:** In COPD patients, long-term correlations (self-similarity) exist in daily FVC, FVC and PEF. The estimates of α are similar and linearly related to each other.

### P873

**Feasibility and safety of mannitol challenge in pre-school children using forced oscillation technique**

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**Background:** The mannitol dry powder challenge is used to identify exercise induced bronchoconstriction (EIB) in adults and school-age children. The forced oscillation technique (FOT) is suitable for assessing lung function in pre-school children and can be combined with inhaled challenge testing in this age group.

**Aims:** This study aimed to assess the safety and the feasibility of a mannitol challenge using FOT in young children with asthma and in healthy controls.

**Methods:** Healthy children and children with exercise induced symptoms (EIS group) aged 3-7 years were recruited. A mannitol challenge (Aridol, Pharmaxis, Australia) was performed. A positive response to mannitol was defined as wheeze on auscultation, persistent cough, SpO2 <90% or increase in respiratory system resistance at 8Hz (Rrs8) > 50% from control. The mannitol challenge was considered safe if the child completed the challenge to the final dose or a positive response was noted.

**Results:** To date, 6 healthy and 10 EIS children have been studied. 14 children successfully completed the mannitol challenge with no adverse events. Two healthy children aged 3 years did not complete the test due to lack of cooperation. Three children with reported EIS responded to the challenge with symptoms, and three children responded by an increase in the Rrs8 by >50% from the control measurement.

**Conclusion:** These preliminary results suggest that a mannitol challenge test is feasible in young children and can be performed safely.

**Funded by:** ANZSRS Research Grant, Asthma Foundation WA.

### P874

**Contribution of β2-adrenoceptors to bronchodilatation during exercise in healthy humans**

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**Background:** Exercise in healthy subjects is usually associated with progressive bronchodilatation, which has been attributed to a decrease of vagal tone.

**Aim:** To examine whether β2-adrenoceptors also contribute to bronchodilatation during exercise in healthy humans.

**Methods:** 14 healthy male volunteers participated in the study. Maximum exercise test was performed at control conditions and after a non-selective β-adrenoceptor blocker (carvedilol 12.5 mg tablets b.i.d until heart rate decreased by 10 beats/min at least) or an inhaled β2-adrenoceptor agonist (albuterol 400 mg through a spacer).

Airway function was estimated from the partial flow at 40% of control forced vital capacity (V’p40) at rest and the slope of linear regression of V’p40 vs. minute ventilation (V‘E) every 2 min during an incremental exercise test until exhaustion.

**Results:** After carvedilol, resting V’p40 was not significantly different from control (2.80±0.98 vs. 2.96±1.38 L s⁻¹) but the V’p40 vs V‘E slope decreased from 0.03±0.019 to 0.01±0.014 L s⁻¹ 1⁻¹ (p<0.05, ANOVA), suggesting less bronchodilator response to exercise. After albuterol, resting V’p40 significantly increased from control to 4.79±1.68 L s⁻¹ (p<0.001) but did not increase further during exercise (V’p40 vs. V‘E slope 0.05±0.012 L s⁻¹ 1⁻¹).

**Conclusions:** In healthy subjects, bronchodilatation during exercise is at least in part mediated by β2-adrenoceptor activation.

### P875

**Ventilation parameters in asthmatic children after one week at 1400 meters altitude**

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**Introduction and background:** Bronchial asthma prevalence is increasing. Many triggers are known but little about protective factors.

**Aims and objectives:** To find out whether 1400 meters altitude could modify ventilation parameters, NO (Nitric Oxide) concentration and clinical symptoms in 13 children after a week of uncontrolled physical activity.

**Methods:** Thirteen asthmatic children were evaluated at arrival and departure from a mountain resort for: FVC, FEV1, FEF 25-75 and exhaled NO concentration. Unscheduled physical activity were encouraged for eight hours daily.

**Results:** All the children showed improvement of FVC, FEV1, FEF 25-75.

**Main ventilation parameters and NO concentration**

<table>
<thead>
<tr>
<th>Main Ventilation Parameters</th>
<th>NO Concentration</th>
</tr>
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<tbody>
<tr>
<td>FVC mean value % predicted</td>
<td>FEV1 mean value % predicted</td>
</tr>
<tr>
<td>Arrival 1.00±0.00 205±16</td>
<td>1.00±0.00 205±16</td>
</tr>
<tr>
<td>Departure 1.00±0.00 165±16</td>
<td>1.00±0.00 165±16</td>
</tr>
</tbody>
</table>

**p<0.05 test paired two tails.**

**Conclusions:** After a week permanence at 1400 meters resort all subjects showed an improvement in ventilation parameters, together with no episode of asthma exacerbations. This study suggests that physical activity in an healthy environment can be safe and feasible for asthmatic children.

### P876

**Airway resistance in COPD**

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**Background:** Chronic obstructive lung disease is characterized by airflow limitation, usually
assessed by forced expiratory maneuvers (FEV1 and FVC). These maneuvers reflect a complex, dynamic relationship between patient effort, muscle strength, elastic recoil as well as airway resistance, which plays a dominant role in airflow limitation. Within the Emphysema versus Airway Disease study (EvA) we examine postbronchodilator values for total resistance, in- and exspiratory resistance (Rin, Rexp) and specific resistance (rSR) in COPD patients (n= 509; GOLD stage I-III, no current smoking).

Mean postbronchodilator values for total airway resistance are higher in patients compared to controls (0.35 vs 0.19 kPa*sec/L). Looking at Rin versus Rexp, the increase in patients is mainly due to a higher Rin (mean 0.50 versus 0.22 kPa*sec/L) compared to Rin (0.25 vs 0.15 kPa*sec/L). Specific resistance, which is adjusted for volume to avoid errors because of hyperinflation, is elevated as well (1.64 vs 0.71 kPa*sec/L). All reported differences in mean values are highly significant with p < 1*E-15. Mean values for Rin and Rexp are remarkably elevated in COPD and show a good association with GOLD stages, so they may be preferred for monitoring of COPD since they are obtained with tidal breathing.

Supported by EU FP7 project #200605.

P877 The predictive value of inspiratory fraction to exercise capacity in patients with stable moderate to severe chronic obstructive pulmonary disease

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Objective: To study the relationship between inspiratory-to-total lung capacity ratio or inspiratory fraction to exercise capacity in patients with stable moderate to severe chronic obstructive pulmonary disease.

Methods: Pulmonary lung function test (PFT) and Cardiopulmonary exercise testing (CPET) were performed in 50 patients with stable moderate to severe chronic obstructive pulmonary disease and 34 controls, and measured the parameters of ventilation and gas exchange. The stopped reasons at the end of exercise testing were noted.

Results: (1) IF was significantly associated with peak peak VO2/Spred (r=0.52, p<0.001) in COPD and remained as independent predictor in the final model: peak VO2/Spred = 65.11 + 0.45IF, SEpred = 35.8 (R2 =0.39, p<0.001), the sensitivity and specificity of IF for predicting exercise capacity were both better than FEV1/Spred. (2) The patients with IF<0.23 had more severe hyperinflation and lower exercise capacity. In the peak exercise, the patients with IF<0.23 had lower peak VT than the patients with IF ≥0.23, and their peak breath frequencies had no significant difference.

Conclusion: Inspiratory fraction provides the efficient information to reflect lung hyperinflation and to estimate the exercise capacity in patients with stable moderate to severe chronic obstructive pulmonary disease, and its predictive value is better than FEV1/Spred.

P878 Effect of pulmonary rehabilitation on systemic inflammatory markers, muscle cross section area and functional parameters in interstitial lung disease

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Introduction: Intersitial Lung Diseases (ILD) are chronic debilitating diseases with severe exercise limitation. We studied the effect of pulmonary rehabilitation (PR) on systemic inflammatory markers, muscle cross sectional area and other functional parameters in patients of ILD.

Aims and Objectives: To evaluate the levels of C-Reactive Protein (CRP), Matrix Metalloproteinase 9 (MMP9), Tissue Inhibitor of Metalloproteinase (TIMP), 6 minute walk distance (6MWD), Mid high Cross Sectional Area on CT (MTCSAeV) and Carbon Monoxide Diffusion Capacity (DLCO) before and after PR in patients of ILD.

Methods: Fourteen patients of ILD were evaluated at baseline and after 4 weeks of standard therapy. Supervised PR along with standard medications was then given for further 8 weeks. Results: Mean values of CRP changed from 5.76±5.11 to 2.18±1.02 mg/L after rehabilitation [p=0.01]. MMP9 was 838.07±522.37 before and 547.93±108.57 ng/ml after PR [p=0.05]. Mean values of TIMP changed from 182.07±105.07 to 660.47±354.85 ng/ml after PR [p=0.04].

The mean values of 6MWD changed from 379.43±47.94 to 493.78±47.47 m after PR [p=0.001]. Levels of DLCO changed from 6.23±2.45 to 13.87±3.85 ml/min/mmHg after PR [p=0.05]. Mean values of MTCSAeV changed from 802.00±141.96 to 1018.00±1752.10 mm2 after PR [p=0.02].

Significant correlation was obtained between MMP9 and MTCSAeV [r=0.70, p=0.005] and between 6MWD and DLCO [r=0.76, p=0.001].

Conclusion: Pulmonary rehabilitation causes significant improvement in systemic inflammatory markers, muscle cross sectional area and functional parameters in ILD patients along with significant improvement in gas exchange.

P979 The effects of swimming training on alterations in structure and function of sternohyoid muscle of model rats of metabolic syndrome

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We investigated the effects of swimming training on alterations in structure and function of sternohyoid muscle in model rats of metabolic syndrome. Male Sprague-Dawley rats were randomly divided into 3 groups: control group (group A), MS group (group B), swimming training MS group (group C). The level of malondialdehyde of sternohyoid muscles in group B was significantly higher than those of group A and group C. The Superoxide dismutase level of sternohyoid muscles in group B was significantly lower than those of group A and group C. The capillary density, capillary-to-fiber ratio (CFR), cross-sectional area of type I and II fiber, percentage of type I fiber of the isolated sternohyoid muscles in group B were significantly lower than those of group A and group C. In group B, mitochondriums were swelling, vacuolization and reduced, myofilibril was dissolved locally. In group C, sternohyoid myofilibril was arranged normally, ultrastructure of mitochondriums was normal roughly, occasionally vacuolization. The tensions of sternohyoid muscle of group B were significantly lower than those of group A and group C. In fatigue test, the tension percentages of sternohyoid muscle of group B were significantly lower than those of group A and group C. We concluded that the abnormalities in histological structure and ultrastructure of upper airway muscle induced by MS, via oxidative stress, led to reduction in contractile function in upper airway muscles, contributing to sleep apnea, and swimming training improved contractile dysfunction of upper airway muscles by inhibiting oxidative stress in MS.

P880 Mechanical ineffectiveness of augmented genioglossus activity in OSA during sleep

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The pathophysiological cause of OSA is sleep-induced decline in dilator muscle activity. However, dilator muscles activity often increases during obstructive apneas and hypopneas (OAHS), but fails to improve airflow. It has been postulated that neuromuscular activity does not increase sufficiently to overcome the negative pressures that develop during obstructed breathing. The present study evaluate this hypothesis.

Methods: Intramuscular GG-EMG, esophageal pressure (Pes) and airflow were recorded in 70 OSA patients. In 6 of the patients, we recorded also EMG of the tongue retractor styloglossus (SG-EMG). While awake, EMGPeas was assessed while patients breathed through a variable resistor, to estimate the EMG required to prevent pharyngeal collapse. During sleep, EMGPeas was evaluated during flow limitation. Pre-arousal peak inspiratory EMG (sleepEMG) was compared to peak EMG at the same Pes during wakefulness (awakeEMG). SleepEMG/awakeEMG (at equal Pes) >1 indicated a level of EMG sufficient to prevent pharyngeal collapse.

Results: Patients had AHII of 51.7±10.5/hr. OAHS triggered increasing negative Pes and increasing GG-EMG. SleepEMG/awakeEMG >1 was observed in all but one patient, with highest (mean of 5 events) ratios of 3.27±1.81. In contrast, SG-EMG maintained tonic activity in 4/6 of the patients during OAHS, and the ratio exceeded 1 in one patient only (0.68±0.58).

Conclusions: In OSA patients, large augmentation of GG-EMG can be observed without improvement in airflow. This mechanical inefficiency is not explained by high inspiratory suction pressures. Co-activation of tongue retractors appears to be reduced during sleep.

P881 Treatment with auto-servo ventilation of patients with sleep-disordered breathing, stable systolic heart failure and concomitant diastolic dysfunction: A randomized controlled pilot study

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Background: Systolic heart failure (HF) is frequently accompanied by diastolic dysfunction and sleep-disordered breathing (SDB). We evaluated, whether...
auto-servo ventilation (ASV, BiPAP ASV, Philips Respironics) improves echocardiographic measures of diastolic function in patients with systolic HF and SDB.

Methods: 32 patients with stable systolic HF and concomitant diastolic dysfunction (age 66±9, LVEF 30.7±%, NYHA class II 72%) and SDB (AHI 48±19, 53% OSA) were randomized to either ASV (n=19) or optimal medical treatment alone (control, n=13). Polysomnography and echocardiography was performed at baseline and after 12 weeks.

Results: AHI improved significantly more in the ASV group compared to the control group (42±13.2% vs. 6±3.7%, P<0.001, respectively). Patients who had impaired left ventricular relaxation, and SDB (8% vs. 5%) had a pseudonormalized filling pattern. At the 12-weeks control visit, diastolic function as assessed by the isovolumetric relaxation time (IVRT, 10.3±3.6 ms vs. 9.3±4.2 ms, P<0.05) and deceleration time (DT, 43.9±88.6 vs. 12.4±68.8, P<0.05) did not significantly improve after ASV treatment. Likewise, the proportion of patients whose diastolic dysfunction improved was non-significantly higher in the ASV than in the control group, respectively (37% vs. 15%, P<0.05).

Conclusions: ASV-treatment efficiently abolishes SDB in patients with stable systolic HF and concomitant diastolic dysfunction. These data provide estimates of effect size and support the justification for the evaluation of the effects of ASV in patients with SDB associated with chronic heart failure – A matched control study

P884 CPAP therapy in idiopathic pulmonary fibrosis (IPF) patients with obstructive sleep apnea

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Background: Recent literature shows an increased incidence of OSA in patients with IPF. However, there are no published studies related to CPAP treatment in these patients.

Aims and objectives: We aimed to assess CPAP effectiveness and adherence in sleep and overall quality of life parameters in IPF patients with OSA.

Methods: Twelve patients with newly diagnosed IPF and moderate to severe OSA were included and CPAP therapy was initiated. The patients completed the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes in Sleep Questionnaire (FOSQ), the Fatigue Severity Scale (FSS), the SF-36 quality of life questionnaire and the Beck Depression scale (BDS) before and 1, 3, 6 months after CPAP therapy.

Results: Statistical significant improvement was observed in the FOSQ at CPAP initiation and after 1 and 3 and 6 months (p<0.05). Improvement, although not statistically significant, was noted in ESS score (p<0.05), PSQ (p<0.04), FSS (p<0.05), SF-36 (p<0.05), and BDS (p<0.05). All patients had risk factors for OSA - age and smoking. Two patients experienced difficulties in CPAP acceptance and stopped usage after the first month. Heat humidification was added in all patients in order to improve compliance.

Conclusion: Effective CPAP treatment, with intense follow up by the CPAP clinic, in IPF patients with OSA, results in a significant improvement in daily living activities based on the FOSQ, namely an OSA specific follow up questionnaire. Improvement, though not statistically significant, was also noted based on other questionnaires, probably related to the multifactorial influences of IPF in physical and mental health.

P885 Obstructive sleep apnea syndrome and cardiovascular diseases risk in patients with COPD

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Purpose: To define the correlation between obstructive sleep apnea syndrome (OSAS) and increasing of cardiovascular risk in patients with chronic obstructive pulmonary diseases (COPD).

Design: There were examined 33 patients in the age of 63.9±1.5 years with COPD stage 2 (85%) and stage 3 (15%). Duration of disease was 10-14 years. - 22 patients (62%) and 15-24 years – 11 patients (33%). 60% of patients were smoking, 40% - of smoking - 14,7±0,48 pack-years. Control group included 10 practically healthy persons.

Methods: Holter monitor test with theopheneurometry, spirometry, X-ray examination, six-minute walk test, calculation of cardiovalvular insufficiency, calculation of occurrence of atrial fibrillation (AFib).

Results: There were revealed correlations between duration of apnea cases and cardiovascularcheological risk in patients with chronic obstructive pulmonary diseases (COPD).

Conclusion: Patients with both COPD and OSAS have evidently increased risk for fatal complications.

P886 The frequency of overlap syndrome in patients who were evaluated in sleep laboratory and its effects on severity of obstructive sleep apnea syndrome and quality of sleep

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‘Overlap Syndrome’ is the coexistence of Obstructive Sleep Apnea Syndrome (OSAS) with Chronic Obstructive Pulmonary Disease (COPD) and asthma. We aimed to determine frequency of COPD and Asthma in OSAS patients and effect of these diseases on quality of sleep and severity of OSAS. The frequency of overlap syndrome in patients who were evaluated in sleep laboratory and its effects on severity of obstructive sleep apnea syndrome and quality of sleep

Banu Salareci, Ali Fidan, Nesrin Kiral, Elif Torun Parmaksiz, Gulsen Sarac, Sevda Sener Comert, Benan Caglayan.
in the sleep laboratory in January 2005-January 2010 were analysed. All cases were examined for COPD, Asthma and severe daytime sleepiness according to Epworth Sleepiness Scale (ESS),Pulmonary function tests and polysomnographic tests were administered to all. For diagnosis of COPD, GOLD criteria, for EGG scoring, Rechtschaffen - Kales criteria and for respiratory scoring, AASM 1999 criteria were used. Out of 998 cases 98.2% were diagnosed as OSAS, 11.1% COPD,6.6% asthma,11.2% of OSAS cases had COPD. Age, frequency of male sex and ESS were significantly higher in patients with OSAS and COPD than patients with OSAS-without COPD. No significant differences in terms of BMI and sleep parameters were found in OSAS+asthma cases (6.7%) - BMI, frequency of female sex and ESS were found to be significantly higher than in patients with OSAS-with asthma, no statistical differences were found in terms of sleep parameters. In older male patients with OSAS+COPD is more frequent than in younger female patients. Asthma is more frequently seen in OSAS than general population. In asthmatics, sleep efficiency is lower, thermore ESS is higher. No relation between severity of OSAS and presence of COPD or asthma was determined. In patients with OSAS, symptoms of COPD and asthma must be questioned and pulmonary function tests administered.

P887

Risk factors of hypercapnia in patient with obstructive sleep apnea

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The severe obesity sometimes leads to a chronic alveolar hypventilation: obesity hypventilation syndrome (OHS). The association with OSAS is frequent. Aim: The aim of the present study is to specify favorising factors that lead to hypventilation in a population of obese persons with SAS and to deduce the type of association between OHS and SAS. Methods: 62 patients were enrolled. We excluded patient with bronchial obstruction and we have compared anthropometric, functional, gasometric and polysomnographic details of the group 1 (G1): OHS+ and of the group 2 (G2): obesity without hypventilation=53. Results: We haven’t identified a difference between the two groups concerning age, sex, frequency of smokers, nasopharynx region abnormalities, AHAS severity and the respiratory functional exploration. We noted that there is a positive interrelation between BMI and Paco2. We identified severe gasometric perturbation in G1 (Paco2=61±17.4 mmHg) versus G2 we noted a moderate hypoxemia. Patients of the group 1 make minimal desaturation of 63±17% and a SaO2 average of 81±20% what is meaningfully important than in the G2.

Conclusion: The alveolar hypventilation in SAS seems to be in correlation with the degree of obesity. The hypcapnia in the OHS is related neither with the SAS nor with obesity. The OHS-SAS association is usual but not syncronous, OHS is an autonomous disease.

P888

The impact of OSA on nocturnal hypoxia in obese patients with chronic asthma

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Background: There is increasing evidence that asthma, obesity and OSA co-exist with resulting increased usage of health care resources. This cohort may have worse asthma control due to increased nocturnal hypoxia augmenting airway and systemic inflammation. The prevalence of OSA and degree of hypoxia in obese patients with asthma remains unclear. Methods: A retrospective survey of obese patients with chronic asthma referred to the sleep clinic between 2009-2010 undergoing overnight sleep monitoring. Male sex was undertaken using RemLogic software (in-hospital polysomnography). Scoring of the respiratory data was as per American Academy of Sleep Medicine (AASM) guidelines 2007. OSA was defined as an apnoea/hypopnoea index (AHI) of ≥5/hour and moderate-severe as ≥15/h.

Results: 26 patients (19 females) were analysed. Mean (SD) BMI =45.2 (10.8)kg/m². Mean (SD) age=45±12.2years. Six had Type 2 Diabetes Mellitus and had hypertension. OSA was found in 12 (46%), 7 (27%) had moderate severe asthma. Those with OSA were more likely to have T3DM (31% vs 12%). There was no significant difference in BMI between the two groups. Those with OSA: (median (IQR))AHI=21.5 (13.45)/yr were more hypoxic during the night compared to those without OSA (AHI=2 (0.93)/yr). Mean nocturnal O2 sats (Mean (SD)): 91.6% (3.4) vs 95.3 (1.2), P=0.003, minimum O2 sats: 80.1% (11.8) vs 90.5% (2.0), P=0.001.

Conclusions: OSA is common in obese patients with chronic asthma. Patients with OSA in this group were more hypoxic during the night. Clinicians looking after obese chronic asthma patients should consider screening for OSA. Prospective studies are required to further establish the prevalence of OSA in obese asthmatic patients, and the value of CPAP in this group.

P889

Complex approach in the study of clinical and functional features in patients with severe bronchial asthma with and without respiratory disorder during sleep

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Aim of study: Comparison of clinical and functional diagnostic criteria in patients with severe bronchial asthma and in combination with obstructive sleep apnea

Materials and methods: 60 patients with severe asthma were divided into 2 groups: 1 group of patients with OSA were 30 patients (16 women and 14 men age (58±2.2) years) and II group of patients without OSA consisted of 17 women and 13 men age (50±2.1) years. In both groups PEV1, ranged from 54±3.1 to (58±2.6) months. The following studies were performed: respiratory function, polysomnography, diurnal blood pressure measurement. Holter monitoring of ECG.

Results: Asthma Control Test score revealed that patients with OSA had poor control of asthma symptoms (15±0.4) compared to patients without OSA (18±0.4) and higher scores for breathlessness on MRC8. Results of the questionnaire of OQ9 revealed that patients with OSA had more symptoms due to asthma and significant limitation of activity (67±1.3) than patients without OSA (60±2.6) (-p<0.05). Patients with OSA had an increase in pulse blood pressure, minimum of daily, a maximum of night, and a marked increase in the average heart rate per night, the increase variability in blood pressure. In the night period, compared with patients without OSA, p=0.05.

Conclusion: The use of a wide range of diagnostic methods will allow for an adequate pathogenetic treatment and improvement of disease control in patients with severe asthma and in combination OSA.

P890

Cardiopulmonary exercise response in children with obstructive sleep apnea syndrome

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Introduction: Cardiopulmonary exercise testing (CPET) is a valuable tool in the evaluation of cardiac and pulmonary function. In adults’ patients with obstructive sleep apnea syndrome (OSAS), recent studies addressed reduced exercise capacity, but there is no data in literature for pediatric patient. Aim: To evaluate cardiopulmonary response to exercise in children with OSAS.

Methods: Twenty seven subjects, without any systematic disease, aged 7 to 14 years (mean age 10.5±1.8 years), referring for evaluation of systematic snoring (>4 nights/week), underwent overnight polysomnography (PSG) and CPET. According to the Apnea Hypopnea Index (AHI) subjects were divided into two groups: A. mild OSAS (1≤AHI<5, n=15). B. moderate – severe OSAS – (AHI≥5, n=12). Control group (group C) consisted of 13 children.

Results: There were no significantly differences in age, sex, BMI among groups (p>0.05). Mild OSAS had 55.6% of children (group A) and moderate to severe 44.4% (group B). According to CPET children with OSAS had shorter duration of exercise (12.4±2.6min vs 13.3±2.5min), significantly lower VO2max (30.4±3.8 mg/kg/min vs 47.6±7.9 mg/kg/min, p=0.013), significantly lower VO2max (%) (77.4±15 vs 92.9±10.5, p=0.002), higher VO2 (%) (46.2±14.7 vs 43.7±1.9) and higher systemic blood pressure level at peak exercise (145±27.4mmHg vs 143.9±20.2mmHg) compared to control group. Children with mild OSAS had higher VO2max (%) (80.8±9.3 vs 73.8±11.7) but not statistically significant compared to moderate - severe OSAS.

Conclusion: The present study demonstrates that young patients (mean age 10.5±1.8 years) with and without mild OSAS, had reduced exercise capacity (lower VO2max) as compared to control group.
Obstructive sleep apnea in patients with idiopathic pulmonary fibrosis
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Background: The outcome of patients with idiopathic pulmonary fibrosis (IPF) is poor. Breathlessness and coughing are usually progressive and about 50% of the patients die within 3 years after diagnosis. The role sleep disordered breathing in IPF should be investigated.

Objective: The aim of this study was to investigate obstructive sleep apnea and associated daytime sleepiness in IPF patients and investigate the correlation between IPF and OSA.

Subjects and methods: 28 patients with IPF and 10 control subjects matched on age and BMI were included in the study. Sleep quality and its daytime consequences were assessed by the Epworth Sleepiness Scale and all-night polysomnography.

Results: 23 patients had an abnormal ESS (82.1%). 24 IPF patients (85.71%) had OSA; 21 patients (75%) had mild-to-moderate OSA, and 3 patients (10.71%) had severe OSA. AHI was statistically significantly correlated with, ESS, FVC, and TLC.

The prevalence of OSA in IPF patients

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild OSA</th>
<th>Moderate OSA</th>
<th>Severe OSA</th>
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<tbody>
<tr>
<td>Patient no.</td>
<td>10</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Patient %</td>
<td>42.85</td>
<td>32.14</td>
<td>14.29</td>
</tr>
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</table>

Conclusion: Patients with IPF are at high risk for OSA that may account for reversible daytime fatigue, possibly wrongly ascribed to IPF. Further, without treatment the sleep deprivation and lack of oxygen caused by sleep apnea increases health risks that have a significant negative effect on prognosis of IPF that already carries a poor prognosis.

Recommendation: Sleep evaluation should be extended to IPF patients routinely and the scientific work should focus on the improvement of sleep quality during sleep and day time.

Reference:

CPAP versus adaptive servoventilator (ASV) in patient with congestive heart failure and sleep disorder breathing
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Objectives: The aim of this study was to evaluate the effects of nocturnal ventilation by two different ventilatory support: CPAP or Adaptive Servo Ventilator (ASV) in patients with heart failure and sleep disorder breathing, in particular on echocardiographic parameters.

Methods: Ambulatory patients with congestive heart failure were screened for presence of Sleep Disorder Breathing (SDB). After a full night polysomnography the patients were divided in OSA, CSA-CSR or noSDB. All patients with SDB were titrated at the begin by CPAP but if CSA-CSR occurred or was not resolved they were switch to ASV.

All patients were evaluated at baseline and after six month of treatment by echocardiographic study and clinical evaluation.

Results: 52 patient were enrolled, age was 63.2±10.06, FE 31.2±8.9. Of them 13 patient (25%) were no SDB,21 were OSA (40%) 18 were CSA-CSR (35%). There was no differences among groups according to age, FE, TAPSE and NT-proBNP. All patients with SDB were admitted to nocturnal ventilation: 14 received CPAP, 16 received ASV while 9 refused treatment. After 6 months, any change was obtained in FE and NT-pro-BNP and in TAPSE, as well as on the other echocardiographic parameters in all groups.

Conclusion: In patients with CHF sleep disorder breathing are very common, however CPAP o ASV nocturnal ventilation have no impact on improvement of echocardiographic parameters.
Background: Recent data suggested that obstructive sleep apnea (OSA) is an important contributor of severe uncontrolled asthma. This study was aimed to investigate clinical features including asthma control, quality of life and airflow inflammation in adult asthmatics with high OSA risk.

Methods: A total of 217 patients with asthma who visited tertiary-care clinic were randomly recruited in this study. They completed Berlin questionnaire validated for Korean population. Patients with high OSA risk showed significantly older age, higher prevalence of hypertension, higher BMI, and non-atopic predisposition. High risk OSA group showed lower ACT score than low OSA risk group, but it was not statistically significant. The expressions of I-κB, IL-18, IFN-γ, and IL-23 were increased with intermittent hypoxia in high OSA risk group than low OSA group.

Conclusion: Asthma-related quality of life is significantly decreased in adult asthmatics with high OSA risk. Further studies are required to clarify the exact mechanism of asthma deterioration in OSA patients with high risk of hypoxia and inflammation.
Concerning APAP parameters, the 95-percentile pressure (P95) was lower in patients with positional OSA (p=0.003). Leaks and residual AHI were not different between the two groups.

Conclusions: We found a high prevalence of positional OSA in patients with mild to moderate OSA. Most patients with positional OSA were not compliant to therapy with APAP (64.7%). So, despite continuous positive airway pressure is considered the gold standard treatment of OSA, patients who did not have compliance should be encouraged for positional therapy.

P900

Automatic computation of apnea–hypopnea index in patients with sleep apnea based on multivariate adaptive regression splines

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Nocturnal polysomnography (PSG) is the gold standard for SAHS diagnosis. Despite its high diagnostic performance, PSG presents some drawbacks since it is complex, expensive and time-consuming. Simplified diagnostic techniques are desirable.

This study proposes a novel method to estimate the AHI based on automated analysis of oxygen saturation data using signal-processing methods as multivariate adaptive regression splines (MARS).

Patients and methods: 240 patients were included in the study. The patients were randomly divided into a training set with 96 patients (52 non SAHS and 44 SAHS) and a test set (60%) with 144 patients (48 non-SAHS and 96 SAHS). Oximetric recordings were parameterized by means of 14 characteristics from four feature subsets: time domain statistics, frequency domain statistics, spectral and nonlinear feature. Regression analysis was performed to estimate the functional relationship between the extracted features and the AHI. Multiple linear regression (MLR) and MARS were evaluated.

Results: The MARS algorithm achieved the highest performance with an intraclass correlation coefficient (ICC) of 0.90 (0.87-0.93), and MLR of 0.80 (0.74-0.85).

The highest accuracy of both algorithms was achieved for a decision threshold of 30 h-1, which represents a more conservative definition of SAHS. The MARS provided a correct decision rate of 93.75% (97.70 – 89.80) whereas the MLR model achieved 90.28 (95.12 – 85.64). Fig. 1 show Bland-Altman plots for MLR and MLP models.

Conclusions: The proposed MLP-based method could be used as an accurate alternative for SAHS diagnosis. Our results indicate a high agreement between actual and predicted AHI by MARS.

P901

Correlation of total sleep time (TST) by SenseWear Armband (SWA) and nocturnal polysomnography (NPSG), in a population with and without OSA

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Portable devices that determine TST may act as an adjunct to level 3 diagnostic devices. The SWA is such a device, and measures TST using a proprietary algorithm. Calculation of TST could improve the accuracy of a level 3 diagnostic device.

Aims: Correlation of TST by SWA and NPSG, in a population with and without sleep apnoea.

Methods: 89 consecutive patients undergoing NPSG because of a suspicion of OSA were an SWA on the same night. Patients were stratified by the presence and severity of OSA. Correlation coefficient for TST were determined between SWA and NPSG for all subjects and in the OSA subgroups.

The prevalence of normal PSG, mild moderate and severe OSA was 22 (24.7%), 31 (34.8%), 12 (13.4%) and 24 (26.9%) of 89 subjects. and the respective correlation coefficients were r=0.66, 0.74, 0.85 and 0.25. Clinically important differences are presented with Bland-Altman plots (Fig. 1 & 2).

Correlation of TST between the two methods was weakest in those with severe OSA. The determination of TST by SWA in a population with severe OSA is likely to be unreliable. NPSG remains the gold standard for determination of TST.
Methods: Between March-September 2010, the patients were submitted to an questionnaire. The sleep study was carried at home, with the Apnealink® device (AL). The Apnea/Hypopnea Index (AHI) was defined as suggestive of SAHS for AHI ≥ 5 event/hour (e/h) and classified as mild (AHI 5-14), moderate (AHI 15-29) and severe (AHI ≥ 30). According to the result of the AHI and the patient’s symptoms, they were referred for treatment.

Results: 118 patients, after the exclusion of 32, 52.7% were male, mean age of 58age ± 7 years. The average body mass index was 29.8±4.5 kg/m² and hemoglobin glycosylated 0.1% 7.2±1.7. There was a history of high blood pressure in 76.8%, Dyslipidemia in 54.6%, Ischemic heart disease in 8%. The patients complained, either frequently or occasionally, of snoring 56.6%, waking up 47%, poor sleep quality 35%, and witnessed apneas 17%, with a Scale of Epworth of 5.6±6.4. The mean AHI of the AL was 1.19±1.11 e/h (0.55). The AHI ≥ 5 was observed in 70.3% of the patients, 29% had AHI 15-29 and 9% AHI ≥ 30.

Conclusion: In our sample we find one high percentage of studies suggestive of SAHS, both mild, moderate and severe. The AL can be a useful tool for the screening of SAHS in patients with DM2 in collaboration with the PC.

P907

A portable device for assessment of daytime sleepiness
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Many studies have shown that sleepiness is a major cause of traffic accidents. Patients with obstructive sleep apnea usually have daytime sleepiness. Ewepth sleepiness scale has been used to subjectively assess daytime sleepiness in patients with OSA, but it was far from perfect. Osler test was a useful alternatively objective test for daytime sleepiness and has been used in clinical practice. However, Osler test was usually performed in hospital. It is important to develop an easy-to-use portable device to assess daytime sleepiness at home. We have recently developed a portable device based on the principles of Osler test. The purpose of the present study was to determine whether the onset of sleep detected by our portable device was the same as that detected by conventional polysomnography. Eight patients with OSA and eight normal subjects were studied. Sleep latency as judged by portable device was the same as that judged by conventional polysomnography and sleep latency measured from patients with OSA (18.1±9.1 minutes) was significantly shorter than that measured from normal subjects (> 40 minutes), p<0.01. In conclusion, the portable device designed for use at home was as useful as conventional polysomnography in assessment of daytime sleepiness. This work was funded by NSFC (Grant No. 8112108001).

P908

The use of bispectral index (BIS) as a marker of sleep staging
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BIS values decrease during sleep and change according to its stages. BIS values below 70 have a high sensitivity and specificity for detecting deep sleep. To analyze the impact of Portapres BP measurement on sleep quality during overnight PSG recordings with additional Portapres monitoring and 20 gender randomly with or without simultaneous Portapres BP measurement. The results of this pre-study suggest that Portapres BP measurement during overnight PSG does not have a clinically relevant impact on sleep quality and might therefore be a good diagnostic tool for future research on HT and BP changes in sleep apnea.

P909

Effectiveness of sequential automatic-manual home respiratory polygraphy scoring
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Introduction: Automatic home respiratory polygraphy (HRP) scoring functions can potentially confirm the diagnosis of sleep apnea-hypopnea syndrome (SAHS)
(obviating technician scoring) in a substantial number of patients. The result would have important management and cost implications.

**Objectives:** To determine the diagnostic cost-effectiveness of a sequential HRP scoring protocol (automatic and then manual for residual cases) as compared to manual HRP scoring, both with in-hospital polysomnography.

**Methods:** We included suspected SAHS patients in a multicentric study and assigned to home and hospital protocols at random. We constructed Receiver Operating Characteristic (ROC) curves for manual and automatic scoreings. Diagnostic agreement for several cut-off points was explored and costs for two equally effective alternatives were calculated.

**Results:** Of 366 randomized patients, 348 completed the protocol. Manual scoring produced better ROC curves than automatic scoring. There was no sensitive automatic or subsequent manual HRP apnea-hypopnea index (AHI) cut-off point. The specific cut-off points for automatic and subsequent manual HRP scorings (AHI>10 in both) had a specificity of 88% and 97%, respectively. The costs of manual and sequential HRP protocols were similar but less than the half that of polysomnography.

**Conclusion:** A sequential HRP scoring protocol is a cost-effective alternative to polysomnography, although with a marginal cost savings compared to HRP manual scoring.

**P910**

**Nasal pressure variation measurement with a microphone: A new low cost tool for diagnosis of obstructive sleep apnoea in a resource poor setting**

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**Background:** Lack of polysomnography in Sri Lanka leads to under investigation of OSA. Nocturnal saturation (SpO2) was used instead. Pressure variations due to turbulent flow through nose measured by a microphone fixed to a nasal cannula can be demonstrated to be proportional to nasal air flow, which allows calculation of obstructive events (OEs).

**Objective:** To test if nasal pressure variation measurement increases accuracy of diagnosis of OSA than SpO2 alone.

**Method:** 31 patients with clinical features of OSA were enrolled. Their overnight nasal pressure variations were picked up by a microphone fixed the distal end of a nasal cannula. The microphone signal was processed with elimination of baseline noise, and airflow measurements were derived. Airflow was analyzed together with SPO2 to calculate AHI.

**Results:** The Epworth sleepiness scale (ESS) of patients ranged 0 to 19 (mean 8) and Mallampati grade (MG) ranged 1 to 4 (mean 2). The mean BMI was 28.4 ± 3.1 kg/m2 (range 20.4 to 40.48). The oxygen desaturation index (ODI), the number of desaturations per hour, ranged 0 to 15 (mean 2). The mean AHI was 8 (range 0 to 40). AHI significantly correlated with ODI (Pearson correlation coefficient = 0.63 p< 0.00). 13 patients were diagnosed with OSA using AHI. ODI alone would result in 4 true positive, 9 false negative and 2 false positive diagnosis of OSA.

**Conclusions:** Nasal pressure variation measured by a microphone can be combined with SPO2 to increase accuracy of diagnosis of OSA in patients with clinical likelihood, in a resource poor setting. Further validation this technique may be used for a low cost portable home based apparatus to derive AHI.

**P911**

**STOP-Bang questionnaire as a preoperative screening tool for obstructive sleep apnoea in bariatric surgery patients**

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**Introduction:** STOP (snoring, tiredness, observed apnea, high blood pressure) questionnaire is a screening tool to identify surgical patients with high risk of obstructive sleep apnoea (OSA). Incorporating BMI, age, neck size, and gender (Bang) has been shown to further increase the sensitivity and negative predictive value. The STOP-Bang questionnaire has not been validated as a screening tool for OSA in patients undergoing bariatric surgery.

**Method:** We retrospectively reviewed prospective data on bariatric surgery patients. Patients were asked to answer the STOP-Bang questionnaire during their preoperative assessment. The BMI, age, neck circumference and gender were documented. All patients underwent overnight polysomnography as one of the assessments prior to bariatric surgery.

**Results:** A total of 49 patients were included. The mean age was 42±12.2 years; 29% males; BMI 48±8.2 kg/m2. We classified 43 patients (88%) as high risk based on the STOP-Bang questionnaire (23 positive responses). A total of 36 patients (73%) were diagnosed with OSA (AHI>5); 13 patients as mild, 10 patients as moderate (30<AHI<15) and 13 patients as severe OSA (AHI>30). The sensitivity of the STOP-Bang questionnaire for all OSA patients (AHI > 5) and for moderate and severe OSA patients (AHI > 15) was 92% and 100%, respectively. The specificity was 33% and 23%. The positive predictive value was 81% and 54%. The negative predictive value was 57% and 100%.

**Conclusion:** The preliminary results of the STOP-Bang questionnaire suggest a high sensitivity to detect bariatric surgery patients with obstructive sleep apnea. The negative predictive value was high only in patients with moderate and severe OSA.

**P912**

**Overnight pulse propagation time derivation from oximetry is associated with daytime blood pressure in patients with sleep apnoea**

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**Introduction:** The state of sleep is characterized by unloading of the autonomic nervous system and represents an opportunity to investigate the properties of the cardiovascular (CV) system. We investigated overnight pulse propagation time (PPT) as an indirect measure of vascular stiffness during sleep and its association with daytime blood pressure (BP).

**Methods:** The digital pulse wave, derived from finger oximetry, was recorded during sleep in 495 subjects (169 females, age 54±12 y, BMI 30.6±9.6 kg/m2, AHI 19±4.23 h) referred to five sleep centers. Office BP and established CV risk factors were assessed. PPT was calculated as the time between the top and the subsequent diastolic notch of the digital pulse wave. Mean PPT across the entire sleep period was calculated.

**Results:** PPT was associated with age, systolic BP, diastolic BP, the number of apneas as well as hypoxic events during sleep (r=0.54, 0.19, -0.21, -0.13, and -0.11, p<0.01 respectively). PPT was lower in patients with hypertension compared to normotensive (160±34 ms vs. 178±47 ms, p<0.01). In a multivariate analysis, PPT was independently associated with age, height, waist, smoking, hypertension and diabetes but not sleep apnea indices.

**Conclusions:** PPT determined by overnight oximetry reflects daytime BP and presence of hypertension. Assessment of PPT during sleep may be a useful tool for classification of overall CV function and risk.

The study was supported by Weinmann GMBH, the Swedish Heart and Lung Foundation and the University of Gothenburg.

**P913**

**Development of a new scale to evaluate sleepiness in obstructive sleep apnea (OSA): The Barcelona sleepiness scale (BSS)**

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**Background:** Excessive daytime sleepiness (EDS) is a common problem with serious consequences for health and social activities of the patients. There is no simple method to reliably quantify sleepiness. Objective methods (Multiple Sleep Latency Test, MSLT; Maintenance of Wakefulness Test, MWT) and subjective ones (Epworth Sleepiness Scale, ESS) are poorly correlated.

**Aim:** To develop and validate a new sleepiness scale for clinical use in OSA.

**Methods:** Generation of items: 30 consecutive patients with OSA and their partners were interviewed using focus group techniques and cognitive interviews generating a preliminary list of sleepiness items. This list was reduced to 16 common items. A composite of MSLT and MWT was calculated as an objective criterion of sleepiness. Exhaustive regression analysis of all the subsets of the list was performed. Mallow’s Cp minimization was used to choose the best item combination.

**Results:** Two items (In the morning, when I get relaxed & In the afternoon, while standing in a line) achieved the minimum Cp score and comprised the BSS. The correlation between the BSS and the composite score of MSLT and MWT was 0.51, much higher than that found with ESS (0.23).

**Conclusion:** Our data suggest that the BSS, a simple sleepiness scale of 2 items, shows the best correlations with objective tests.

Support by R01AT00318.

**P914**

**The role of desaturation index evaluated by nocturnal pulse oximetry in recognition of sleep apnea syndrome in patients with morbid obesity**

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**Introduction:** The nocturnal pulse oximetry is used as a validated screening tool for the diagnosis of obstructive sleep apnea syndrome (OSAS) in patients with morbid obesity. The nocturnal pulse oximetry is used as a validated screening tool for the diagnosis of obstructive sleep apnea syndrome (OSAS) in patients with morbid obesity.

**Method:**We retrospectively reviewed prospective data on morbid obesity patients. Nighttime oximetry was recorded with a pulse oximeter. A combined oximetry and sleep apnea apnea index was derived as the product of AHI and the percentage of time below 90% SPO2.

**Results:** A total of 34 patients were included (23 females, age 48±14 years). The mean AHI was 31±9 h. The mean percentage of time below 90% SPO2 was 15±5%. The correlation between the AHI and the percentage of time below 90% SPO2 was 0.73 (p<0.001).

**Conclusion:** The nocturnal pulse oximetry is used as a validated screening tool for the diagnosis of obstructive sleep apnea syndrome (OSAS).

158s
P915
The diagnostic value of self-reported symptoms for the detection of sleep apnea syndrome in stroke patients
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Introduction: Sleep apnea syndrome (SAS) is a common sleep disorder in stroke patients and associated with decreased functional recovery, increased risk of recurrent stroke and mortality. Despite the high prevalence and poor functional outcome, no guidelines for SAS screening in stroke rehabilitation are available.

Objective: This study evaluated the predictive value of a self-report symptom questionnaire, socio-demographic and clinical variables for detection of stroke patients with a high risk of SAS.

Methods: 306 stroke patients were screened with pulse-oximetry to determine their oxygen desaturation index (ODI). An ODI ≥ 15 was classified as a high risk of SAS. Potential predictors included socio-demographic variables, disease characteristics (history of stroke, hypertension), and self-reported symptoms (snoring, apneas, restless legs, morning headaches, waking up feeling unrefreshed, daytime sleepiness, falling asleep during daytime, fatigue, concentration loss, irritability and mood changes). With univariate logistic regression analysis, the associations between potential prognostic indicators and the primary outcome of ODI ≥ 15 were examined. Significant variables (p-value ≤ 0.20) were selected for a backward multivariate logistic regression and checked for co-linearity.

Results: The high risk of SAS was predicted by gender, body mass index, systolic blood pressure and the presence of the self-reported symptoms apneas, snoring, restless legs, morning headaches, waking up feeling unrefreshed, daytime sleepiness, falling asleep during daytime, fatigue, concentration loss, irritability and mood changes. The associations between potential prognostic indicators and the primary outcome of ODI ≥ 15 were examined. Significant variables (p-value ≤ 0.20) were selected for a backward multivariate logistic regression and checked for co-linearity.

Conclusion: The diagnostic value of self-reported symptoms SAS alone is very low in stroke patients. Therefore, socio-demographic and clinical variables should be included in the screening of SAS in stroke rehabilitation.

102. Pulmonary circulation: clinical aspects of PAH and associated PH

P916
Analysis of BMPR2 mutations, and endothelin-1 and nitric oxide synthase genes polymorphisms in pulmonary arterial hypertension
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PAH may be heritable. Much of what is known about the genetic basis of PAH is related to bone morphogenetic protein receptor 2 (BMPR2). We studied variants in BMPR2, endothelin-1 (ET-1) and nitric oxide synthase 2 (NOS2).

Patients with idiopathic and associated PAH were included. DNA was amplified for the 17 validated amplicons spanning the coding sequence of BMPR2 gene. For ET-1 gene the polymorphism K198N was selected because homozygous for Asn (T/T genotype) have higher levels of ET-1. NOS2 play a key role in endothelial dysfunction. CCTTT repeat polymorphism was studied. Larger studies are needed to confirm the significance of these findings.

Conclusion: Frequency of pathogenic mutations in BMPR2 in non heritable PAH was 14%. It would be interesting to perform functional studies of non pathogenic mutations to test their effect on BMP proteins. CCTTT repeat polymorphism showed statistical differences between patients and controls. K189N (G/T) polymorphism in ET-1 gene showed similar distribution.

P917
Evaluation of acute right ventricular failure in scleroderma and idiopathic pulmonary arterial hypertension
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Background: The ability to maintain adequate right ventricle (RV) function is paramount to survival in pulmonary arterial hypertension (PAH). However, little is known about RV function in patients with established PAH who are hospitalized for acute RV failure. Since RV adaptation is often worse in scleroderma-associated PAH (SSc-PAH) than in patients with idiopathic PAH (IPAH) despite similar afterload, we sought to compare RV function in hospitalized PAH patients using tricuspid annular plane systolic excursion (TAPSE), a non-invasive measurement of RV function that strongly associates with invasive hemodynamics and survival in both SSc-PAH and IPAH.

Methods: 47 patients with SSc-PAH or IPAH were evaluated during their first admission to a hospital for RV failure. All patients received transesophageal echocardiography. Vital signs and survival from time of admission were recorded.

Results: This cohort was composed of 91% females, with mean age 56 (range 23-81). There were 68% SSc-PAH and 32% IPAH patients. Mean TAPSE was 0.3 cm larger in IPAH compared to SSc-PAH (1.4cm ± 0.424, vs. 1.1cm ± 0.33, p=0.01). This relationship persisted despite controlling for age, admission vital signs, and time since diagnosis. 1-year mortality was 47%. Relative risk of mortality was 53% less in the IPAH group than in those with SSc (10% ± 0.32 vs. 63% ± 0.49, p=0.004).

Conclusion: SSc-PAH patients admitted with acute RV failure had both lower TAPSE and higher 1 year mortality than those with IPAH. This association suggests that TAPSE may offer prognostic information in patients with acute RV failure. Larger studies are needed to confirm the significance of these findings.

P918
Non-invasive versus invasive hemodynamic evaluation in an heterogeneous pulmonary hypertension population: When echo goes in the cath-lab
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Aim: To evaluate the accuracy of doppler echocardiography (DE) in estimating the key measurements of right heart catheterization (RHC) in an heterogeneous pulmonary hypertension population: When echo goes in the cath-lab

Methods: One hundred thirty-five consecutive patients referred to our PH tertiary center from January to December 2011 underwent standard DE within 1 hour of a clinically indicated RHC.

Results: Twelve/135 (9%) did not have PH. Of 123 PH patients with PH, 54 (40%) had group 1, 39 (29%) group 2, 22 (16%) group 3, and 8 (6%) group 4. PH echo showed a satisfactory correlation to invasive evaluation.

Conclusion: Despite DE is frequently inaccurate in estimating the CWP leading to a misclassification in 22/123 (18%) of analyzed patients. In particular, sensitivity of echo for pre-capillary PH was 82% and specificity 83%.

103. Pulmonary vascular diseases, pathobiology, and treatment

P919
Effect of targeted therapy on circulating endothelial progenitor cells in pre-capillary pulmonary hypertension
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Introduction: Endothelial dysfunction plays a key role in the development of...
pulmonary hypertension (PH). Bone marrow-derived endothelial progenitor cells (EPCs) may differentiate into functioning endothelial cells and contribute to endothelial repair.

**Aim:** To investigate whether the number of circulating EPCs in patients with pre-capillary PH differs from control subjects and to assess the effects of target therapy on circulating EPCs.

**Methods:** 36 control subjects (55±3 yrs) and 39 treatment naïve patients with pre-capillary PH (50±13 yrs; mean pulmonary arterial pressure 44±13 mmHg). 33 patients had pulmonary arterial hypertension (PAH) (17 idiopathic; 16 associated with chronic thromboembolic pulmonary hypertension (CTEPH)). 28 patients were re-evaluated at 6 months after the initiation of target therapy. The number of circulating EPCs was measured using flow cytometry. Circulating EPCs were defined as CD34+/CD133+ cells from a population that did not express CD45bright and expressed as the percentage of lymphomonocytic cells.

**Results:** In patients with pre-capillary PH the number of circulating EPCs was lower than in control subjects (Md 0.060 [0.037-0.075] and 0.086 [0.063-0.120] % lymphomonocytes, p<0.01)and was not correlated with functional class or hemodynamic measurements. After 6 months treatment, in patients with PAH (n=14) circulating EPCs increased from 0.058 (0.048-0.069) to 0.073 (0.050-0.097) % lymphomonocytes, respectively.

**Conclusion:** Patients with pre-capillary PH have reduced numbers of circulating EPCs that seems to increase as a result of targeted PH therapy. Supported by grants from SEPAR, SOCAP and GSK.

**P920**

**HBAlC in pulmonary arterial hypertension – A marker of prognostic relevance?**

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**Background:** Patients with pulmonary arterial hypertension (PAH) exhibit impaired glucose metabolism and increased insulin resistance. The clinical consequences of these metabolic changes are not known.

**Patients and methods:** We assessed HBAlC levels (indicative of perturbed glucose metabolism) in 115 patients newly diagnosed with PAH (79 female, 36 male; mean age 48.8 years; idiopathic n=66, collagen vascular disease n=17, congenital heart defect n=19, pulmonary veno-occlusive disease n=8, porto-pulmonary n=5). No patients had been diagnosed with diabetes, or received antidiabetic medication or systemic steroids. After initiation of pulmonary vasoactive treatment, patients remained in long-term follow-up.

**Results:** At initial presentation patients were in an advanced stage of disease (mean pulmonary arterial pressure 53±18 mmHg, median pulmonary vascular resistance 767 dyn.s.cm-5, cardiac index 2.3±0.8 l.m-1.min-1) with a six-minute walking distance of 131±70 m. They were categorised as NYHA functional class III-IV.

The HBAlC was 5.7±3.3% (75%). The 5-year survival rate for the entire group was 68%. Univariate Kaplan-Meier analysis and multivariate Cox proportional hazard regression analysis revealed that initial HBAlC quartile had a significantly better 5-year survival rate compared with the highest (83.6% versus 50.6%; log-rank p=0.038). Correcting for demographic and clinical covariates HBAlC was a predictor of all-cause mortality with a hazard ratio of 2.29 (95% CI 1.20 to 4.38; p=0.02) per 1 Unit increase.

**Conclusion:** In patients with pulmonary arterial hypertension, the HBAlC level at time of diagnosis is an independent predictor of long-term prognosis.

**P921**

**Efficacy and safety of oral bosentan in patients with Down’s syndrome and pulmonary arterial hypertension due to congenital heart disease**

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**Aim:** To evaluate the long-term effects of oral bosentan in adult patients with pulmonary arterial hypertension (PAH) due to congenital heart disease (CHD) with and without Down’s syndrome.

**Methods:** WHO functional class, 6-minute walk test (6MWT) and hemodynamics

<table>
<thead>
<tr>
<th>Clinical and hemodynamic variables before and after oral bosentan treatment in patients with and without Down’s syndrome</th>
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<tr>
<td>Down’s syndrome (n=18)</td>
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<tr>
<td>Basal</td>
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<tr>
<td>WHO functional class</td>
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<tr>
<td>Travelling distance (m)</td>
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<tr>
<td>mPAP (mmHg)</td>
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<tr>
<td>QP (l/min/m²)</td>
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<tr>
<td>PPQxS</td>
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<td>PVR (WU. m²)</td>
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<td>mPAP; mean pulmonary arterial pressure; QP: pulmonary cardiac index. PPQxS, pulmonary vascular resistance index.</td>
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</table>

PH patients with and without Down’s syndrome were assessed at baseline and after 12 months of bosentan therapy in CHD-PAH patients with and without Down’s syndrome.

**Results:** Seventy-four consecutive patients were enrolled: 18 with and 56 without Down’s syndrome. After 12 months of bosentan therapy, both groups showed an improvement in WHO functional class, 6-minute walk distance and hemodynamics. No differences in the efficacy of therapy were observed between the two groups.

**Conclusions:** Bosentan was safe and well tolerated in adult patients with CHD-related PAH with and without Down’s syndrome during 12 months of treatment. Clinical status, exercise tolerance, and pulmonary hemodynamics improved, regardless of the presence of Down’s syndrome.

**P922**

**Assessment of left ventricular function in COPD**

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**Introduction/Background:** To evaluate the left ventricular (LV) function in chronic obstructive pulmonary disease (COPD) in absence of known LV disease by echocardiography.

**Methods:** The study was an observational cross sectional study including 50 cases of stable COPD patients. Confirmation of cases for COPD were done by GOLD criteria and staged accordingly. Known cases of LV disease diagnosed on the basis of history, clinical findings, echocardiography and other investigations were excluded from the study. All cases were subjected to 2D echocardiography for LV evaluation.

**Results:** LV diastolic dysfunction was noted in 84% cases and both systolic and diastolic dysfunction was recorded in 2% case. We found statistically significant positive correlation of the LV diastolic dysfunction with the age of the patients, duration of symptoms and stage of diseases. But we did not find any significant co-relation between LV dysfunction with nature of symptoms and chest x-ray findings.

**Conclusions:** We concluded that there was a definite association between LV diastolic dysfunction and COPD even if the known causes of LV disease were excluded. We suggested that left ventricular function should be evaluated in COPD patients not responding to usual management even in absence of clinical evidence of LV disease.

**P923**

**Role of right ventricular ejection fraction by electrocardiogram-gated 320-slice CT in pulmonary hypertension**

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**Purpose:** Right ventricular function is an important determinant of exercise capacity and survival in pulmonary hypertension (PH). We aimed to study correlation of right ventricular ejection fraction (RVEF) determined by 320-slice CT with hemodynamic factors in patients with PH.

**Materials and methods:** 59 subjects (17 male, 56±13 yrs) with PH (41 chronic thromboembolic pulmonary hypertension and 18 pulmonary arterial hypertension) underwent enhanced retrospective ECG-gated volume 320-slice CT (Aquilion ONE, Toshiba) and right heart catheterization (RHC). CT images were reconstructed every 5% from 0.95% of the R-R interval. RV end-systolic and end-diastolic true volumes were measured from 3-dimensional reconstruction and used to calculate RVEF. We compared RVEF with the results of RHC.

**Results:** In 320-slice CT, RVEF were 46±4.14%. In RHC, mean mPAP (mPAP), pulmonary systolic (SV) were 41.5±11.3 mmHg, 655±317 dyne.s.cm-5 and 63.7±17.7 ml, respectively. The correlation coefficient of RVEF with mPAP, PVR, SV were -0.52 (<0.001), -0.63 (<0.001) and 0.61 (<0.001), respectively.

**Conclusions:** RVEF by ECG-gated 320-slice CT correlated significantly with PVR and SV in subjects with PH.

**P924**

**Relevance of persistent foramen ovale in PAH patients on pulmonary vasoactive treatment**

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**Background:** Persistent foramen ovale (PO) has been suggested to improve outcome in pulmonary arterial hypertension (PAH), despite causing hypoxaemia.

**Methods:** We evaluated the impact of PO on long term follow up in patients with PAH and severe hypoxaemia (pO2 < 65 mm Hg in air) on pulmonary vasoactive treatment. PO was detected on contrast-enhanced transcranial doppler sonography (TCD). After diagnosis of PAH the patients were started on treatment with PDE 5 inhibitor, endothelin receptor antagonist or prostanoids and remained in regular follow up.
Both patient groups exhibit the same baseline haemodynamic and clinical characteristics (P<0.05 for the differences in age and in pulmonary arterial pressure at rest (RAP)).

Results: Between January 2010 and December 2011 we detected 65 patients with PAH and severe hypoxaemia (age 57±14 years, 34 males, 39 IPAH, 18 PAH associated with CTD, 5 portopulmonary hypertension, others: 3). In 27 patients a PFO was detected on TCD (group 1). In 26 patients a PFO could be excluded (group 2). 12 patients had to be excluded because of ambiguous result in TCD.

Introduction: HIV-associated pulmonary hypertension (P-PAH) is an uncommon complication of the natural history of HIV infection and an independent factor of death in HIV-infected patients, regardless of the use of High Activity Antiretroviral Therapy (HAART).

Results: 3 patients were diagnosed as HIV-PAH (prevalence 0.25%). All the patients died within 2 years. Hepatitis C virus was present in 2 cases. There was a positive response to therapy with HAART at the moment of diagnosis of PAH. All of them had an initial positive response to therapy with bosentan. At 2 years from the beginning of the follow 2 patients had died by congestive cardiac failure.

Conclusion: The bibliography reflects, confluence with HIV-PAH is very common in the patients with PAH-HIV. There is a big variability in the evolution of the disease, the immunological status of the patients and the development of PAH. We did not find any predictive clinical or laboratory markers regarding which patients would have a poor prognosis. Because of PAH is the main cause of death in patients with HIV infection, and its low prevalence, a strategy for active search could increase early diagnosis so making easier both treatment and control of the disease.

P926 Effects of oral dual ERA therapy on pulmonary function testing and 6MWT in patients with idiopathic pulmonary fibrosis and pulmonary hypertension

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PH can be present in 37% to 59% of patients with IPF and is a predictor of mortality, which appears to be the cause of additional burden of exercise capacity. The aim of our study was to investigate the role of oral dual ERA therapy in 2 groups of patients with PH associated to IPF with or without Bosentan therapy during 24 months. The primary endpoint was the change of exercise capacity up to month 24, measured by a modified 6MWT. We evaluated retrospectively 16 patients: 8 pts (6 M; mean age of 72 yrs old) with moderate-sever PH and IPF (mPAP measured by RCH estimated as a mean value of 38±4.8 mmHg), treated with Bosentan (PH-IPF ERA group); 8 pts (5 M; mean age of 70 yrs old) with moderate PH and IPF not treated with Bosentan (PH-IPF control group). At baseline, there were differences about hemodynamics and pulmonary functional test profile between the two groups of pts. At T 24, the 6MWT increased in PH-IPF ERA group showing a mean increase of +150 mt, while in the PH-IPF control group we observed a reduction of 41% compared to the 6MWT values baseline (p = 0.003) in PH-PD group treated with ERA, FVC% and DLOC% were reduced of 8% and 32%, respectively, while in PH-IPF control group were reduced of 6.6% and 22% compared to the baseline (p = 0.009). The NYHA functional class was decreased in group treated with ERA (3.5 vs 2, p = 0.009) and improved in control group (2.12 vs 3.52, p = 0.007). In patients with moderate-severe PH and idiopathic pulmonary fibrosis, treated by Bosentan, there was a clinical improvement, measured by a six minute-walk test and a change in NYHA functional class, without affecting pulmonary functional test.

P927 Efficacy of exercise training in congenital heart disease associated pulmonary hypertension

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Objective: This prospective study was to assess the efficacy of exercise training as add-on to medical therapy in patients with pulmonary arterial hypertension associated with congenital heart disease (CHD-PAH).

Methods: Patients with invasively confirmed CHD-PAH received in-hospital exercise training for 3 weeks and continued at home. Efficacy parameters were evaluated at baseline, after 3 weeks and 15 months. Medical treatment remained unchanged during 15 weeks after baseline. The survival rate was assessed in a follow-up period of 21±14 months.

Results: Twenty consecutive patients (16 female, 4 male, mean pulmonary arterial pressure 60±23 mmHg, 9 patients were operated, 10 ASD, 11 VSD, 1 PFO, 2 PDA, 10 Eisenmenger syndrome were included. Patients significantly improved the mean distance walked in 6 minutes compared to baseline by 63±47 meters after 3 weeks (p<0.001) and by 67±59 meters after 15 weeks (p=0.001). Quality of life score (p=0.005), peak oxygen uptake (p<0.003) improved significantly by exercise training after 15 weeks. The 1- and 2-year survival rates were 100%. In one patient lung transplantation was performed 1 year after exercise training.

Conclusion: Exercise training as add-on to medical therapy may be effective in patients with CHD-PAH, improving quality of life, work capacity and further prognostic relevant parameters. It was also associated with an excellent long-term survival. Further randomized controlled studies are needed to confirm these results.

P928 The utility of brain natriuretic peptide in patients with stable chronic lung diseases

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Background: Cor pulmonary and pulmonary hypertension with chronic lung diseases are related to low exercise capacity and poor prognosis. Plasma brain natriuretic peptide (BNP) is a useful biomarker for monitoring of heart failure.

Objective: The aim of our study is to investigate the utility of BNP in stable chronic lung diseases (COPD, intestinal pneumonia, post-tuberculous lung disorder and others).

Methods: 111 patients with chronic lung diseases (male/female=73/38, age 74.8±8.0 yrs; excluding AF, rhythm, LVEF<40% and renal dysfunction) who were admitted to a three-weeks comprehensive inpatient pulmonary rehabilitation program, were assessed by pulmonary function tests, 6-minute walking test, and health-related quality of life as evaluated by SF-36. Plasma BNP was measured and echocardiography was also performed.

Results: It made no difference among types of lung disease for BNP (56.4±57.2 pg/ml, mean±SD). BNP (44-4.6±12.2 mmHg, mean±SD) and LVEF (62.3±11.5%, mean±SD). LVEF was not correlated with BNP. Compared BNP normol group (<18.4pg/ml) with high group (≥18.4pg/ml), there was a difference for BNP score at rest (0.8±0.77, 2.02±6.57, p=0.004*7) and 6MWD (262.2±73.3, 188.5±93.0, p=0.004*4). BNP was significantly correlated with 6MWD (r=0.2270, p=0.047*). BNP was also correlated with LVEF and SpO2 both at rest and on effort. But no significant correlation was shown between BNP and RVSP (r=0.1541, p=0.1540). Also, BNP was not correlated with QOL score (SF-36) and pulmonary function.

Conclusions: Plasma BNP was correlated with exercise capacity in stable chronic lung diseases. BNP may be a useful biomarker for administrating cor pulmonary and pulmonary hypertension with chronic lung diseases.

P929 Resolution of portopulmonary hypertension (PPOH) following liver transplantation

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Resolution of portopulmonary hypertension (PPOH) in chronic liver disease is an uncommon and usually benign event. However, when resolution occurs in patients with PPOH due to chronic liver disease, the possibility that there will be a sustained improvement of pulmonary pressures is unknown. In this prospective study, we determined whether patients referred for liver transplantation with PPOH, a consequence of portal hypertension (POPH), will have resolution of PPOH following liver transplantation.
Aims: To summarize the Mayo Clinic medical management and LT outcomes in moderate to severe POPH.

Methods: From 2002-2012, we analyzed the pulmonary vasoconstricting (PV) treatments and LT outcomes in consecutive POPH patients with right heart catheterization (RHC) criteria: mean pulmonary artery pressure - MPAP ≥ 35 mmHg and pulmonary vascular resistance - PVR ≥ 3 Wood units). All patients underwent sequential transesophageal echocardiography (TEE; both pre and post-LT) and RHC (pre-LT baseline, with therapy and intraop; not done post-LT). TTE assessed right ventricle (RV) size, function and RV systolic pressure estimate (RVSP).

Results: We managed 65 POPH patients; LT was attempted in 13/65 patients only if PV therapies resulted in MPAP < 35 mmHg and PVR < 5 wood units or normalization of PVR (< 3 Wood units). RV size and function were abnormal in all patients pre-LT. Mean pre-LT baseline treated hemodynamics were significantly improved: MPAP (44 ± 32 mmHg, p < 0.04); CO = 6.1 ± 9.7 L/min, p < 0.005; and PVR (5.9 ± 2.3 Wood units, p < 0.02). Intraoperative death (1), transplant hospitalization (death) (1) occurred. All survivors (9/13) normalized RV function; 6 normalized RV size; 69 were weaned off PV therapies. Post-LT mean RVSP improved significantly vs pre-LT (33 mmHg; range 26-41 vs 71 mmHg; range 38-121).

Conclusions: LT can result in POPH resolution (defined by sequential TTE) and liberation from PV therapies in selected patients.

P930 Factors determining outcome in patients with heart failure and normal ejection fraction
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Background: Patients with heart failure and normal left ventricular ejection fraction (HFNEF) face an adverse outcome. Our aim was to identify factors that determine prognosis.

Methods: Patients diagnosed according to current ESC guidelines were recruited. Death and/or hospitalization for HF were defined as primary outcome variables. Outcome groups were compared with respect to potential prognostic predictors using the t-test. Multivariable logistic regression analysis determined whether parameters of interest were associated with adverse outcome. P < 0.05 indicated statistical significance.

Results: Between December 2010 and January 2012, 49 patients (34 f/15 m, mean age 70 ± 8 years) were registered. After a mean follow-up of 5.4 ± 9 months, 14 (29%) patients were hospitalized or died. The adverse outcome group was characterized by higher body mass index (BMI, 35 ± 5 vs 29.4 ± 5, p < 0.005), higher systolic pulmonary pressure on echo (sPAP in mmHg, 69 ± 15 versus 55 ± 14, p < 0.005), shorter 6-minute walk distance (6-MWD in m, 271 ± 131 versus 364 ± 100, p = 0.019), higher transpulmonary gradient (TPG in mmHg, 15.4 ± 8 versus 12.4 ± 4, p = 0.013) and a higher pulmonary vascular resistance (PVR in dynes·cm−2, 2.3 ± 0.97 versus 19.8 ± 71, p = 0.030). Diabetes mellitus II (DM II) (75% versus 24%, p < 0.002) and atrial fibrillation (92% versus 51%, p = 0.033) were more prevalent among patients with adverse outcome. In the multivariable regression model, only DM II (OR 25.34 [95% CI, 2.06 to 311.45]; p = 0.012), BMI (OR 1.25 [95% CI, 1.00 to 1.56]; p = 0.02), and PVR (OR 1.02 [95% CI, 1.00 to 1.05]; p = 0.032) remained independent predictors of outcome.

Conclusions: Presence of DM II, higher BMI and higher PVR worsen prognosis in HFNEF patients.

P931 Pulmonary hypertension frequency in patients with chronic obstructive pulmonary disease exposed to biomass or tobacco smoke
Bunyamin Sertogullarinda, Hasan Ali Gumrukcuogulu1, Cengizhan Sezgi2.
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Introduction and aim: Pulmonary hypertension (PH) is a common complication of COPD. This study was designed to investigate the PH frequency and its relations in hospitalized tobacco and biomass exposed COPD patients.

Methods: The study was a retrospective review of inpatients with COPD defined by higher body mass index (BMI, 35 ± 5 vs 29.4 ± 5, p < 0.005), higher systolic pulmonary pressure on echo (sPAP in mmHg, 69 ± 15 versus 55 ± 14, p < 0.005), shorter 6-minute walk distance (6-MWD in m, 271 ± 131 versus 364 ± 100, p = 0.019), higher transpulmonary gradient (TPG in mmHg, 15.4 ± 8 versus 12.4 ± 4, p = 0.013) and a higher pulmonary vascular resistance (PVR in dynes·cm−2, 2.3 ± 0.97 versus 19.8 ± 71, p = 0.030). Diabetes mellitus II (DM II) (75% versus 24%, p < 0.002) and atrial fibrillation (92% versus 51%, p = 0.033) were more prevalent among patients with adverse outcome. In the multivariable regression model, only DM II (OR 25.34 [95% CI, 2.06 to 311.45]; p = 0.012), BMI (OR 1.25 [95% CI, 1.00 to 1.56]; p = 0.02), and PVR (OR 1.02 [95% CI, 1.00 to 1.05]; p = 0.032) remained independent predictors of outcome.

Conclusions: Presence of DM II, higher BMI and higher PVR worsen prognosis in HFNEF patients.

P932 A study of suspected pulmonary embolism (PE) in pregnancy management and a survey of guideline awareness
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Introduction: A recent report showed PE as a major cause of maternal death in the UK (CMACE/BLOG 2011:118(Suppl.)1:20-25); delays in diagnostic tests, treatment and poor knowledge of radiological safety are contributing factors. The Royal College of Obstetricians & Gynaecologists provides a protocol for suspected PE (Greet, I.A et al RCOG Green-top Guideline No 28 Feb 2007).

Aims: To gauge the level of guideline-awareness in medical trainees and evaluate the management of suspected PE in pregnancy in a UK District Hospital.

Methods: A survey of medical trainee knowledge of investigative pathways, radiation-exposure risks and guideline awareness. We also analysed management of pregnant women with suspected PE between 2009-11.

Results: 76% of medical trainees and 58% of Respiratory SpRs were unaware of guidelines and had poor knowledge of radiation risks.

Table 1. Respondents’ score of relative radiation risk to fetus: lowest (1) to highest (4) from the most commonly used investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Actual</th>
<th>Average Score</th>
<th>Difference</th>
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<tr>
<td>USS</td>
<td>1</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>CXR</td>
<td>2</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td>CTPA</td>
<td>3</td>
<td>3.8</td>
<td>0.8</td>
</tr>
<tr>
<td>QSCAN</td>
<td>4</td>
<td>2.7</td>
<td>-1.3</td>
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</table>

p<0.25 respondents.

41 women had symptoms of PE and were investigated as shown.

3 patients had PE confirmed (7.3%). Only 15% of women were investigated as per RCOG guidelines.

Conclusion: Our study revealed poor guideline-awareness for PE in pregnancy highlighting the need for better dissemination of these guidelines to medical trainees.

31
LaFarge/Miettinen's formula for the assumption of oxygen consumption (VO2) is one of the most used in hemodynamic calculations. Considering the importance of VO2 for the calculation of hemodynamics needed for disease evaluation (e.g. pulmonary hypertension), the need for an acceptable agreement between assumed and measured VO2 becomes obvious. A well-known variation of the original formula is the one by Bergstra. In both equations, age, sex and BSA are factors determining the VO2 plus the heart rate (HR) in the original formula. We compared directly measured VO2 with values calculated by both the LaFarge/Miettinen and the Bergstra equations. VO2 of 122 volunteers (20-65y) was directly measured by the Innocore™ (Innovision). VO2 was then recalculated by both the equations. Directly measured VO2 (VO2,DM) was 30.3±84 ml/min in males, 22.4±52 ml/min in females. VO2 calculated by Bergstra was 29.8±42 ml/min in males, and 23.3±48 ml/min in females. VO2 by LaFarge/Miettinen was 25.9±24 ml/min in males, 18.2±21 ml/min in females. Direct comparison of VO2,DM with calculated VO2 showed significant differences between all the methods. Factors found to be influencing the VO2 in our cohort included sex, HR and BSA whereas age seemed to have no effects. Significant correlations were found between VO2 and hemoglobin, oxygen saturation (SpO2), fitness level and systolic blood pressure.

Comparison of directly measured VO2 values with assumed data obtained by both the LaFarge/Miettinen and Bergstra equations showed that none of the formula is satisfying in terms of agreement with measured data. Using VO2 equations may result in major bias of hemodynamics and we therefore urge that resulting data should be interpreted critically.

Background: Pulmonary hypertension (PH) is associated with dysfunction of pulmonary endothelium. Stress- and pressure-dependent arterial endothelial dysfunction has been found in various cardiovascular diseases and data in PH is limited. The aim of this study was to evaluate peripheral endothelial function in IPAH and CTEPH and the relation to right heart function.

Methods: Flow-mediated dilation (FMD) of the brachial artery was determined in 26 patients (55±15y, PAPm: 48±13mmHg, PVR: 837±476 dyn s cm⁻5) with IPAH or CTEPH and 14 healthy controls. FMD was defined as the maximal change in relative vessel diameter after reactive hyperemia. Right ventricular function was examined by echocardiography.

Results: Patients and controls were similar in terms of peripheral flow conditions and cardiovascular risk factors including intima-media thickness (IMT) (IMT: 0.57±0.14 vs. 0.59±0.14 mm, p=0.39). Patients with PH demonstrated impaired peripheral endothelial function (FMD absolute change: 0.17±0.15 vs. 0.26±0.14 mm, p=0.008, relative change: 5.32±5.31 vs. 8.12±5.15%, p=0.01). There were no differences in peripheral endothelial function between IPAH and CTEPH (FMD: 3.39±5.76 vs. 4.12±3.80%, p=0.69). A correlation with right atrial diastolic area (RAAa) was found (r=0.43, p<0.01).

Conclusions: In addition to changes of the pulmonary vascular bed, PH is associated with peripheral arterial endothelial dysfunction in patients with IPAH and CTEPH. An increased RAAa points to chronically increased RV filling pressures and therefore a failing ventricle. The negative correlation with FMD might be regarded as result of impaired hemodynamics rather than a primary endothelial defect.

103. Pulmonary circulation: clinical PAH, registries and treatments

P935
Assessment of pulmonary hypertension in patients over 70
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Background: Recent registry data suggests that the average age of patients with PAH is rising. Pulmonary hypertension affects elderly people and there is increasing prevalence of cardiac and respiratory disease with age.

Methods: We report the findings for 120 consecutive patients aged over 70 referred to a tertiary service during 2008-09 for invasive haemodynamic studies to confirm or exclude a diagnosis of pulmonary hypertension.

Results: Four patients died within 30 days of referral and before being assessed, 15 patients did not undergo cardiac catheterisation. 50% of those assessed had an associated connective tissue disease. 36 patients had resting pulmonary artery pressures <25mmHg, eleven with respiratory and ten with cardiac disease to explain their symptoms. 65 patients were diagnosed with pulmonary hypertension following invasive studies: 19 related to left heart disease, 7 related to chronic lung disease, 7 CTEPH, five mixed aetiology, and 27 PAH. Three patients with idiopathic PAH, one case associated with an atrial septal defect, 23 with connective tissue disease. Follow up log10NT-proBNP testing in 24 patients with PAH showed a significant reduction at 12 months (-0.21, p<0.05 students’ t-test).

Conclusion: Pulmonary hypertension of all types may be present in older patients. Thoracic assessment may provide insight into the drivers of symptoms in older patients and help to guide treatment, which can be successful.

P936
Pulmonary hypertension in a district general hospital
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Introduction: There is an increasing awareness to identify patients with pulmonary hypertension (PH). Classification of the underlying cause defines further management and referral to specialist centres.

Aim: To assess the burden of PH at St Richard’s Hospital, which serves a population of 230,000.

Methods: All departmental transhoracic echocardiographs (TTEs) between 1st January 2009 and 30th June 2009 were reviewed using ERS suggested criteria to identify patients with possible PH and likely PH. Further investigations were performed to identify the underlying aetiology in those with likely PH.

Results: A total of 2038 TTEs were reviewed. 93 (5%) had likely PH with a pulmonary artery systolic pressure (PASP) of >50mmHg. 624 (31%) had possible PH with either the presence of additional echocardiographic variables suggestive of PH or a PASP 37-50mmHg. Of those with likely PH, 48% were male and 52% were female. The median age was 45 years (range 32-98). The overall mortality rate was 39% at 1 year and 58% at 2 years. Only 13% had right heart catheterisation locally.

Further Investigations In Patients Without Significant Left Heart (LH) Disease on TTE

<table>
<thead>
<tr>
<th>Percentage of Patients (%)</th>
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<tbody>
<tr>
<td>HRCT Chest</td>
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<tr>
<td>Other CT/Chest</td>
</tr>
<tr>
<td>CTPA</td>
</tr>
<tr>
<td>V/Q Scan</td>
</tr>
<tr>
<td>Abdominal USS</td>
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Further Investigations In Patients With Significant Left Heart (LH) Disease on TTE

<table>
<thead>
<tr>
<th>Percentage of Patients (%)</th>
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<tbody>
<tr>
<td>Lung Disease being CT</td>
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<tr>
<td>Lung Disease being CT</td>
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<tr>
<td>No Clear Diagnosis</td>
</tr>
<tr>
<td>Cardiac Shortening</td>
</tr>
<tr>
<td>53%</td>
</tr>
<tr>
<td>5%</td>
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</table>
P937
Pulmonary arterial hypertension prototype for national protocol and registry
Masb Marjahi1, Fanak Fahimi1, Babak Shariatzadeh1, Mohammad Reza Masjedi1,2,3,4,5,6,7. 1,2,3,4 National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran; 5, 2Clinical Chemical and Critical Care, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran

Background: Pulmonary Hypertension (PH) has been defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization. The idiopathic form so called idiopathic pulmonary arterial hypertension (iPAP) is a fatal disorder with a prevalence of 8.6 per million of population. In the current report we introduced a registry site for iPAP patients, named www.pah.ir for better delivery of subsidized antiphypertensive medications (now only Bosentan).

Methods: The registry was opened since November 2009. The first step of this action is to add iPAP patient’s information with a username and password in the site. Data entry is only available to the physicians and healthcare organizations via internet that are given a personalized username & password for entry. Following the patient’s profile submission in the site, a scientific committee composed of a cardiologist and a pulmonologist who are selected by Ministry of Health (MOH), would then evaluate the data. The eligibility of the patient to receive the medications is announced in the site after evaluation. If a patient is eligible, 82% of bosentan cost is paid by MOH.

Results: Till now, one hundred and sixteen patients (82 females, 34 males) are registered. Measured mean pulmonary arterial pressure by right heart catheterization was 69.24±17.63 mmHg (ranging from 35 to 115 mmHg).

Conclusion: The first online Iranian registry program for iPAP patients has recently been started and it is believed that this national program will supply essential information for health care providers in the field.

P938
Pulmonary hypertension: The experience of a large UK district general hospital
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Introduction: Recent advances in therapy make early identification of patients with Pulmonary Hypertension (PH) important. The 2008 consensus statement reported an average UK treatment rate of 24.9 per million. (1)

Aim: Our institution is a District General Hospital serving a population of 330,000. Our aim was to compare our treatment rate to the national average since the appointment of a physician with an interest in PH.

Method: Retrospective casenote review of patients attending our monthly PH clinic since 2006.

Results: We identified 102 Outpatient and 35 Inpatient referrals. 28 went on to receive specialist treatment for PH; mean age 66 (range 36-85); 24 female 4 male. Diagnoses: Chronic thromboembolic 10, Idiopathic 8, Collagen vascular disease 5, Congenital left to right shunt 2, COPD 2 and Portal hypertension 1. Haemodynamics (mean): Cardiac catheter: mean Pulmonary Artery Pressure (PAP) 66±16 mmHg (n=22, range 22-78), cardiac output 4.8±4.8 (n=22, range 2.5-7.7), cardiac index 2.8±1.8 (n=22, range 1.47-5.14) and pulmonary vascular resistance 760±220 (n=22, range 123-1600). Echocardiography: systolic PAP 66±40mmHg (n= 13), 13±4(10). Treatment: Oral Monotherapy 11, Prostanoid Monotherapy 1, Combination therapy 10. Intolerant of therapy 1, Pulmonary Endarterectomy 6, Transplant referral 4, Shunt repair 1.

Outcome: 18 out of 28 patients survive on medical and surgical therapies. This is equivalent to 54 patients treated per million, considerably higher than the national average [1].

Conclusion: Diagnosis and treatment rates for PH in the UK can be substantially improved in many areas by developing local services with the support of the regional Specialist centre.


P939
Stability of a new formulation of intravenous epoprostenol sodium
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Epoprostenol sodium with (undisclosed) excipients (epoprostenol XX) is a new formulation of epoprostenol, a pulmonary arterial hypertension treatment. This study assessed stability and determined shelf-life of epoprostenol XX. Stability of epoprostenol XX, either diluted for immediate use and tested at 25°C, 30°C and 40°C for up to 72h, or following storage for up to 8 days at 5°C after reconstitution and immediate dilution with further exposure at 25°C and 30°C for up to 48h, was assessed at 3,000, 15,000 and 60,000 ng/mL. Potency was measured by HPLC.

The time period over which potency remained ≥90%, relative to 100% at time 0, determined shelf-life. Relative potency of diluted epoprostenol XX for immediate use was temperature-dependent and remained ≥90% after storage at 25°C, 30°C and 40°C for 48h, 24h and 8h, respectively (3,000 ng/mL), 48h, 24h and 12h, respectively (15,000 ng/mL), and 72h, 48h and 24h, respectively (60,000 ng/mL).

The relative potency of reconstituted and immediately diluted epoprostenol XX after storage for 8 days at 5°C was ≥95% and remained ≥95% after further storage for 24-48h at 25°C or 30°C, depending on concentration. The table shows shelf-life of epoprostenol XX based on these results.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Maximum shelf-life of diluted solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3,000 ng/mL</td>
<td>Diluted solution for immediate administration for 48h at 5°C</td>
</tr>
<tr>
<td>and &lt;15,000 ng/mL</td>
<td>Diluted solution stored for 48h at 5°C</td>
</tr>
</tbody>
</table>

P940
Pulmonary arterial hypertension: Long term effects of oral ambrisentan on clinical status, exercise capacity and haemodynamics
Michele D’Alto, Emanuele Romeo, Paola Argiento, Anna Correra, Berardo Sarubbi, Antonello D’Andrea, Antonietta Caronna, Maria Pignatello, Nicola Grimaldi, Rafaela Calabro, Maria Teresa Russello. Cardiology, Second University of Naples, Monaldi Hospital, Naples, Italy

Aim: To evaluate the efficacy and safety of oral ambrisentan in adult patients with pulmonary arterial hypertension (PAH) by assessing its long term effects on clinical status, exercise capacity and cardiopulmonary haemodynamics.

Methods: This was a single-centre, open-label, single-arm, prospective study. Clinical status, resting transcutaneous oxygen saturation (SpO2), 6-minute walk distance, serumology and RHC were assessed at baseline (before starting ambrisentan therapy) and at one year follow-up.

Results: Twenty-seven consecutive adult patients (18 female, age 51±1y) with PAH (15 with idiopathic, 7 with congenital heart disease-related and 5 with connective tissue-related PAH) were enrolled. No patient treated with ambrisentan developed aminotransferase concentrations >3 times the upper limit of normal. After 12±4 months of therapy, an improvement in clinical status, 6-minute walk distance, pro-brain natriuretic peptide and haemodynamics was observed.

Clinical and haemodynamic variables at baseline and after oral ambrisentan therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Follow-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO FC</td>
<td>2.8±0.4</td>
<td>2.5±0.5</td>
<td>0.0027</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>322±166</td>
<td>350±162</td>
<td>0.0005</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>58±335</td>
<td>392±15</td>
<td>0.008</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.4±0.5</td>
<td>2.7±0.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>PVR (dyne/cm²)</td>
<td>10±6</td>
<td>8±4</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Conclusion: Long term ambrisentan therapy is safe and well tolerated at 12-month follow-up. Outcome in a significant improvement in clinical status, exercise capacity and cardiopulmonary haemodynamics.

P941
Incidence of subdural hematoma in patients with pulmonary arterial hypertension (PAH) in two randomized controlled clinical trials
Gerald Simoncini1, Lie-Ju Hwang1, Simon Teal2, Nazzareno Galleri2, 1Dept of Pneumology and TIC, Hospital Antoine Béclère, Paris, France; 2Institute of Cardiology, University of Bologna, Italy; 3Speciality Care Business Unit, Pfizer Inc., New York, United States

Background: Recent reports have emerged of increased incidence of subdural haematoma in patients with PAH, a serious adverse event with high mortality and morbidity. We evaluate the event rate in two randomized controlled trials, SUPER-1/2 and PACES-1/2.

Methods: In SUPER-1/2, 277 patients (IPAH, CTD-, CHD-PAH, WHO FC II-IV, mean baseline PVR 810.5 dyne/cm²) naive to targeted therapy received placebo or sildenafil 20/40/80mg TID for 12 weeks. In the open-label extension (OLE) phase patients were up-titrated (as tolerated) to 80mg TID. In PACES-1/2, 267 patients (IPAH, CTD-PAH, WHO FC II-IV, mean baseline PVR 810.5 dyne/cm²) were stable on IV epoprostenol received placebo or sildenafil (up-titrated to 80mg TID, as tolerated) for 16 weeks. Patients in both OLE trials received sildenafil for ≥3 years. Treatment with conventional agents (anticoagulants, diuretics, digoxin, oxygen, calcium-channel blockers) was permitted. We determined the annual event rate of subdural haematoma by treatment exposure in person-years. Patients on therapy does not include days on placebo.

Results: 2 patients experienced subdural haematoma, both during OLE, one received placebo in PACES-1, one sildenafil 40mg TID in SUPER-1. Patients were...
female, aged 58 and 62 years, diagnosed with IPAH, WHO FC III, mean PVR 557 (PACES-1) and 1073 dynes·cm⁻² (SUPER-1) at baseline. Both patients received oral anticoagulants. In SUPER-1 and PACES-1, 73 and 82% of patients were on anticoagulants, respectively. Incidence of subdural haematoma in these 2 studies was 0.0015 events/patient-year.

**Conclusion:** Subdural haematoma is a rare event in PAH patients in these 2 randomized controlled trials.

**P942**

Long-term bosentan therapy improves exercise capacity and hemodynamics in sarcoidosis-associated pulmonary hypertension

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**Introduction and Rationale**

Therapeutic options in sarcoidosis-associated pulmonary hypertension (SHP) are limited. We evaluated the long-term efficacy of Bosentan in SHP.

**Methods:** Out of 60 consecutive patients with SHP retrospectively reviewed, 45 were eligible for Bosentan therapy and followed for 36 months. We recorded baseline characteristics, hemodynamics and 6-minute walk distance (6MWD) before/after treatment, side effects, and vital status. Statistical analysis was performed using Student t-test and 1-way ANOVA.

**Results:** There were 66% Blacks; 64% women, with mean age of 53 years. Most patients (62%) had pulmonary fibrosis, and mean diffusing capacity was 37%. Additional SHP therapy was required in 45% cases; bosentan was discontinued in 5 patients due to liver abnormalities (incidence 1%). One- and 3-year survival rates were 73% and 48%. In 29 patients that remained on bosentan at three years, there were significant improvements in the 6MWD (p=0.005) and hemodynamics.

**Conclusions:** A subset of SHP patients may benefit from bosentan therapy.

**P944**

An international survey of current pulmonary arterial hypertension (PAH) management

Ioana Preston¹, Barbara Hinzmann², Nicholas Badwen³, Henning Tie牲⁴.

¹Pulmonary and Critical Care and Sleep Medicine Departments, Tufts University School of Medicine, Tufts Medical Center, Boston, United States; ²Global Market Research Department, Bayer HealthCare Pharmaceuticals, Berlin, Germany; ³Healthcare Department, Ipsos MORI, London, United Kingdom; ⁴Medical Clinic 2, University of Giessen Lang Centre, Giessen, Germany

**Background:** The therapeutic approach to PAH is evolving, multiple classes of agents are available and physicians from expert centres and the community treat this condition.

**Objectives:** To compare therapeutic management of PAH between countries and explore physicians’ attitudes towards PAH-specific therapies.

**Methods:** Quantitative online survey conducted in 5 European countries, the US, and Canada during 2010. Physicians involved in PAH treatment decisions with experience in managing PAH for ≥2 years completed a perceptual questionnaire. Retrospective clinical records from last 5 patients (pts) seen by each physician were analysed.

**Results:** 472 physicians (43% cardiologists, 29% pulmonologists, 20% rheumatologists, and 8% internists), 62% based in pulmonary hypertension centres, entered data for 2360 pts. Among those, 51% had idiopathic PAH and 42% had PAH associated with other conditions; 38% had significant physical limitation (NYHA functional class III/IV) at diagnosis. US pts were more likely to be diagnosed in the community (40%) than pts in Europe (6%) and Canada (28%). Globally, 73% were on PAH-specific therapy, with PDE-5 inhibitors, endothelin receptor antagonists, and prostacyclins used in 57%, 54%, and 26%, respectively. Of pts treated, 29% were on combination therapies; highest usage was in the US (36%) and lowest in Italy (17%). For 95% of pts, their physicians were satisfied to some degree with the current treatment regimen. Main reasons for satisfaction included symptom control or improvement and stable disease condition.

**Conclusions:** This multinational survey highlights significant differences in PAH management between countries and illustrates physicians’ perceptions of treating this condition.

**P945**

Comparison of the pharmacokinetic, pharmacodynamic, and safety profiles of three different formulations of intravenous epoprostenol sodium

Laurent Nicolas, Marcelo Gutierrez, Jasper Dingemans. Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland

A change in exipient of epoprostenol sodium, an i.v. pulmonary arterial hypertension treatment, from glycine-mannitol (epoprostenol GM, Flolan®) to arginine-mannitol (epoprostenol AM, Veletas®) or to undisclosed excipients (epoprostenol XX) has led to improvements in stability of the latter two formulations. The pharmacokinetic (PK), haemodynamic, safety, and tolerability profiles of these formulations were compared in this 2-part study. 20 healthy males in Part 1 and 20 different subjects in Part 2 received epoprostenol AM and epoprostenol XX, and epoprostenol GM and epoprostenol XX, respectively, in a crossover design, in sequential 2h i.v. infusions of 2, 4, 6 and 8 ng/kg/min.

PK profiles were assessed by analysing plasma concentration-time curves of the primary epoprostenol metabolites 6-keto-prostacyclin F1α (kPF) and 13,14-dihydro-prostacyclin F1α (dPF) obtained after treatment with the different epoprostenol formulations. For Part 1, the ratio of the geometric means (90% CI) of AUCs(0–∞) calculated after epoprostenol AM and epoprostenol XX treatment was 0.91 (0.88–0.95) for kPF and 0.88 (0.84–0.92) for dPF. For Part 2, the ratio of AUCs(∞) determined after epoprostenol GM and epoprostenol XX treatment was 0.97 (0.91–1.03) for kPF and 1.08 (1.02–1.14) for dPF. Haemodynamic variables, assessed by echocardiography, showed similar increases in cardiac output, cardiac index, and heart rate for all formulations with maximum values attained after 6–8h. Almost all subjects reported ≥1 adverse event.

These results suggest the 3 formulations of i.v. epoprostenol sodium have the same PK, haemodynamic, safety, and tolerability profiles.

**P946**

Lack of relevant pharmacokinetic interactions between the new dual endothelin receptor antagonist macitentan and sildenafil in healthy subjects

Patricia Sidharta¹, Paul van Giersbergen¹, Michael Wolzt², Jasper Dingemans³.

¹Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland; ²Clinical Pharmacology, Medical University of Vienna, Austria

Macitentan, a new potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). As PAH treatment may involve combination therapy of an ERA with sildenafil, the mutual pharmacokinetic (PK) interactions were investigated using a randomised, 3-way crossover study.
design (AC-055-106). Twelve healthy male subjects were treated as follows: A) macitentan alone for 4 days (loading dose of 30 mg, thereafter 10 mg o.d.), B) sildenafil alone for 4 days (20 mg i.d. on Days 1–3 and 20 mg o.d. on Day 4), C) treatments A and B combined. Plasma concentrations of macitentan and its pharmacologically active metabolite ACT-132577 (A and C) and sildenafil and its N-desmethyl metabolite (B and C) were measured on Day 4. Tolerability was assessed daily. The PK of macitentan was not altered (geometric mean ratios for Cmax and AUC, close to 1.0 with 90% confidence intervals within 0.8–1.25 bioequivalence limits) by sildenafil while the exposure to ACT-132577 decreased (Cmax, 0.82 [0.76–0.89]; AUC, 0.850 [0.80–0.91]). Exposure to sildenafil increased in the presence of macitentan (Cmax 1.26 [1.07–0.89]; AUC, 1.15 [0.94–1.41]), while that to N-desmethylsildenafil was unaffected. All treatments were well tolerated but combined treatment resulted in a higher incidence of adverse events (most commonly headache) and decreased diastolic blood pressure.

As no clinically relevant PK interactions were observed between macitentan and sildenafil, dose adjustment of either compound is not necessary during combined treatment.

P947

EPITOME-2: Evaluation of a new formulation of epoprostenol sodium in pulmonary arterial hypertension patients switched from an originally approved formulation

Oleger Sitbon1, Marion Delcroix2, Emmanuel Berrog3, Anco Boonstra4, Pilar Escriptano Sabi3a, Nazzareno Galibi4, John Granton5, David Langleben6, Thomas Piister7, Jean-Christophe Lemari8,9, Gerald Simonneau1,2, 3Service de Pneumologie, Hôpital Universitaire de Bicêtre, Université Paris-Sud, Le Kremlin Bicêtre, France; 2Pneumologie, Académie Hospitalière Gstaadspital, Gstaad, Switzerland; 3Servicio de Pneumología, Hópital Côte de Nacre-CHU, Caen, France; 4Pulmonology, VU University Medical Center, Amsterdam, Netherlands; 5Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain; 6Institute of Cardiology, University of Bologna, Italy; 7Pulmonary Hypertension Program, Toronto General Hospital, Toronto, Canada; 8Jewish General Hospital, McGill University, Montreal, Canada; 9Global Medical Science, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 10Effi-Stat, Effi-stat, Paris, France

Introduction: Epoprostenol sodium originally approved with glycine-mannitol excipients (epoprostenol GM; Flolan®) is an i.v. pulmonary arterial hypertension (PAH) treatment. Epoprostenol sodium with undisclosed excipients (epoprostenol XX) is a new formulation with improved room temperature stability and simplified storage requirements. EPITOME-2 is an ongoing PAH study evaluating switch from epoprostenol GM to epoprostenol XX.

Methods: Adult PAH patients treated with epoprostenol GM for ≥12 months and on a stable dose for the last 3 months were switched to epoprostenol XX. Changes from baseline to 3 months were evaluated for cardiac haemodynamic and clinical parameters, including pulmonary vascular resistance (PVR) and WHO functional class (FC). Safety and tolerability were also evaluated.

Results: Of the 42 patients enrolled, data are available for the first 10 completers. Mean (range) age was 45 (25–78) years and 5 were female. Mean (range) time from diagnosis was 10.57 (1.6–37.1) years. Following switch, patients remained on a stable epoprostenol XX dose at 3 months. There was no change from baseline to 3 months were evaluated for cardiac haemodynamic and clinical parameters. mPAP, mmHg 54.7 (42–65) 55.0 (37–73) CO, L/min 5.7 (4.3–6.7) 5.7 (4.6–7.4) WHO FC I, II, III (n) 1,5,4 1,6,3

Conclusion: Epoprostenol XX dose, haemodynamics and WHO FC.

Parameter

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
</tr>
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<tbody>
<tr>
<td>Dose, ng/kg/min</td>
<td>25 (7–58)</td>
<td>25 (7–58)</td>
</tr>
<tr>
<td>PVR, dyne/cm²/m²</td>
<td>666 (455–1164)</td>
<td>685 (356–1327)</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>54.7 (42-65)</td>
<td>55.0 (37-73)</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.7 (4.3–6.7)</td>
<td>5.7 (4.6–7.4)</td>
</tr>
<tr>
<td>WHO FC I, II, III (n)</td>
<td>1.5,4</td>
<td>1.6,3</td>
</tr>
</tbody>
</table>

Conclusions: There are no indications thus far of unexpected safety, tolerability, efficacy or dosing issues arising from switching patients to epoprostenol XX.

P948

Outcomes from use of targeted therapy in pulmonary hypertension associated with sarcoidosis (PHAS)

John Cannons, Colm McCagh, Joanna Pepke-Zaba, Karen Sheares. Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge, United Kingdom

Pulmonary hypertension is a recognised complication of sarcoidosis and may arise from several aetiological pathways. We report our experience of patients with PHAS-GroupV on targeted treatment.

Retrospective study of patient outcomes with PHAS. All patients underwent right heart catheterisation satisfying criteria for diagnosis of PAH. We reviewed 16 patients, 10 of whom died in mean f/u 32m. Patients dichotomised into 2 groups (responders and non-responders) based on improvement in log ntproBNP and PVR, dyne/cm²/m². Responders (n=8) Non-responders (n=5) p value

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=8)</th>
<th>Non-responders (n=5)</th>
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<tr>
<td>Age, y</td>
<td>60.8, 58.8</td>
<td>58.8</td>
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<tr>
<td>Gender, M:F</td>
<td>4.4, 1.2</td>
<td>1.2</td>
<td>0.32</td>
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<tr>
<td>Follow up, m</td>
<td>54.8, 17.4</td>
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<td>0.02</td>
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<tr>
<td>Sarcoid stage Blandy</td>
<td>5.3, 1.4</td>
<td>1.4</td>
<td>0.66</td>
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<tr>
<td>NYHA Functional Class</td>
<td>7.1, 5.1</td>
<td>5.1</td>
<td>0.81</td>
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<tr>
<td>mPAP</td>
<td>52.6, 45.4</td>
<td>45.4</td>
<td>0.11</td>
</tr>
<tr>
<td>CI</td>
<td>1.85, 1.64</td>
<td>1.64</td>
<td>0.20</td>
</tr>
<tr>
<td>PVR, dyne/cm²/m²</td>
<td>648, 685</td>
<td>685</td>
<td>0.046</td>
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<tr>
<td>FVC, %</td>
<td>61, 66</td>
<td>66</td>
<td>0.64</td>
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<tr>
<td>KCO, %</td>
<td>50, 53</td>
<td>53</td>
<td>0.79</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>7, 52</td>
<td>52</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusion: In this cohort of patients with PHAS, ambrisentan proved to be safe and efficacious for the therapy of PHAS patients. Ambrisentan resulted in significant improvement in hemodynamics and normalization of RV size, function and PVR in the majority of the patients.

P949

Ambisentan for therapy of portopulmonary hypertension (POPH): Update on safety and efficacy

Rodrigo Caru-Ceba, Karen Swanson, Michael Krowka. Pulmonary and Critical Care, Mayo Clinic, Rochester, MN, United States

Aim: To present an update of the long-term hemodynamic response and clinical outcomes of POPH patients treated with ambisentan.

Methods: Observational study of POPH patients from 01/2007 to 12/2011 treated with ambisentan. Clinical data, baseline and follow up thoracic echocardiograms (TTE) and right heart catheterisations (RHC) were accomplished and compared.

Results: A total of 27 patients with POPH were started on ambisentan (female=15). Median age (IQR) was 56 (53-60). Median follow up 874 days (472-1548). Medium time on ambisentan 391 days (259-839). Ten patients underwent liver transplantation successfully. Nine out of 27 patients died, 7 deaths due to complications of chronic liver disease, one patient of sepsis, and one died of an acute coronary syndrome. Follow up RHC data were available in 20 patients. Mean pulmonary artery pressure (mPAP) improved from 42 mmHg (35-57) to 38.5 (28-43.5), p=0.007; pulmonary vascular resistance (PVR) improved from 434 dyne·sec·cm⁻⁵ (311-611) to 228 (154-361), p=0.001; and cardiac output increased from 6 L/min (5.7-4.7) to 7.9 (6.4-9.2), p=0.005. TTE data showed that RV size and function improved in 19 and 18 patients respectively. Ambisentan was well tolerated in all but one patient who developed severe edema and required discontinuation after 2 weeks of initiation. No significant elevation of transaminases requiring discontinuation of the medication was identified.

Conclusion: In this cohort of patients with POPH, ambisentan proved to be safe and efficacious for the therapy of POPH patients. Ambisentan resulted in significant improvement in hemodynamics and normalization of RV size, function and PVR in the majority of the patients.

P950

Lack of relevant pharmacokinetic and pharmacodynamic interactions between the new dual endothelin receptor antagonist macitentan and warfarin in healthy subjects

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Macitentan, a new, potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). In this study (AC-055-105),
the effect of macitentan on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of warfarin was investigated in 14 healthy male subjects. Subjects received treatment sequence A/B or B/A separated by a 2-week washout. Treatment A: macitentan for 8 days (loading dose of 30 mg, thereafter 10 mg o.d.). On Day 4, a single dose of 25 mg warfarin was given with macitentan. Treatment B: A single dose of 25 mg warfarin on Day 1. Blood samples were assessed for warfarin PK (R- and S-warfarin) and PD (INR and Factor VII). Plasma trough levels of macitentan and its active metabolite, ACT-132577, were determined. Twelve subjects were included in the PK/PD analysis. The plasma concentration-time profiles of R- and S-Warfarin (Figure 1) and PD parameters of INR and Factor VII were comparable between treatments.

Warfarin did not impact the trough levels of macitentan and ACT-132577. Both treatments were well tolerated. Based on these results, no dose correction of macitentan or warfarin is needed when using these drugs together.

**P951 Absorption behavior of riociguat (BAY 63-2511): Bioavailability, food effects, and dose proportionality**

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**Introduction:** Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is currently investigated in the treatment of PH. Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent sGC stimulation and increasing sGC sensitivity to low NO levels.

**Aim:** To characterize the biopharmaceutic properties of riociguat including absolute bioavailability (BA), interaction with food, and dose-proportionality.

**Methods:** Pharmacokinetics (PK) following IV and oral administration of immediate release tablets were characterized in 3 open-label, randomized, crossover studies in healthy male subjects: absolute BA (n=22), food effect at 2.5 mg (n=24), and dose-proportionality over 0.5–2.5 mg (n=24). Safety and tolerability were also assessed.

**Results:** Absolute BA was 94% (90% CI: 83–107). A high-fat breakfast delayed absorption with little effect on the extent of riociguat absorption (ratio AUCoral/AUCfasted 88% CI: 82–95). PK were dose-proportional over 0.5–2.5 mg (common slope of AUC 1.09 [90% CI: 1.04–1.14]; Cmax 0.98 [90% CI: 0.93–1.04]).

**Conclusion:** Riociguat shows complete oral absorption, and no clinically relevant food effect. At 0.5–2.5 mg, riociguat systemic exposure increased dose-proportionally over 0.5–2.5 mg (n=24). Safety and tolerability were also assessed.

**P952 Effect of ambrisentan, bosentan and macitentan on human hepatic uptake and efflux transporters**

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**Background:** The putative mechanism for hepatic adverse reactions observed with bosentan, an endothelin receptor antagonist (ERA), is inhibition of the hepatic transport of bile salts (Fattinger K 2001). The ERA ambrisentan has a low risk of hepatic adverse reactions.

**Objective:** Bosentan, ambrisentan and macitentan, an experimental ERA in clinical development, were tested for inhibition of hepatic transporters in vitro.

**Methods:** Inhibition constants (IC50) were measured for human BSEP, sodium taurocholate cotransporting polypeptide (NTCP), multidrug resistance protein 2 (MRP2), P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), and OATP1B3 in transfected cell-lines. Known inhibitors were used as positive controls.

**Results:** The most potent inhibition observed was for OATP1B1 (range 2 μM to 47 μM). Ambrisentan had no measurable effect on BSEP and NTCP while inhibition was observed for bosentan and macitentan. The most potent inhibition of these transporters was observed for macitentan with IC50 values of 12 and 8 μM for BSEP and NTCP, respectively.

**Conclusions:** Macitentan inhibited hepatic transporters the greatest whilst ambrisentan showed little or no effect.

**P953 Bosentan influence on catecholamines levels in patients with idiopathic arterial pulmonary hypertension**

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**Aim:** To assess the influence of endothelin receptor antagonist Bosentan on catecholamines levels in pts with idiopathic pulmonary arterial hypertension (IPAH).

**Methods:** In the single-center comparative study we included 35 pts aged 35.2±9.6ys with IPAH confirmed by RHC (WHO Functional Class (FC) II-IV) without systemic inflammation signs. On top of stable therapy with anticoagulants, diuretics, glycosides, calcium antagonists for at least 3 months, Bosentan therapy was started 62.5 mg twice daily for 4 wks. At wk4 the pts were randomized 1:1 by the envelope method to bosentan 125 or 250 mg/day. At baseline, at wk3 and wk12 the pts underwent the clinical and lab assessment, including catecholamines (HPLC).

**Results:** At baseline IPAH groups were comparable by age, sex, disease duration, hemodynamic parameters. In both groups the levels of norepinephrine were significantly higher than normal values (139.9±41.2). Otherwise the epinephrine levels were decreased as compared with controls (69.4±12.1).

**Conclusion:** In IPAH pts Bosentan therapy influenced on catecholamines levels by significant reduction of initially increased norepinephrine levels. This effect was more pronounced in Pts treated with Bosentan 125mg daily.

**P954 Endothelin-1 downregulates BMP signaling in pulmonary artery smooth muscle cells**

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Increased endothelin-1 (ET-1) and decreased bone morphogenetic protein (BMP) receptor type 2 (BMPR2) signaling pathways have been shown to be implicated in the pathogenesis of pulmonary arterial hypertension (PAH). However, little is known about the interaction between these two signaling pathways and its implication in the generation of altered pulmonary artery smooth muscle cell (PA-SMC) phenotype in PAH.

We therefore quantified BMP signaling in PA-SMCs isolated from PAH patients and the effects of ET-1 treatment on the expressions of BMPR2, BMP agonists (BMP4) and antagonists (gremlin-1, gremlin-2 and noggin) in PA-SMCs.

We therefore quantified, by RTQ-PCR, the gene expressions of BMPR2, BMP agonists (BMP4) and antagonists (gremlin-1, gremlin-2 and noggin) in PA-SMCs. We therefore quantified, by RTQ-PCR, the gene expressions of BMPR2, BMP agonists (BMP4) and antagonists (gremlin-1, gremlin-2 and noggin) in PA-SMCs.
ET-1 (10-6M and 10-7M) on the expression of these BMP signaling members in PA-SMCs. Furthermore, we observed that oral BH4 supplementation increased in PA-SMCs isolated from PAH patients. Stimulation of control PA-SMCs with ET-1 induced an increase in mRNA encoding BMP antagonists (gremlin-1, gremlin-2 and noggin), while BH4 supplementation expression decreased dose-dependently. However, in ET-1 treated PA-SMCs, BH4 supplementation expression did not change. Furthermore, treatment levels of BMPR2 and BMP antagonists were similar as those observed in PA-SMCs isolated from PAH patients. Evidence derived ET-1 seems to contribute to altered BMPR2 signaling observed in PAH patients.

104. Pulmonary circulation: clinical diagnosis, treatment, end-points and animal models

P955
PLA2 polymorphism of platelet glycoprotein Ib/IIa but not Factor V Leiden and prothrombin G20210A polymorphisms is associated with venous thromboembolism in an animal model of bleomycin-induced lung fibrosis.

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Introduction: Inherited thrombophilic gene polymorphisms have been linked to the pathogenesis of venous thromboembolism (VTE). As they are very limited data on these polymorphisms in Iranian population we aimed to investigate them in these patients.

Methods: 72 patients with VTE and 306 healthy control subjects were recruited to the study. Genotyping from EDTA taken venous blood for the factor V Leiden (FVL), prothrombin (FII) G20210A, methylene tetrahydrofolate reductase (MTHFR) C677T and PLA2 polymorphisms was undertaken by PCR – RFLP.

Results: 570 investigated polymorphisms with the mean of 0.792 per individual and 151 with the mean of 0.494 were found in patients and control respectively (p=0.001). FVL and FII G20210A were found in 5.6% and 1.4% of the patients compared with 2.3% and 1% of the controls respectively (p=NS). PLA2 polymorphism of GPIIb/IIla was seen in 27.8% and 10.1% in patients and controls respectively (OR=3.4, CI: 1.08-6.44, P<0.001). 21.5% of carrier VTE patients compared with 9.6% of carrier controls had confluence of more than one genetic risk factor (P=0.007) and more recurrent events were occurred in them. Patients with PL A2 polymorphism had more recurrent events than the other patients (P=0.02). Patients with more than one genetic risk factors and recurrent events were younger.

Discussion: Higher prevalence of PLA2 polymorphism of GPIIb/IIla in VTE patients demonstrates the impact of this polymorphism in the pathogenesis of VTE in this population that need to manage these patients differently.

P956
Tetrahydrobiopterin improves pulmonary vascular remodeling following mouse-intraaeraloeal bleomycin administration

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Background/Objective: Pulmonary hypertension in pulmonary fibrosis portends a poor prognosis. Recent evidence suggests that tetrahydrobiopterin (BH4), the cofactor of nitric oxide synthase, is involved in pulmonary hypertension. However the role of BH4 in pulmonary hypertension secondary to pulmonary fibrosis is unknown. The current study investigated the role of BH4 on pulmonary remodelling in an animal model of bleomycin-induced lung fibrosis.

Methods: C57Bl/6J mice were instilled intra-tracheally with a single dose of bleomycin at 3.75 U/kg at day 1. BH4 (20mg/kg) or vehicle (control) was administered orally once a day, from day 1 until the end of experiment (day 14). At the end of the treatment period, mice were sacrificed and plasma, lungs and hearts were removed. Plasma BH4 concentration was measured by high performance liquid chromatography. The right ventricular (RV) wall of the heart was dissected free from the blood and weighed along with the left ventricle wall plus septum (LV + S), and the resulting weights were reported as RV/LV + S ratio to provide an index of right ventricular hypertrophy. TGF-β1 and ET-1 gene expression were measured by real-time RT-PCR in lung homogenates as pulmonary vascular remodeling markers.

Results: Bleomycin reduced ∼2.3-fold the BH4 plasmatic levels, augmented the RV/LV + S ratio to 0.075 mg/mg over control, and increased the ET-1 and TGF-β1 gene expression to ∼2.5-fold and ∼6-fold versus control respectively. Oral BH4 suppressed the bleomycin-induced right ventricular hypertrophy and reduced the ET-1 and TGF-β1 gene expression to control levels.

Conclusions: BH4 inhibits blomycin-induced right ventricular hypertrophy in mice.

P957
Molecular analysis of genes BMPR2 and KCNA5 in Spanish patients with pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH, OMIM 178000) is a rare and progressive vascular disorder characterized by obstruction of precapillary pulmonary arteries. PAH results from extensive remodelling of the pulmonary vasculature caused by an increased muscularization of small arteries and the twinning of the intima that leads to obliteration of small pulmonary arteries. Without treatment, progression of pulmonary hypertension leads to right ventricular failure and death in three years from diagnosis. Approximately 75% of patients with the familiar form of PAH have a mutation in the gene encoding bone morphogenetic protein receptor type II (BMPR2). However, some other candidate genes have been advocated, including potassium voltage-gated channel, shaker-related subfamily, member 5 (KCNA5). We included 30 PAH patients and 50 controls. The DNA extraction was performed with Qiagen FlexiGene DNA kit. BMPR2 and KCNA5 genes were amplified by PCR and sequenced. A total of 20 BMPR2 nucleotide changes were identified in 22 of 30 patients with PAH. Only 3 changes were identified with the Polyphen software as pathogenic (p.C84F, p.Q26L and p.W928Stop). These mutations were found in 4 patients. For KCNA5 gene 10 nucleotide changes were detected in 11 patients. Three were classified as pathogenic (p.F169R, p.R148P and p.E208X) we have found these mutations in 4 patients. None of the pathogenic mutations identified here were detected in a panel of control individuals from control endomorphisms.

In conclusion, mutations in genes BMPR2 and KCNA5 have been detected in the 28.5% of our pool of patients indicating that these genes are the most important genes implicated in the development of PAH.

P958
The German version of the Cambridge Pulmonary Hypertension Outcome Review (CAMPFHR) – Four-stage translation and validation

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Background and objective: Individuals with precapillary pulmonary hypertension (PH) experience impaired quality of life (QoL). A disease-specific outcome measure, the Cambridge Pulmonary Hypertension Outcome Review (CAMPFHR) is validated in English. We translated the instrument and validated it for German-speaking population.

Methods: A multi-step procedure including bilingual translation process, lay panel assessment, cognitive debriefing interviews, validation and evaluation was performed. It included 107 patients with precapillary PH (60 females, age 60+15 years) from centres in Austria, Germany and Switzerland.

Results: The translation process was straightforward. The field-test interview participants found the questionnaires relevant, comprehensible and easy to complete. Psychometric analyses showed that the German adaptations were successful. High test-retest coefficients for the scales after controlling for change in respondent’s QoL (FC: 0.92 to 0.96, EC: 0.85 to 0.99) indicated a high degree of reliability. The CAMPFHR scales had good internal consistency (Cronbach’s alpha coefficients 0.90 to 0.92 and 0.88 to 0.92, respectively). Also the three CAMPFHR scales (symptoms, activity limitations and quality of life) had excellent test-retest reliability (r=0.90-0.91, P<0.001) and internal consistency (Cronbach’s alpha >0.90).

Predicted correlations with the NYHA class, the 6-minute walking distance and the Nottingham Health Profile provided evidence of an excellent construct and group validiy of the CAMPFHR scales.

Conclusions: We have shown the CAMPFHR to be valid and reliable in the German population and recommend its use in clinical practice.

P959
Reference values for the 6-minute walk test in healthy children

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Background: The 6-minute walk test (6MWT) is a simple and reliable tool to assess exercise capacity in various diseases. The aim of this study was to establish reference values for the 6MWT in healthy children and adolescents in middle
Europe and to investigate the impact of age, anthropometrics, heart rate, blood pressure and reported physical activity on the distance walked.

Methods: Age- and sex-stratified children and adolescents between 5-17 years had short questionnaire assessments about the health state and physical activities. Thereafter anthropometrics and vitals were measured, a 6MWT was performed according to guidelines and exercise vitals were reassessed.

Results: Age-adjusted 6MWT distance from 496 children (252 girls) was obtained. Age, height, weight and the exercise heart rate all predicted the distance walked according to different regression models: age was the best single predictor and mostly influenced walk distance in younger age, anthropometrics were more important in girls and adolescents. Exercise heart rate was an important distance predictor in addition to age and outreach anthropometrics in the majority of subgroups assessed.

Conclusion: Performing the 6MWT is feasible and practical in children and adolescents. The 6MWD depends mainly on age, however, exercise heart rate, height and weight significantly add information and should be taken into account mainly in adolescents. Reference equations allow to predict 6MWT distance and may help to better assess and compare outcomes in young patients with cardiovascular diseases.

P960
The adenosine A2B receptor antagonist GS-6201 reduces small artery muscularization and plasma endothelin-1 in a short term cigarette smoke exposure model
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Adenosine plays an important role in the development and progression of lung injury with increased levels of adenosine and expression of A2B receptors. The A2B antagonist GS-6201 has shown anti-inflammatory effects in an acute model of cigarette smoke-induced lung injury. We have previously shown that exposure to cigarette smoke induces small artery remodelling and increased pulmonary arterial pressures in the guinea pig. Because A2B adenosine receptors are highly expressed in the pulmonary vasculature, we hypothesized that the A2B antagonist GS-6201 may prevent this remodeling. We exposed groups of six guinea pigs to 5 cigarettes per day 5 days per week for 4 weeks; groups were given oral vehicle, GS-6201 in doses of 1, 10 and 30 mg/kg (QD) 2 hours prior to smoke exposure, and a group was exposed to room air. 24 hours after final exposure, the animals were anesthetized and pulmonary arterial pressure was measured directly. One lung lobe was lavaged, and inflammatory cell counts obtained, one lobe was inflated with agarose for morphometric analysis of muscularization of small pulmonary arteries. Plasma was obtained for measurement of endothelin-1 (ET-1).

We found that cigarette smoke induced a non-significant increase of the pulmonary arterial pressure, but a significant increase in small arterial muscularization that was reduced by GS-6201 in a dose-dependent manner. Plasma ET-1 was increased by smoke exposure, and significantly decreased in a dose-dependent manner by GS-6201 as well. Our data suggest that adenosine receptor A2B antagonists may prevent the development of COPD associated pulmonary hypertension.

P961
End-tidal CO2 pressure may facilitate differential diagnostics between PH patients with chronic heart or lung disease and CTEPH
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Background: End-tidal CO2 pressure (PETCO2) is a simple parameter, which may be assessed at rest or during exercise during cardiopulmonary exercise testing (CPET). PETCO2 changes have been described in patients with cardiac failure and acute pulmonary embolism, as well as in pulmonary hypertension (PH), but it is not known if PETCO2 may be helpful in differentiating between PH subgroups.

Patients and methods: We retrospectively investigated PETCO2 data of patients with a meanPAP > 25 mmHg at rest, due to chronic left heart (LH-PH), and pulmonary disease (LH-PH) or CTEPH. PETCO2 was measured at rest and during maximal exercise. Mean values were compared by ANOVA and multiple comparisons were performed with Scheffe as post hoc test.

Results: N=46 patients were included (LH-PH: n=14, mean PAP 40±11 mmHg, PVR 327±188 dyn s cm⁻⁵, PWP 21±5 mmHg; Lu-PH: n=15, meanPAP 34±8 mmHg, PVR 441±266 dyn s cm⁻⁵, PEVI10.2%±3.7%); CTEPH: n=17, meanPAP 46±10 mmHg, PVR 732±308 dyn s cm⁻⁵). PETCO2 at rest was 4.97±1.04 mmHg, 4.70±1.19 mmHg, and 3.55±0.71 mmHg in LH-PH, Lu-PH and CTEPH patients. The PETCO2 difference between LH-PH and CTEPH was 1.38 (CI 95% 0.48 to 2.29 p=0.001), and between Lu-PH and CTEPH 1.14 (CI 95% 0.24 to 2.04 p=0.007). Comparable similar results were obtained with PETCO2 during maximal exercise.

Conclusion: PH caused by CTEPH is characterized by lowered PETCO2 as compared to PH due to chronic heart or lung disease.

P962
Human pentraxin 3 (PTX3) as a novel biomarker for the diagnosis of pulmonary arterial hypertension
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Background: Although inflammation is an important feature of pulmonary arterial hypertension (PAH), the usefulness of local inflammatory markers as biomarkers for PAH is unknown. In this study, we tested plasma concentrations of human pentraxin 3 (PTX3), a local inflammatory marker, would be a useful biomarker for detecting PAH.

Methods: Plasma PTX3 concentrations were evaluated in 50 PAH patients (27 with idiopathic PAH, 17 with PAH associated with connective tissue disease (CTD-PAH), and six with congenital heart disease). 100 age and sex-matched healthy controls, and 34 disease-matched CTD patients without PAH. Plasma concentrations of B-type natriuretic peptide (BNP) and C-reactive protein (CRP) were also determined.

Results: Mean PTX3 levels were significantly higher in all PAH patients than in the healthy controls (4.0±0.37 vs. 1.9±4±0.99 mmHg, respectively; P < 0.001). Using a threshold level of 2.84 mmL, PTX3 yielded a sensitivity of 74.0% and a specificity of 84.0% for the detection of PAH. In CTD-PAH patients, mean PTX3 concentrations were significantly higher than in CTD patients without PAH (5.02±0.69 vs. 2.40±0.14 mmHg, respectively; P < 0.001). There was no significant correlation between plasma levels of PTX3 and BNP or CRP. Receiver operating characteristic (ROC) curves for screening PAH in patients with CTD revealed that PTX3 (area under the ROC curve 0.866) is superior to BNP. Using a PTX3 threshold of 2.85 mmL, maximized true-positive and false-negative results were obtained (91.4%, specificity 85%).

Conclusion: Plasma concentrations of PTX3 are more excellent than BNP in the detection of PAH, especially in patients with CTD.

P963
Acute vasoreactivity testing with sildenafil vs nitric oxide in patients with PAH
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Introduction: Vasoreactivity testing with inhaled nitric oxide (iNO) is recommended in patients with pulmonary arterial hypertension (PAH) because of therapeutic and prognostic implications. Sildenafil is a promising agent for acute vasoreactivity testing since it is more stable and easier to handle than iNO. But it is not known if the acute responses to sildenafil and NO are equal.

Objectives: The aim of this study is to compare acute vasoreactivity in response to sildenafil vs iNO in patients with PAH.

Methods: In this retrospective, open-label, and single-centre study we included all patients who were admitted to our adult pulmonary hypertension unit from 2002 to 2011, met the criteria for PAH, and underwent vasoreactivity testing with iNO and sildenafil.

Results: 198 patients were included. 9.6% of the patients met the responder criteria (as defined by the current guidelines) for iNO and 11.6% for sildenafil. Intra-individually, the responses in mPAP and cardiac index (CI) after sildenafil and NO administration correlated (r=0.516, p<0.001, r=0.451, p<0.001). At mean there was a significantly higher CI after sildenafil than after iNO application (CIANO=2±0.4±0.69m[mL/min/m²], CIiNO=2.56±0.76ml/min/m²). Applying the current response criteria, the sensitivity to detect NO-responders by sildenafil vasoreactivity was 81.3%, the specificity was 94%, the positive predictive value was 56/

Conclusions: In PAH patients the vasoreactive response to sildenafil is stronger than to iNO. The intra-individual vasoreactive responses to both drugs correlate. The sensitivity to detect NO-responders by using sildenafil for vasoreactivity testing was moderate, but the positive predictive value was low.

P964
The clinical role of routine non-invasive parameters in the diagnostic work-up of patients with risk for pulmonary hypertension
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Background: The work-up of patients with risk for pulmonary hypertension (PH) is challenging. Doppler Echocardiography is the most specific non-invasive screening tool, but the role of other routine measures in the diagnostic work-up of patients is not clearly defined. We hypothesized that a diagnostic algorithm using a combination of simple non-invasive parameters might help to identify patients with PH.

Objective: Pulmonary hypertension (PH) is diagnosed by right heart catheterization. Doppler Echocardiography is the most specific non-invasive screening tool, but the role of other routine measures in the diagnostic work-up of patients is not clearly defined. We hypothesized that a diagnostic algorithm using a combination of simple non-invasive parameters might help to identify patients with PH.
Patients and methods: We retrospectively analyzed all patients who received a right heart catheterization and a routine non-invasive assessment between 2005 and 2010. The pretest probability for PH was 50%. As first step, the ratio of the S and R waves of lead I of the ECG (<0.9) was considered as right axis deviation (RAD). In a second step, further simple non-invasive parameters were analyzed by logistic regression for their association with PH.

Results: We included n=395 patients. RAD was present in n=87 of them. Within these, n=82 had PH, and n=5 did not, revealing a positive predictive value of 94%. In the remaining n=308 patients, we identified n=60 patients with a combination of NT-proBNP>393pg/Ml, DICO<0.5, arterial SO2<95% and Borg dyspnoe score<3 at the end of six-minute walk test, of which only n=4 suffered from PH revealing a negative predictive value of 93%.

Conclusion: Our retrospective analysis on a large, heterogeneous cohort of subjects including patients with and without PH suggests that the combination of simple, non-invasive parameters allows a reliable identification of subjects both with a very high and with a very low probability of PH. Further validation in prospective, population based studies is needed.

P965
Patients’, relatives’ and practitioners’ views on pulmonary arterial hypertension
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Purpose: To study practitioners’, patients’, and relatives’ views regarding pulmonary arterial hypertension (PAH) and identify potential improvements in medical care strategies.

Methods: A qualitative study based on semi-structured interviews involving 16 patients, 4 relatives, and 9 practitioners.

Results: Patients, relatives, and physicians have divergent perspectives on PAH. The discrepancies identified concerned their perceptions of the illness and its impact on patients’ daily lives. Patients had a broader view, including social, identity, financial, and functional dimensions of PAH impact on their lives, while practitioners’ views were more focused on functional aspects. The study also pointed out divergent approaches among physicians to assessing patients’ New York Heart Association functional class. The expectations of patients, relatives, and physicians also differed. Patients expected improvement in PAH diagnosis and better coordination between primary care physicians and PAH medical centers. They also valued reduction of side effects, less restrictive medications, and greater consideration of their views in the medical decision making process. Physicians’ expectations focused more on identifying and validating therapeutic strategies.

Conclusion: Our results suggest several potential improvements in patient management. Finally in order to obtain more consensus-based treatment and to achieve a more uniform approach of PAH functional impact assessment process. The findings may also be useful for enhancing therapeutic education for patients and their families. Finally, this qualitative database may help develop patient-reported outcome measures with better content validity.

P966
A slower life in a smaller world. Patients’ perspective on living with pulmonary arterial hypertension
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Background: The pulmonary arterial hypertension (PAH) patient management pathway is often defined from the clinician or commissioner perspective. We wanted to go an in-depth understanding of the patient self reported experience living with PAH.

Objectives: Working to understand how a diagnosis of PAH impacts a patient’s quality of life. Exploring the journey through first symptoms to specialist care and the ‘life changes’ needed.

Methods: Over 1000 General Practitioners were approached to put forward patients with PAH to participate in semi-structured, in depth qualitative interviews designed to determine the key themes emerging from the individual experiences of PAH. Interviews were audio-recorded for subsequent analysis using interpretive phenomenological analysis methodology.

Results: A total of 8 patient view interviews were analysed who had the following underlying aetiologies: IPAH (n=3) and AChD (n=5), aged between 30 – 70 years and treated with different targeted PAH therapies. Patients interviewed were being managed at 4 different PAH Specialist Centres in the UK. Areas where patients’ needs were perceived not to be met by healthcare delivery included: 1) patient information materials did not cover PAH impact on co-morbidities, 2) dealing with a crisis on their own, 3) effective counseling when treatment fails, 4) securing disability allowance, 5) being able to live a normal life, 6) minimising the impact of PAH on their family.

Conclusions: Specific areas have been highlighted where healthcare delivery does not meet patients’ needs. Living with a rare disease has its own unique challenges requiring careful consideration with potential to further improve the patient experience.

P967
Exhaled nitric oxide in reactive pulmonary hypertension
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Background: Pulmonary hypertension (PH) frequently complicates heart failure. In some patients, pulmonary vessels undergo reactive changes due to the chronic elevation of the left ventricular pressure, resulting in severe pulmonary hypertension and increased transpulmonary gradient (TPG). There is evidence that nitric oxide (NO) synthesized by the respiratory epithelium plays a role in the regulation of pulmonary artery pressure.

Aims and objectives: To evaluate whether exhaled NO has a role in reactive PH

Methods: Seven patients with reactive PH (rPH) were compared to 14 patients with passive PH (pPH) and to 15 control patients without PH. All the patients underwent heart catheterization, lung function tests and exhaled NO (FENO), assessed at multiple flow-rates. Alveolar NO and bronchial NO flux (JawNO) were calculated using the slope-intercept model.

Results: The results are displayed in the Table.

Comparison of haemodynamics. lung function and JawNO among CP, rPH, pPH patients

Patient with PHs had significantly lower FEV1/VC% ratio, lung diffusion (TLCO) and JawNO. JawNO was closely inversely related to TPG (r=0.385, p=0.032). Conclusion: It is still unknown why some patients develop severe and/or fixed PH with the same degree of elevated left-sided filling pressure. Our findings suggest that decreased bronchial NO flux and lung diffusing capacity may contribute to reactive PH.

P968
Unique hemodynamic profile of HIV+ patients with portal hypertension: Comparison with HIV-associated PAH and porto-pulmonary hypertension
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Introduction and objectives: HIV-associated PAH (HIV-PAH) and porto-pulmonary hypertension (PoPH/TN) have well described cardiovascular profiles. However, little is known about the hemodynamic characteristics when both conditions coexist (HIV-PoPH/TN). We hypothesise that in these cases right heart catheterisation (RHC) findings differ from those with HIV-PAH and PoPH/TN alone.

Methods: We performed a retrospective analysis of consecutive patients with HIV-PAH, PoPH/TN and HIV-PoPH/TN and compared their baseline RHC results: right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary artery occlusion pressure (PAOP), cardiac index (CI), pulmonary vascular resistance index (PVRI) and pulmonary artery saturation (Psat). One-way ANOVA and Student t-test between groups were used for analysis.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-PAH</th>
<th>PoPH/TN</th>
<th>HIV-PoPH/TN</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>12.4 (6.4)</td>
<td>7.6 (4.3)</td>
<td>13.9 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>45.5 (16.8)</td>
<td>46.9 (10)</td>
<td>48 (13.7)</td>
<td>ns</td>
</tr>
<tr>
<td>CT (L/min/m2)</td>
<td>2.3 (0.8)</td>
<td>3.4 (1.2)</td>
<td>2.6 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>10.2 (3.5)</td>
<td>8.9 (3.2)</td>
<td>10.8 (3.9)</td>
<td>ns</td>
</tr>
<tr>
<td>PVRI (Wood/m2)</td>
<td>13.8 (12.5)</td>
<td>14.8 (14.2)</td>
<td>15.3 (8.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Psat (%)</td>
<td>60 (12)</td>
<td>68 (9)</td>
<td>57 (12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean (SD).*
Results: We identified 93 patients; 37 HIV-PAH, 40 PoPHTN and 16 HIV-PoPHTN. Table 1 presents their hemodynamic characteristics. Table 2 shows comparisons between two groups.

Table 2

<table>
<thead>
<tr>
<th>HIV-PAH vs PoPHTN</th>
<th>HIV-PAH vs HIV-PoPHTN</th>
<th>HIV-PoPHTN vs HIV-PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>mRAP</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>PAOP</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PVRi</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>PAssat</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p value (non-significant omitted for clarity).

Conclusion: HIV-PoPHTN has a similar hemodynamic profile to HIV-PAH. Both groups have worse RV function compared to PoPHTN.

P969
Cardiac index by thermodilution and from non-invasive pulse pressure profiles analysis in PAH
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Background: Cardiac index (CI) is an essential parameter to assess severity of pulmonary arterial hypertension (PAH). It is usually measured by thermodilution (TD) during right heart catheterization (RHC).

Aim: We aimed to compare CI measured in PAH patients by RHC to Modelflow© (MF) method from non-invasive fingertip pulse pressure profiles, testing the hypothesis that MF is reliable for CI evaluation in PAH.

Methods: We simultaneously determined CI at rest by TD (CITD) and MF (CIMF) in 22 consecutive patients diagnosed with PAH. Cardiac output (CO) was the mean of 3 values for TD and 100 beat-by-beat values for MF. CI was calculated as CO/body surface area.

Results: Clinical and RHC data are reported in the table. The figure shows (right) CITD as a function of CIMF (Regression line: y = 0.9024x + 0.5382, R² = 0.86) and (left) a Bland–Altman analysis (Mean: 0.22; limits of agreement: -0.56 and +0.99).

Clinical and Hemodynamic characteristics

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>48 ± 16.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio: M/F</td>
<td>1.75</td>
</tr>
<tr>
<td>Right atrial pressure, mmHg</td>
<td>5.6 ± 3.2</td>
</tr>
<tr>
<td>Pulmonary artery mean pressure, mmHg</td>
<td>49.9 ± 15.8</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mmHg</td>
<td>9.3 ± 4.1</td>
</tr>
<tr>
<td>Cardiac index by Thermodilution, l/min/m²</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>Cardiac index by Modelflow, l/min/m²</td>
<td>3.5 ± 1.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units</td>
<td>8.0 ± 4.7</td>
</tr>
</tbody>
</table>

Conclusions: We simultaneously determined CI at rest by TD (CITD) and MF (CIMF) in 22 consecutive patients diagnosed with PAH. Cardiac output (CO) was the mean of 3 values for TD and 100 beat-by-beat values for MF. CI was calculated as CO/body surface area. The CITD as a function of CIMF (Regression line: y = 0.9024x + 0.5382, R² = 0.86) and (left) a Bland–Altman analysis (Mean: 0.22; limits of agreement: -0.56 and +0.99).

P970
Heart rate variability: Possible implications for management of pulmonary arterial hypertension patients
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The aim: to study heart rate variability (HRV) and its relationships with pulmonary hemodynamics and level of NT-proBNP in pulmonary arterial hypertension (PAH) patients.

Material and methods: 6 patients with idiopathic PAH and 3 with congenital heart disease associated PAH with (mean age 31±12 years, 7 patients with FC II and 2 patients with FC III by NYHA/WHO) were enrolled. All subjects underwent right heart catheterization. Level of NT-proBNP was determined in blood. The short-time ECG records obtained in supine position and during orthostatic test were analyzed by Poly-Spectrum software (Neurosoft, Russia). Nine healthy subjects served as a control.

Results: Severe pulmonary hypertension was found in all patients with mean pulmonary arterial pressure 53±14 mmHg, resting pulmonary vascular resistance 1180±550 dyn s cm⁻⁵. Total power of PAH patients ranged from 150 ms² to 2540 ms² with the very low frequency and low frequency bands predominance in the spectral structure. The orthostatic test caused dramatic lowering in all HRV indices in PAH subjects. Borderline values of NT-proBNP (up to 400 pg/ml) in PAH subjects were accompanied by some decrease in HRV. Simultaneously, significantly increased NT-proBNP levels (400-3200 pg/ml) were associated with marked HRV lowering both in supine position and during orthostatic test.

Conclusion: Patients with severe PAH were shown with individual various range of HRV parameters, correlating with the level of a neurohumoral activation marker NT-proBNP. HRV can be used in clinical practice to monitor progression of right-sided HF and, consequently, to determine prognosis in PAH patients.

P971
Impact of a wireless implanted pulmonary artery pressure monitoring system in heart failure patients with comorbid chronic obstructive pulmonary disease
Gerard Criner1, Robert Bourge2, Raymond Benza3, Philippe Adamsson4, William Abraham5, Brad Jeffries6, Pam Cowart6, Jordan Bauman6, Lyubomyr Solovy2, Marta Karapinka2, Olha Yelisyeyeva1, Khrystyna Semen1, Matthias Geyer1, Henning Tiede2, Andreas Rieth3, Ardeschir Ghofrani1, Ulf Müller-Ladner1, Robert Dinser4, Walter Hermann1, William Abraham4, Brad Jeffries6, Pam Cowart6, Jordan Bauman6, Khrystyna Semen1, Matthias Geyer1, Henning Tiede2, Andreas Rieth3, Ardeschir Ghofrani1, Ulf Müller-Ladner1, Robert Dinser4, Walter Hermann1

The CHAMPION trial enrolled 550 patients with NYHA class III HF who were followed for an average of 15 months. In the treatment group, clinicians used PAP data to guide therapy decisions in addition to standard care versus standard care in the control group.

Results: In the entire CHAMPION cohort, treatment had a 37% reduction in HFH rates (0.46 vs. 0.73, HR 0.63, 95% CI: 0.52-0.77; p<0.0001, Anderson-Gill). In the subgroup of 187 patients with comorbid COPD, treatment had a 41% reduction in HFH rates (0.55 vs. 0.96, HR 0.59, 95% CI: 0.44-0.81; p=0.0099). Reductions in PAP were analyzed using an area under the curve (AUC) methodology. Overall, treatment had an average AUC reduction of 201.5 mmHg days compared to an increase of 106.5 mmHg days in control (p=0.0299, ANCOVA). In the COPD subgroup, treatment had an average reduction of 353.1 mmHg days compared to a reduction of 57.0 mmHg days in control (p=0.367).

Conclusion: Patients with COPD experience high HFH rates but have pronounced benefit from PAP monitoring. Further investigations that analyze the relationship between PAP, COPD, and HF and its implication towards new treatment strategies are warranted.

P972
Is nailfold videocapillaroscopy a valuable diagnostic tool in pulmonary hypertension?
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Background: Pulmonary hypertension (PH) can be based on idiopathic pulmonary arterial hypertension (iPAH), connective tissue diseases such as systemic sclerosis

Conclusion: As previously reported for healthy subjects, MF could be useful for CI estimation in PAH but a calibration against a reference method is required.
(SSC-PAH), left heart disease (LHD-PH), chronic obstructive pulmonary disease (COPD-PH), or chronic thromboembolic events (CTEPH).

Objectives: Analysis of microvascular patterns of patients with PH has been performed using nailfold videocapillocoscopy (NVC). The benefit of NVC in PH was evaluated with focus on SSC patients.

Methods: NVC was performed in 81 patients. 2nd-5th fingers were bilaterally analyzed. Pictures were scored for capillary density (CD, capillaries/mm), and dimensions. Parameters such as hemorrhages and neoangiogenesis or capillary alterations such as ectasia (>20μm) and giant shape (>50μm) were qualitatively assessed.

Results: 14.8% had iPAH, 14.8% LHD-PH, 7.4% COPD-PH and 17.2% CTEPH. 45.7% had SSC and 12.3% SSC-PAH. The CD in SSC-PAH was significantly lower compared to all other PH forms (4.9 ± 10.2, 11.7 ± 9.4 and 9.7 ± 4.9 in iPAH, LHD-PH, COPD-PH and CTEPH; p < 0.001), but did not differ compared to SSC non-PAH (4.7 ± 0.73). In general, capillary dimensions were larger in SSC-PAH (80%), but to some extent present in other forms (e.g. COPD-PH 71.4%). Giant capillaries were only present in SSC (84.6% and 70%). Hemorrhages occurred in all disease forms of this study, mostly in CTEPH (85.7%) and SSC (80%).

Conclusions: Capillary density in SSC-PAH is a powerful tool to discriminate mostly in COPD-PH (85.7%) and SSc (80%).

P973 Right ventricular global strain and right ventricular dysfunction can predict success to pulmonary vasodilators therapy in PH patients

Beatrice Lamia, Luis-Carlos Molano, Catherine Viacroze, Antoine Cavelier, Jean-Francois Sarfati, Pierre Million and Caref Caumes
University of Rouen, France

Background: Transthoracic echocardiography (TTE) is used to evaluate right ventricular (RV) function in pulmonary hypertension (PH) patients. RV function is assessed using TAPSE or RV end-diastolic area/LV end-diastolic area ratio (RVEDA/LVEDA). RV speckle tracking strain can quantify regional contraction. Pulmonary vasodilators can improve functional status and prognosis but their effects on RV function are poorly described. The aim of our study is to test whether response to pulmonary vasodilators can be predicted by change in RV regional strain.

Methods: 16 patients were prospectively included. They underwent right heart catheterization, usual and 2D strain TTE at baseline and after 3 months of pulmonary vasodilators. PDE5 inhibitors, endothelin receptor antagonists, prostacyclin (single or combination therapy). Success or failure to pulmonary vasodilators were defined according to the guidelines.

Results: At baseline, TAPSE was 44 ± 11 mmHg, PAOP 11 ± 3 mmHg, cardiac index 3 ± 0.07 ± 3 L/min/m², RVEDA/LVEDA 1.03 ± 0.03, RV global strain 12.29 ± 5.34% and RV dysynchrony: 124/78 μsec. A change in global RV strain higher than 70% (>100 to 122%) could predict success to pulmonary vasodilators with a specificity of 100%, a change in RV dysynchrony of 96 μsec could predict success to treatment with a sensitivity of 100%. Change in TAPSE or RVEDA/LVEDA were not accurate enough to predict response to pulmonary vasodilators.

Conclusions: Success to pulmonary vasodilators therapy in PH patients can be predicted by changes in regional right ventricular contraction using longitudinal right ventricular strain and right ventricular dysynchrony analysis.

P974 Role of C-terminal pro-endothelin in pulmonary hypertension

Ralf Kaiser, Philipp M. Lepper, Robert Balz, Heinrich Willems. Dept Internal Medicine V, University of Saarland, Homburg/Saar, Saarland, Germany

Introduction: The endothelin pathway is upregulated in various forms of pulmonary hypertension. Its disease promoting activity has lead to the development of endothelin receptor blockers as specific therapeutics. The highly unstable active product of the endothelin cascade.

Methods: We examined 36 patients retrospectively. Therapy was applied following contemporary guidelines. Samples of platelet free EDTA plasma were stored at -80°C since collection between 2000 and 2003. Biomarker levels were determined by a Kryptor compact (BRAHMS, Germany) according to vendor instructions.

Results: Patients were categorized according to DanaPoint classification as class 1 (n=16), class 2 (n=1), class 3 (n=9), class 4 (n=8) and renal failure (n=6). The mean follow-up time was 4.67 years. Survivors had significantly lower levels of CT-proET (53.7 [31.2-171.8] vs 91.1 [30.6-151.6] pmol/L, p=0.006). ROC analysis for survival yielded an AUC of 80.8%. The optimized cut-off for survival was determined as 65pmol/L. The log-rank test of Kaplan-Meier-analysis for survival was highly significant (p=0.01) with a hazard ratio of 3.06.

Conclusions: CT-proET was significantly elevated in non-survivors of the follow-up period. Optimized cut-offs at 65pmol/L resulted in a significant Kaplan-Meier-analysis for survival. CT-proET-levels above 65 pmol/L are associated with decreased survival in pulmonary hypertension. CT-proET might be a useful biomarker to determine high-risk patients, while offering the advantage of a stable product of the endothelin cascade.
P977 Prevalence of respiratory symptoms and airflow obstruction in a nationally representative random sample in England

Maria M.7, Jenny Mindell7, Rachel Craig1, Joanne Clarke1, Anne Moger1, Kevin Holton1, Robert Winzer1, Sue Hill1.1, Department of Health, Medical Directorate, London, United Kingdom; 2Department of Epidemiology & Public Health, London, United Kingdom; 3NutCen Social Research, NatCen Social Research, London, United Kingdom; 4Cambridge University Health Partners, Addenbrooke’s Hospital, Cambridge, United Kingdom

Introduction: Chronic Obstructive Pulmonary Disease (COPD) causes 23,000 deaths p.a. in England with direct health costs of over £1bn. 835,000 people are registered on general practice (GP) COPD registers. An estimated 2.7 million are undiagnosed. Poor symptom recognition by the public and clinicians contributes to late diagnosis.

Aims: To estimate the prevalence of respiratory symptoms and airflow obstruction in the population of England.

Methods: The annual Health Survey of England is a cross-sectional study of a random, nationally representative sample of 8,000 adults. It includes detailed interviews and objective measures by nurses. The 2010 survey focused on lung disease and included spirometry (without bronchodilator).

Results: 15% of men and 23% of women aged 16+ had MRC dyspnoea score 2-5; half of these scored 3-5. 4% of men and 5% of women had ever been told by a doctor that they had chronic bronchitis, emphysema or COPD, compared with GP register prevalence of 1.6%. Measured FEV1/FVC ratio was inversely associated with income. FEV1/FVC was below 5th centile (indicating probable airflow limitation) in 8% of men and women; only a quarter of these had been told by a doctor that they had chronic bronchitis, emphysema, or COPD.

Conclusions: This large population survey confirms that substantial numbers of people experience respiratory symptoms and probable undiagnosed airflow obstruction. Failure to diagnose COPD early matters because it adversely affects outcomes and quality of life. To tackle this, a national Outcomes Strategy for COPD and Asthma has been launched to promote lung health awareness, earlier diagnosis and proactive disease management.

P978 Prevalence of COPD in Algerian military

Kherbi Salah. Pneumologie, HIMIRC, Constantine, Algeria

The Survey is about one of the determinants of the chronic obstructive pulmonary disease (COPD), tobacco and the military environment. The objective is to measure the prevalence of this pathology and to make a first assessment of it in order to elaborate an efficient anti-tobacco policy and to associate a better handling of this pathology within our institutions.

It is a through a transversal survey that uses the questionnaire and the spirometry on a population of soldiers and civilian staff working for the army aged 40 years and more, current smokers or former smokers having accumulated 10 P/Y and more, belonging to 10 randomly chosen military camps belonging to the fifth military region. So 720 men have been included in the investigation and have been questioned during the period of November 01/2008 to October 31/2009.

The prevalence of the chronic obstructive pulmonary disease (COPD) is of 5.35% for the whole population, of 6.37% for current smokers and 3.75% among the former smokers. The prevalence of the different stages of severity is of 2.67% for the two stages I and II. The active tobacco addiction or weaned was the only factor of risk found with a percentage of 43.15% and 36.06% respectively, associated with the passive tobacco addiction.

The chronic obstructive pulmonary disease (COPD) in the military institution is a real problem that challenges medical community and decision-makers on the emergency of the elaboration of a health policy based on the prevention through strict measures of struggle against the tobacco addiction and the early detection of patients in a precarious stage by the practice of the minimal advice and the popularization of the breath measure.

P979 A detached island residents’ smoking habits and their prevalence of COPD

Yoshihide Yanagita1, Kahori Oue2, Takako Tanaka1, Hideaki Senjyu1. Medical Science, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan; 2Department of Rehabilitation Medicine, Nagasaki-Urino Hospital, Nagasaki, Japan

Background: The prevalence of COPD is high worldwide. It has been reported that the prevalence rate of subjects aged 40 years and over is about 8.6% in Japan. However, no reports have examined the prevalence of COPD by region, such as whether there are differences in subjects living in urban areas, or on a detached island.

Aims and objectives: The purpose of this study was to evaluate the influence of the region (mainland versus a detached island) on the general population’s smoking habits and the prevalence of COPD or respiratory function. A general population of 5221 subjects was targeted.

Methods: All of the candidates’ health survey items (age, sex, body composition, smoking habit, Brinkman Index, respiratory function and COPD disease) were investigated. Candidates were classified into a mainland group and a detached island group according to the location of the institution that performed their medical checkup, and each health survey item and respiratory function parameter were compared.

For the statistical analysis, two-sample t-tests, chi-square tests, and Mann-Whitney U tests were used.

Results: The former smoker rate (mainland 51.7% vs detached island 73.7% p<0.001) and Brinkman Index (mainland 322.0±497.7 vs detached island 406.2±416.7 p<0.001) were higher in the detached island group. Nevertheless, the prevalence of COPD was lower in the detached island group (mainland 8.5% vs detached island 7.0% p<0.05).

Conclusions: According to the guidelines of the GOLD, tobacco smoke is a primary factor related to the development of COPD. Our findings indicate that the living environment is also related to the prevalence of COPD.

P980 Distribution of COPD patients in the GOLD assessment framework by exacerbations

G. Nadeau1, L. Adamack1, M. Small1, 1Respiratory Center of Excellence, GSK, Uxbridge, United Kingdom; 2Adelphi Real World, Adelphi Group, Macclesfield, United Kingdom

In GOLD 2011 proposes a new COPD assessment framework focussed on symptoms measured by the COPD Assessment Test (CAT™) or the mMRC and on risk based on poor lung function (FEV1<50%) and a history of ≥2 exacerbations in the previous year. This analysis focuses on exacerbations.

The 2011 Adelphi Disease Specific Programme dataset was used to understand the distribution of patients in the GOLD framework. Exacerbation events defined as those not brought under control by rescue medication were recorded by physicians. We included 1041 EU COPD patients with documented CAT, mMRC, FEV1 and exacerbation history in the previous year (401 (38.5%) were from primary care and 640 (61.5%) from specialty clinics. Almost all (97.7%) were on maintenance treatment. 104 subjects (10%) reported good health status (CAT<10); only 7 of these were repeat exacerbators or had poor lung function. 4 of all patients (48.6%) had no exacerbations and 18.5% had 1 exacerbation in the previous year.

% Distribution based on Exacerbation History - (n)

<table>
<thead>
<tr>
<th>GOLD Quadrant</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.9% (63)</td>
<td>1.3% (4)</td>
<td>9% (60)</td>
</tr>
<tr>
<td>B</td>
<td>35.4% (268)</td>
<td>13.2% (137)</td>
<td>9% (60)</td>
</tr>
<tr>
<td>C</td>
<td>0.3% (3)</td>
<td>0.1% (1)</td>
<td>0.3% (3)</td>
</tr>
<tr>
<td>D</td>
<td>5.0% (32)</td>
<td>3.9% (41)</td>
<td>32.5% (339)</td>
</tr>
<tr>
<td>Total</td>
<td>48.6% (366)</td>
<td>18.5% (193)</td>
<td>32.9% (342)</td>
</tr>
</tbody>
</table>

In observational databases, 1 exacerbation increases the risk of future exacerbations and negatively impacts health status and outcomes. Therapeutic interventions reduce the number and severity of exacerbations in patients with 1 or more exacerbations. Nearly 1/5 of patients in the Adelphi dataset had 1 exacerbation in the previous year and would fail to be included in GOLD high risk category. These observations may have important clinical implications.

References:

P981 Chronic bronchitis phenotype in subjects with and without COPD: The PLATINO study

Maria Montes de Oca1, Ronald J. Halbert2, Maria Victoria Lopez1, Rogelio Perez-Padilla3, Carlos Talamo1, Dolores Moreno1, Adriana Muñoz1, Jose Roberto Jardim1, Gonzalo Valdivia1, Julio Pertuz2, Ana Maria B. Menezes1, 1Pulmonary, Universidad Central de Venezuela, Caracas, Venezuela; 2School of Public Health, UCLA, Los Angeles, United States; 3Pulmonary, Universidad de la Republica, Montevideo, Uruguay; 4Pulmonary, Institute of Respiratory Diseases, Mexico City, Mexico; 5Pulmonary, Federal University of São Paulo, Brazil; 6Public Health, Pontificia Universidad Católica de Chile, Santiago de Chile, Chile; 7Faculdade de Medicina, Universidade Federal de Pelotas, Brazil

Background: Little information exists regarding the epidemiology of chronic bronchitis (CB) phenotype in unselected COPD populations. We examined the prevalence of CB phenotype in COPD and non-COPD subjects of the PLATINO study, and how it is associated with important outcomes.

Methods: Post-bronchodilator FEV1/FVC<0.70 was used to define COPD. “Phlegm most days, at least three months a year for ≥2 years” was used to define CB. We also analyzed another definition: “cough and phlegm most days, at least three months a year for ≥2 years”.

Results: Spirometry was performed in 5,314 (759 COPD and 4,554 non-COPD). The proportion of subjects with and without COPD and CB defined as “phlegm most days, at least three months a year for ≥2 years” was 14.4 and 6.2%, respectively. Using the other definition the prevalence was lower (COPD 7.4%, and non-COPD 2.5%). Among subjects, with COPD those with CB had worse lung function and general health status, and had more respiratory symptoms, physical activity limitation, and exacerbations.

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SUNDAY, SEPTEMBER 2ND 2012
Conclusions: Our study helps to understand the prevalence of CB phenotype at a particular point in time and suggest that CB in COPD is possibly associated with worse outcomes.

Prevalence characteristics of COPD in never smokers

Ramadan Balk
Ibrahim Elmahallawy
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Background: Smoking is by far the most important documented cause for COPD. However, COPD can still be recorded among a percentage of non-smoker patients, due to other different causes.

Methods: This study comprised 300 COPD patients, 230 patients (76.66%) were men and 70 patients (23.34%) were women. The mean age of the patients was 60.7±5.35 years (range 42-83 years).

Results: 300 COPD patients were included in this study, 120 (40%) were never smokers and 180 (60%) were ever smokers. Women made up 41.7% of the never smokers (50 of 120) and 11% of the ever smokers (20 of 180). Never smokers were significantly older than smokers (65.08±5.03 years vs 56.33±6.7 years (P < 0.001)) and were more likely to be women (41.7% vs 11% (P < 0.001)).

Never smokers made up to 40% (120/300) of all COPD cases; 78% (70/90) of all GOLD stage II cases, 45.5% (50/110) of all GOLD stage III cases. Among never smokers, 58.3% (70/120) fulfilled the criteria for GOLD stage II and 41.7% (50/120) fulfilled the criteria for GOLD stage III and no patients fulfilled the criteria of either GOLD stage IV. Never smokers were shown to have more occupational exposure to organic and inorganic dust and irritating gases at work place [41.7% (50/120) vs 27.7% (50/180), P < 0.05], more biomass exposure [41.7% (50/120) vs 0% (P < 0.001)], less education [41.7% (50/120) vs 72.2% (130/180), P < 0.001], more exposure to passive smoking [75% (90/120) vs 22.2% (40/180), P < 0.001].

Conclusions: Never smokers still constitute a significant proportion of the Egyptian COPD patients.

Profilin dyspnoea in primary care patients with COPD

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Objectives: Identify descriptors of clinically significant dyspnoea in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods: A COPD cohort was identified in the UK General Practice Research Database (GPRD) using a record of COPD diagnosis in 2008 and nearest recorded spirometry (FEV1/FVC <70%). Dyspnoea was identified using Medical Research Council (MRC) dyspnoea scale, recorded as a part of the Quality Outcomes Framework, during observation period, from the latter of Apr1 2009 or cohort entry until censoring (earliest of death, transfer out of practice or follow-up end at March 31 2011). The first MRC score recorded, within observation period, defined patients as (A) with (MRC ≥ 3) or (B) without (MRC < 3) clinically significant dyspnoea, other traits were collected on or before MR C score date. Stepwise multivariate logistic regression estimated independent associations with dyspnoea.

Results: 38,256 COPD patients with MRC dyspnoea score were identified: females 46%, mean age (SD) 70 (10) yrs, GOLD stage I=15%, II=50%, III=27%, IV=6%. Of these, 16,919 (44%) reported clinically significant dyspnoea. Most of these, 75.5%; exposure time more than 20 years, smokers and non/ex smokers, BMI, FEV1 and FEV1/FVC were measured and their correlation calculated generally and separately, for younger and older than 51 years, in both sexes.

Results: In men,generally,BMI strongly positively correlated with both FEV1 and FEV1/FVC (p<0.001),the same in smokers,but less in non/ex-smokers (p< 0.02),with stronger significance in older than 51 years (p< 0.001) than in younger (p< 0.03).In women older than 51 years BMI strongly positively correlated only with FEV1 (p<0.001), especially in years BMI didn't show any significant correlation with both FEV1 and FEV1/FVC.

Conclusions: Gender and age are unchangeable risk factors for every chronic disease and COPD as well.These data,showing that BMI strongly positively correlates with both lung function parameters in men and only with FEV1 in women,especially in smokers and older than 51 years,with absence of any correlation in women younger than 51, may indicate that pathophysiologic changes in COPD are different, but sex and age dependent.

Body mass index (BMI) and lung function decline with age in COPD patients

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Introduction: Body mass index (BMI) and lung function physiologically decline with age, but in COPD that is an inevitable consequence of disease too. Other changes that come with ageing are menopause and andropause, affecting BMI and lung function, as well. Average age for woman entering the menopause is 51 and andropause is suggested to start in men between 40 and 60 years (mean 50 years).

Aim: To examine influence of gender and age on correlation between BMI and lung function among COPD patients.

Material and methods: In 341 COPD patients (269 men and 72 women) older than 40 years smokers and non/ex smokers BMI, FEV1 and FEV1/FVC were measured and their correlation calculated generally and separately, for younger and older than 51 years, in both sexes.

Results: In men,generally,BMI strongly positively correlated with both FEV1 and FEV1/FVC (p<0.001),the same in smokers, but less in non/ex-smokers (p<0.02), with stronger significance in older than 51 years (p< 0.001) than in younger (p<0.03). In women older than 51 years BMI strongly positively correlated only with FEV1 (p<0.001), especially in years BMI didn’t show any significant correlation with both FEV1 and FEV1/FVC.

Conclusions: Gender and age are unchangeable risk factors for every chronic disease and COPD as well. These data, showing that BMI strongly positively correlates with both lung function parameters in men and only with FEV1 in women, especially in smokers and older than 51 years, with absence of any correlation in women younger than 51, may indicate that pathophysiologic changes in COPD are different, but sex and age dependent.

Cardiovascular comorbidity and mortality in patients with chronic obstructive pulmonary disease

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Aim: To determine the prevalence of cardiovascular diseases (CVDs) and cardiovascular mortality in patients with chronic obstructive pulmonary disease (COPD).

Method: COPD patients (n=3571) were checked if they had CVDs (CAD – coronary artery disease, HF – heart failure, AH – arterial hypertension, CCP – chronic cor pulmonale, CVD – cerebrovascular disease) and mortality. Of these, 2642 (74%) were male and 929 (26%) were female, aged 65 (SD: ± 9.7), and FEV1 = 49.8 (± 18.9%) pred. The risk for CVDs (OR - Add Ratio) was compared with that of 150 controls.

Results: Among COPD patients 84.5% had CVDs: 59% (GOLD B), 74% (GOLD B), 86% (GOLD III) and 99% (GOLD IV) (OR =3.5, p=0.001), OR=1.9. Correlation was found between age and prevalence of CVDs: 47.8% (40-49yrs), 71.6% (50-59yrs), 85% (60-69yrs) and 96.9% (>70yrs) (p<0.001).

Patients with COPD had a higher prevalence of CVDs and cardiovascular risk: CAD (66%; OR = 1.8), HF (74%; OR = 1.9), AH (45%; OR = 1.2), CCP (46%; OR = 3.8) and CVD (33.3%; OR = 1.6). In 33% of COPD deaths cardiovascular causes of death were found: 36.7% myocardial infarction, 33.3% pulmonary embolism, 12.2% HF and 18% of CVD.

Conclusion: The study found an increased risk and mortality from cardiovascular diseases, especially in adult patients with severe COPD.
Prevalence of comorbidities in subjects with airflow obstruction in Japan
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Background: COPD is one of the leading causes of mortality in Japan. Little is known about the prevalence of comorbid conditions in subjects with COPD in Japan.

Objective: The aim of this study was to examine the prevalence of comorbidities between subjects with and without airflow obstruction (AO).

Methods: This study included 19,340 subjects (11,549 men, 7,791 women), aged 16-96 years, who underwent spirometric lung function tests at a medical check-up held between April 2009 and March 2010 at the Japanese Red Cross Kumamoto Health Care Center, Kumamoto, Japan. Data on medical history and life style information were collected by means of an interview questionnaire. All subjects were evaluated by a physician. AO was defined according to Global Institute for Chronic Obstructive Lung Disease (GOLD) criteria (FEV1/FVC<0.7).

Results: In logistic regression models adjusted for age, smoking and BMI, prevalence of subjects with diabetes (odds ratio [OR], 1.28; 95% confidence intervals [95%CI], 1.10-1.51), asthma (OR, 4.09; 95%CI, 3.15-5.31) and lung cancer (OR, 3.84; 95%CI, 1.89-7.80) were significantly higher in subjects with AO compared to subjects without AO in male. In female, prevalence of subjects with hypertension (OR, 1.43; 95%CI, 1.15-1.79), diabetes (OR, 1.40; 95%CI, 1.05-1.86), asthma (OR, 3.22; 95%CI, 2.22-4.67) and lung cancer (OR, 4.52; 95%CI, 1.62-12.62) were significantly higher in subjects with AO compared to subjects without AO.

Conclusions: This study documented that numerous comorbidities are frequently associated with AO. Therefore, efforts toward earlier detection of AO and the identification of comorbidities may become an integral part of the core prevention of COPD.

Metabolic and cardiovascular comorbidity in COPD patients classified using the GOLD 2011 assessment framework
P988
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Background: Chronic obstructive pulmonary disease (COPD) represents an important and increasing burden worldwide. COPD often coexists with other diseases that may have an impact on prognosis.

Aims: To evaluate the association between different COPD severity levels and comorbidity in Italian patients of general practitioners (GP).

Methods: Prospective observational study in different Italian areas. 176 GP enrolled 2288 patients with COPD diagnosis. Questionnaires were used to collect data on COPD management, health status and quality of life. Univariate analyses were used to assess the relationship between COPD severity levels (mild, moderate, severe, very severe) and demographic characteristics (age, sex), smoking habits, comorbidities. Multinomial regression analysis was used to assess the relationship between COPD severity levels and comorbidity adjusting for demographic characteristics and smoking habits.

Results: Univariate analyses showed a significantly higher frequency of high severity levels in males, older age, ex-smokers, subjects with cardiovascular dis-eases, osteoporosis/skeletal muscle dysfunction, anemia, depression and weight loss. The Multinomial regression analysis confirmed the associations between COPD severity and COPD and cardiovascular disease (OR 1.30; severe COPD and cardiovascular disease (OR 1.35), osteoporosis/skeletal muscle dysfunction (OR 1.43), anemia (OR 2.06) and weight loss (OR 2.77); very severe COPD and weight loss (OR 6.34) and depression (OR 2.50).

Conclusions: This study indicates that COPD stages are significantly associated with different kinds of comorbidities which need to be taken into account in disease management.

COPD and comorbidity in somatic practice
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The aim of our study was to determine the clinical features of comorbidity in patients with COPD and other somatic pathology. Based on the evidence of post-mortem autopsies, we planned to examine the characteristics of occurrence and the structure of comorbidity. We analyzed the 3469 deaths cases of patients admitted to hospital due to decompensation of somatic pathology. Comorbidity was found in 2751 (78.3%) cases (1035 men (37.6%) and 1716 women (62.4%)). The average age of patients with comorbidity was 72.6 years old (by men - 69.4 and by women - 76.1). We found that the greatest number of nosological units (5.9 diseases per person) occurs in elderly patients (80-89 years). Combination of the two diseases occur in 17.5% of patients with comorbidity, three diseases - in 34.9%, four diseases - in 26.9%, the five diseases - in 14.7% and more than 5 disease - in 6% of patients with somatic pathology. For example, chronic obstructive pulmonary disease in 57.5% of cases combined with arterial hypertension, in 74.6% of cases - with coronary heart disease, in 97.3% of cases - with chronic cerebrovascular disease, in 63.5% of cases - with the pathology urogenital system, in 22.1% of cases - with diabetes mellitus type 2. Comorbidity in patients with COPD in 18% of the cases makes it difficult identify malignant tumor, in 13.5% - intracerebral hemorrhage, in 13% - acute myocardial infarction, in 8.3% - chronic cerebrovascular disease, in 7.6% - ischemic heart disease, in 6.8% - stroke, in 5.2% - aortic dissection and in 4.8% of cases - mesenteric thrombosis. Comorbidity alters the clinical picture and course of underlying disease (ex. COPD), the nature and severity of its complications and degrades the quality of life of patients.

Disease severity and complexity in patients with acute exacerbation of chronic obstructive pulmonary disease in Lazio, Italy
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Population based estimates of disease severity and comorbidity in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD) give insight into the burden of this degenerating condition on patients and health care systems. Hospitalized COPD patients were characterized in terms of COPD severity and complexity. A cohort of 21,144 residents in Lazio, discharged after acute COPD exacerbation in 2006-9 was enrolled from the Hospital Information System. Disease severity was defined as presence of admissions during 12 months prior to index admission with diagnosis of COPD, respiratory failure (RF), invasive respiratory procedures, transfer to intensive care, COPD emergency visits, or oxygen therapy (O2), linked
from drug claims register. Comorbidities were retrieved from index admission and admissions during 24 months before.

More than half of patients were men (53.9%), mean age was 74.6 years for men and 76.8 years for women. RF and O2 were the two factors detected more often (46.9% and 21.9%, respectively), with higher values in men (RF: 48.5%, O2: 24.5%). Most important comorbidities were hypertension (24.8%), diabetes (20.4%), ischemic heart disease (13.0%), heart failure (12.6%), arthritism (12.3%), pulmonary infections (10.3%), and cerebrovascular disease (9.5%), with higher prevalence in men for all but diabetes and hypertension.

Patients requiring for acute exacerbations are typically old and more often men. Almost half of patients are affected by respiratory failure, more than a fifth is treated with oxygen. Many patients suffer from cardiovascular disease or diabetes. Partially funded by National Medicines Agency, Prot. FARM8ZBT93.

**P992 Characteristics of COPD exacerbations in Greece**

Foteini Mali1, Zoe Danili1, Eleni Bania2, Evangelos C. Alexopoulos3, Foteini Malli1, Zoe Daniil

Characteristics of COPD exacerbations in Greece P992

Partially funded by National Medicines Agency; Prot. FARM8ZBT93.

Men for all but diabetes and hypertension.

Important comorbidities were hypertension (24.8%), diabetes (20.4%), ischemic heart disease (13.0%), heart failure (12.6%), arthritism (12.3%), pulmonary infections (10.3%), and cerebrovascular disease (9.5%), with higher prevalence in men for all but diabetes and hypertension.

Patients requiring for acute exacerbations are typically old and more often men. Almost half of patients are affected by respiratory failure, more than a fifth is treated with oxygen. Many patients suffer from cardiovascular disease or diabetes. Partially funded by National Medicines Agency, Prot. FARM8ZBT93.

**Methods:** The cohort consisted of 390,269 adults, between 1994 and 2008, went through a fee-for-service, standard panel of health screening program. COPD was defined by Gold criteria. Mortality and cancer incidence were identified in an average of 8.5 years of follow-up. Cox proportionate model was used to calculate the hazard ratios (HR).

**Results:** More men (48.5%) than women (38.8%) and more smokers (53.7%) than non-smokers (37.3%) had COPD, with a mean age of 50. The excess all-cause mortality for smokers (HR: 2.51) was three times larger than non-smokers (HR: 1.53), when compared to those without COPD. Not only smokers (4.5-fold) but also non-smokers (1.4-fold) had lung cancer mortality significantly increased, implying the independent effect from COPD. Other than lung cancer and respiratory diseases, COPD had increased risks for CVD (HR: 1.76), including ischemic heart disease (HR: 1.63) and stroke (HR: 1.80), and kidney diseases (HR: 2.32). The extra-pulmonary causes constituted 77% for non-smokers and 58% for smokers.

**Conclusion:** Three quarters of the excess deaths among nonsmoking COPD subjects died from causes beyond the lungs. They had increases in stroke, heart renal and infectious diseases, in addition to lung cancer. These extra-pulmonary risks, under-appreciated by clinicians and unaware of by the patients, are major challenges to overcome.

**P994 Insufficient education about COPD is main factor for low diagnosis rate**

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**Background and aims:** To evaluate if prolonging duration of education and testing COPD campaign will increase presentation for testing (spirometry) and number of newly diagnosed COPD cases, in population exposed to risk factors.

**Methods:** One-week campaign was conducted in 2009-2010 and 2 weeks in 2011 on World Day of COPD. Target population had open access to office based spirometry tests. Through personalized letters from President of Romanian Society of Pneumology that inform about 12 reasons to take a spirometry test and the consequences of COPD, population was encouraged to access informative COPD web-site. The primary outcome measure was number of newly-diagnosed cases of COPD as a result of campaign.

**Results:** In 2009 (1 week campaign), 3494 persons presented for testing, 847 were newly diagnosed with COPD (24% diagnosis rate). In 2010 (1 week campaign), 4058 persons were tested, 1259 were diagnosed (29% diagnosis rate). In 2011, 2 weeks campaign resulted in 10523 persons tested, 3593 new diagnosed COPD patients (34% diagnosis rate). Growth 2011/2010 for persons presenting to test was 148%, vs 23% growth 2010/2009; for new diagnosed COPD patients, growth 2011/2010 was 186%, vs 48% 2010/2009.

**World Day of COPD Campaign results 2009-2011**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of person tested</th>
<th>Number of new diagnosed patients with COPD</th>
<th>Diagnosis rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 (1 week)</td>
<td>3494</td>
<td>847</td>
<td>24</td>
</tr>
<tr>
<td>2010 (1 week)</td>
<td>4058</td>
<td>1259</td>
<td>29</td>
</tr>
<tr>
<td>2011 (2 weeks)</td>
<td>10523</td>
<td>3593</td>
<td>34</td>
</tr>
</tbody>
</table>

**Conclusion:** Prolonging duration for awareness disease campaign on case-finding for COPD increased testing presentation and interest for learning on COPD. Intensifying efforts for education, not limiting only to celebrating event as World COPD Day, can increase diagnosis rate.

**106. Healthcare utilisation and treatment of asthma and COPD**

**P995 Health, social and economic consequences of chronic obstructive pulmonary disease (COPD): A controlled national study**

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Rationale: The objective direct and indirect costs of COPD among adults and the treatment are incompletely described.

**Methods:** From the Danish National Patient Registry (1998-2010), 171,557 (83,338 men and 88,219 women) COPD patients (ICD-10 diagnoses: J44.0 - 44.9) were identified and included. For every patient, four age-, sex- and socioeconomic-matched control citizens were randomly selected from the Danish Civil Registration System (322,233 men and 342,588 women).

Statistics Direct costs were extracted from the Danish Ministry of Health, Danish Medicines Agency and National Health Security and indirect costs were based on data from the Coherent Social Statistics.

**Results:** After 12 years only 33.1% of the COPD patients were still alive compared to 61.4% of the control citizens.

COPD were associated with significantly higher rates of health-related contact, medication use, unemployment, and accounted for increased socioeconomic costs. The annual mean excess health-related cost for each patient with COPD was € 6121 before and € 5990 after diagnosis, respectively, compared to controls. Patients with COPD had medication, hospital and total health costs 2.3-times higher than controls and overall employment rates 30% lower than controls. Employed COPD patients earned only around 58% of the income of controls. These socioeconomic consequences were present even 11 years prior to the first diagnosis in patients with COPD, and increased with disease advancement.

**Conclusion:** COPD has major socioeconomic consequences for the individual and for society. Mortality and morbidity from COPD is very high and earlier disease detection could have a greater impact on disease complications.
Methods: From the Danish National Patient Registry (1998-2010), 171,557 (83,338 men and 88,219 women) COPD patients (ICD-10 diagnosis: J44.0 - 44.9) were identified and included. Of these 50.3% (86,260) were married or co-lived with a spouse. For every spouse, four age-, sex- and socioeconomic-matched control citizens were randomly selected from the Danish Civil Registration System (346,524). Statistics Direct cost were extracted from the Danish Ministry of Health, Danish Medicines Agency and National Health Security and indirect costs were based on data from the Coherent Social Statistics.

Results: Even 11 years prior to the first diagnosis in a COPD patient, being a spouse were associated with significantly higher rates of health-related contact, medication use, unemployment, and increased socioeconomic costs. Compared to controls, the annual mean excess health-related cost for each spouse of a COPD patient was €3,118 before and €1,820 after the COPD diagnosis and the spouses received an annual mean excess social transfer income of €1,045 before and €381 after the COPD diagnosis. The annual mean excess medical costs was €2,925 lower than that of an employed control before and €1,454 after the COPD diagnosis.

Conclusions: For the first time ever the major socioeconomic consequences for the spouses of COPD patients has been shown and needs to be addressed in the future. In addition mortality and morbidity from COPD is very high and earlier disease detection could have a greater impact on disease complications.

Influence of statin treatment on cancer mortality in COPD patients: Retrospective observational cohort study

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Background: The anti-inflammatory and immunomodulatory stator properties have been suggested for preventing cancer development in patients with Chronic Obstructive Pulmonary Disease (COPD). However, the effect of statin on cancer mortality in COPD patients is poorly documented. The study endpoint is to evaluate the impact of statin on cancer mortality of COPD patients.

Methods: Based on a large pharmaceutical French database of the North area, a retrospective cohort study was conducted in order to evaluate the effect of statin on cancer mortality in COPD patients. Analysis, based on a Cox proportional hazards model, was performed and handled as a time-dependent variable, included the 66,429 individuals 40 years old or more who had at least one pharmacological dispensation between 01/01/2000 and 05/11/2007. In this cohort, 9531 COPD patients were identified, 18.1% of COPD patients were considered exposed to statin treatment.

Findings: The overall death rate of COPD patients is 40.8%. The various causes accountable for COPD patients’ death were: cardiovascular diseases for 33.7%, respiratory diseases for 33.7% and cancer for 24.8%. Statin treatment was significantly associated with a decrease of cancer mortality in COPD patients with estimates (hazard ratio [95% CI], p value) at 0.586 [0.465-0.739], p<0.001.

Interpretation: It seems that statin delivery to COPD patient reduces the cancer death rate. However the result has to be checked out by prospective randomized trials.

Relative exposure to inhaled steroids (ratio “ICS-to-total-asthma therapy”): Concordant data from electronic medical records, claims data and patient-reported outcomes

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Background: In claims data, computation of “ICS-to-total-asthma therapy” ratios (R) has shown interest to identify asthmatics more at risk of exacerbations, as a result of insufficient exposure to ICS for their level of disease severity. Ratios have seldom been computed from other data sources. The relationship between asthma outcomes and ratios was studied, from different sources: electronic medical records (EMRs), claims data, and patient-reported outcomes (PROs) obtained from a pharmacy-based survey.

Methods: In all settings, the primary comparison was between non users (R=0%), inadequate ICS users (0<R<0.5%) and adequate ICS users (R≥50%), as to asthma-related hospitalizations, use of oral steroids (OCS) or antibiotics (ATB), and Asthma Control Test (Pharmacy-based study).

Results: In claims data (n=2,142, mean age=27 yrs, 53% females), inadequate users had higher rates of hospitalizations (p=0.0087), oral steroids or antibiotics use than other groups (p<0.001 for both): OCS and ATB use were more common (p<0.0001 for both) among inadequate users in EMRs (n=4,587, mean age=28 yrs, 54% females). In the pharmacy-based survey (n=919, mean age=37 yrs, 55% females), inadequate users were more likely to be poorly controlled, hospitalized for asthma and to receive OCS or ATB (p<0.0001 for all).

Conclusions: Despite differences in study designs and patients baseline characteristics, conclusions were highly concordant between the 3 data sources, with evidence of poorer control in inadequate users. Advantages and limitations of each data source for the interpretation of ratios will be discussed.
P1003

Co-morbidities are associated with prolonged hospital length of stay (LoS) in patients with COPD.

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Respiratory Medicine, Homerton University Hospital, London, United Kingdom

Identification of factors leading to prolonged hospital stay may help to find patients who need targeted approaches to management. Appropriate resource allocation would help to reduce the time spent in hospital. Co-morbidities are common in COPD and may lead to prolonged admissions. We performed a retrospective case note analysis of patients with COPD who had admissions lasting longer than average. Spearman’s correlation and Mann-Whitney test were used to identify relationships between co-morbidities and LoS. Data were obtained for 204 patients (mean age 73.9, 135 males) who had 267 hospital admissions of duration greater than 9 days in a one-year period. The total number of bed-days was 6127. 38 patients (19%) had more than one admission, the number of admissions ranging from 2 to 7. These 38 patients occupied 2509 bed-days (41% of total).

LoS was found to be correlated with greater age (p = 0.005) and the presence of respiratory infection diagnosed by the admitting team. Cardiac arrhythmias seem to be associated with prolonged LoS (p = 0.01). As might be expected, patients who were admitted with exacerbations of COPD alone (i.e. no other reason for admission identified) had shorter LoS compared with those who had other identified reasons for admission (p = 0.028). No definite correlations were found with heart failure, ischaemic heart disease, psychiatric history or stroke. Other co-morbidities seen included pulmonary embolism and lung cancer, but the numbers were low and the results for these were therefore inconclusive.

We conclude that age, dementia, and the presence of respiratory infection are factors associated with prolonged stay.

P1004

Frequency and length of admission in patients with chronic obstructive pulmonary disease (COPD) as co-morbidity (Co) in a university hospital setting. A cross sectional study

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About 20% of the Danish adult population suffers from COPD [1]. About 50% of the patients are undiagnosed. COPD patients often have Co which may lead to hospitalization [2]. To analyze the frequency of COPD as Co among hospitalised patients, the number of undiagnosed COPD patients and patients without COPD (PwC) in regards of the cause of hospitalization, and duration of hospitalization for PC and PwC as Co.

Aalborg University Hospital covers all medical and surgical specialities. A one day cross-sectional study was performed on patients > 18 years of age. A spirometry was performed. Smoking habits, prior lung function measurements, prescribed lung medicine were recorded. The final diagnosis was registered after one month. 583 patients were admitted to the participating units. 147 couldn’t participate, 47 didn’t wish to participate. 111 weren’t available at the time of the examination. 12 were excluded. 215 patients participated, 28% (61/215) suffered from COPD. 77% (47/61) were diagnosed at the examination. 36.1% (22/61) of the PC were admitted with infections, the majority non-pulmonary. The admission period was not significantly longer for PC as co-morbidity (mean 13.03 days) compared to PwC (mean 12.1 days), (p=0.24). 28% of hospitalised patients suffered from COPD. 77% were diagnosed at our examination.

PC were primarily admitted with infectious diseases. There was no significant difference in length of stay in hospital between PC and PwC as co-morbidity.

References:
The aim: to evaluate the dynamics of consumption of drugs for the treatment of bronchial asthma (BA) in Yaroslavl in 2008-2010.

Methods: Prospective cohort study; the data of healthcare and pharmacy department. There were chosen 4 groups of drugs: inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), short-acting bronchodilators (SABD), combination drugs (ICS/LABA); also consumption of beclometasone (B), fluticasone (F), fluticasone/salmeterol (FS) and budesonide/formoterol (BF) was estimated.

Results: In 2008 more than 74% of patients had moderate and severe asthma requiring mandatory prescription of ICS, including combination ICS with LABA, in accordance with international guidelines for BA. In 2010 the share of such patients has increased to 77.5 percent. In 2008 the share of patients receiving ICS was 49%, in 2009 - 42%, in 2010 - 39%; LABA consumption slightly decreased to 7%, 8% and 4%, respectively. The use of SABD had a slight tendency to increase: 12%, 16%, 19%. It should be noted that the number of registered patients with BA in the city has not significantly increased (in 2008 - 7308, in 2010 - 7426). In 2004, patients with BA received 11775 packs of B, 4(1) packs of fluticasone F, 36(1) packs FS, BF was not assigned. In 2010 intake of B was 8277 packs, increase use of F and combination drugs (F - 3500, BF - 2284, FS - 6410 packs). In 2004 patients with BA consumed 589,89 g ICS. In 2010, this volume increased to 681,93 g. In 2010, the share of the modern combined drugs increased to 27% of all anti-asthma drugs.
Acute asthma in Buenos Aires

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Objective: To establish if management of acute asthma in the emergency rooms in Buenos Aires follows the international guidelines

Method: We conducted an anonymous survey to physicians from 48 public hospitals (25 from Buenos Aires and 23 from sub urban zone) during March/April 2011.

Results: One hundred sixty three medical doctors from emergency rooms were surveyed (Graduation year 1999-09), forty-two (25%) were pediatricians. There was no departmentalised respiratory hospital in each zone. 93% of the medical doctors responded that they commonly treated patients with acute asthma. However, 48% did not have guidelines or protocol in the emergency room, whereas 65% commented that they did not have access to any poster, checklist or guide for acute asthma management. 91% of the doctors explained that they had a pulse oxymeter in the emergency room but only 18% reported that they had a Peak expiratory Flow Meter. More than 80%, informed that they used nebulised salbutamol in the first hour of treatment, 39% associated to inopram and more than a third used systemic corticosteroids through intravenous route. More than three quarters of the doctors gave a written plan to the patient but a short course of oral costoscosteosters was prescribed only by 20% of the surveyed doctors.

Conclusion: This survey showed that management of acute asthma in Buenos Aires does not follow international recommendations and guidelines.

Variation of seasonal (monthly) hospitalizations in asthmatic patients:

Difference between allergic and non allergic asthma

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Background: The seasonality of asthma hospitalizations (AH) may reflect the variation of triggers exposure. The recognition of clear seasonal (monthly) patterns of asthma hospitalizations may allow preventive strategies to be developed.

Objective: The aim of this study was to determine if there is a seasonal (monthly) pattern to asthma hospitalizations in patients with allergic and non-allergic asthma.

Methods: This study retrospectively analyzes the seasonality of AH in our depart-ment of pneumology, between January 2006 and December 2011. We evaluated all AH occurring this period for patients with Allergic Asthma (AA) and Non-Allergic Asthma (N-AA). The diagnosis and classification in AA and N-AA were made according to the results of skin prick testing (SPT) to common allergens. Patients with AA defined as those with ≥3 positive SPT and patients with N-AA defined as those with negative SPT.

Results: There were 82 AH in 50 patients with a mean age of 47 years and a sex ratio of 0.47. There were 38 AH in 27 patients with AA (9 males, 18 females) and 44 AH in 23 patients with N-AA (7 males, 16 females).

Conclusion: These findings suggest that AH have a different clear seasonal (monthly) variation between patients with AA and N-AA. The seasonality in AA admissions was far more pronounced than in N-AA. These results may offer significant opportunities for improved disease management.

Hospitalizations for asthma in Portugal from 2000 to 2008: Different trends in different regions

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Objective: To study regional differences and time trends of hospitalizations due to asthma in Portugal between 2000 and 2008. 39% associated to ipratropium and more than a third used systemic corticosteroids

Results: 28,707 patients were hospitalized due to asthma (0.3% of total admissions in the same period). Globally, the rate of hospitalizations for asthma per 100 000 adults declined from 15.9 in 2000 to 40.1 in 2008 per 100 000 adults.

Conclusion: Overall, the rate of hospitalizations for asthma is decreasing over years (with a global decrease of 7.5 per 100 000 inhabitants in the 9 years). Further analysis should be performed in order to understand why the Algarve had such a steep increase while the other regions had decreases.

Participation in the ARGA study: Long term impact on asthma management

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Background: Preliminary results of “Respiratory allergic diseases: monitoring study of GINA and ARIA guidelines (ARGA)” study show a poor effect of a medical education course on Global Initiative for Asthma (GINA) guidelines in improving asthma management.

Aim: To evaluate the long term impact of participating in a prospective study on Italian General Practitioners (GP) focused on monitoring the utilisation of GINA and Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines for asthma and allergic rhinitis management.

Methods: 107 GP enrolled 936 asthmatic patients (mean age 44yrs). For each pa-tient, a self-administered questionnaire on respiratory allergic diseases/symptoms, daily activity limitations, quality of life (by RHINASTHMA questionnaire), dis-ease control (by Asthma Control Test – ACT), self perception and the relative form filled in by GP were available at baseline and follow up 12 months after.

Results: Comparing baseline with follow up, asthma outcomes show an improve-ment: from 54.2 to 67.4% for asthma control, from 85.2 to 80.0% for asthma-like symptoms in the last 12 months, from 71.9 to 67.2% for daily activity limitations, from 61.2 to 66.6% for good health self perception and from 21.7 to 18.9 for quality of life score.

Conclusion: Involvement in a prospective study on asthma management seems to produce a long term effect in GP attitudes ameliorating their asthmatic patients quality of life.

This work was supported by the “Italian Medicines Agency (AIFA)”, within the independent drug research program, contract no. “FARM05765A”.

The education of physicians GINA and GOLD and a registration of chronic lung diseases in adult population of the Russian Federation

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Objective: To study the effects of educational programs GINA and GOLD on a registration of chronic lung diseases (CLD) according to the forms of State statistical reporting.

Material and methods: We analyzed a morbidity (M) and an incidence of disease (ID) in adults 18 years and older according to Federal State statistical observation (M – ICD-10 code N12, ID – ICD-10 code J45-J46) for the period from 2004 to 2010. The mean levels of M and ID were calculated at 100 000 adul t population of Russian Federation.

Results: Since 2004 the large educational programs GINA and GOLD were ex-tended among physicians. During seven years M CB and EL decreased gradually from 1552.9 to 1435.6 (p<0.01), i.e. 7.6% in 2010. ID CB and EL from 2004 to 2010 increased from 203.9 to 254.0 of cases (p<0.01), the growth rate was +24.6% in 2010. M COPD and BE gradually increased: M was +39.8% (from 487.1 to 680.8; p<0.01) and ID was +52.2% (from 42.1 to 64.1; p<0.01) at 2010. M BA was increased by +16.4% in 2010 year from 719.0 to 861.7; p<0.01. The highest ID BA (+16.7%) was in 2006: 52.6 (2004) and 61.4 (2006) accordingly (p<0.01). In subsequent years ID BA declined and the growth rate was only +5.7% in 2010 (54.4cases). The similar trends in M and ID were observed throughout the territories of the Russian Federation.

Conclusion: Educational programs have had a significant impact on the registration of CLD in adults of the Russian Federation.
107. Occupational asthma

**P1015**

Chemical exposure and lung function in the fragrance industry: A multi-site cross-sectional study

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Introduction: Fragrance production employees are exposed to large quantities of chemical mixtures, at exposure levels significantly higher than the final consumer. Aims and objectives: To answer the research question: Is fragrance industry employees, is occupational respiratory exposure to chemicals linked to a reduction in lung function?

Methods: A cross-sectional study was designed, using an exposed group (fragrance production) and a control group (non-exposed industry employees). 5 UK fragrance companies took part, total sample size was 112 (exposed n=60, controls n=52), calculated as sufficient to achieve 80% power and 5% significance. Spirometric measurements (FEV1, FVC, PEF) were taken pre- and post-shift, and cross-shift decline was calculated. Questionnaires were completed regarding potential confounding factors (smoking, body mass index, personal or family history of respiratory problems). Analysis of covariance (ANCOVA) was performed using the statistical package SPSS (v18).

Results: Adjusted mean difference between groups (exposed vs. control) for each outcome was not observed to be statistically significant (table below). Family history of respiratory problems was observed to have a significant effect on PEF ($p<0.043$).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted mean difference</th>
<th>95% CI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1*pred</td>
<td>-0.236</td>
<td>-1.383 - 1.899</td>
<td>0.757</td>
</tr>
<tr>
<td>FVC*pred</td>
<td>-0.236</td>
<td>-2.410 - 1.937</td>
<td>0.830</td>
</tr>
<tr>
<td>PEF*pred</td>
<td>0.619</td>
<td>-2.518 - 3.756</td>
<td>0.696</td>
</tr>
</tbody>
</table>

*Adjusted for smoking, body mass index, personal history of respiratory problems, family history of respiratory problems.

Conclusions: Occupational respiratory exposure to chemicals used in fragrance production did not have a significant effect on lung function.

**P1016**

Across-shift decrease in fractional exhaled nitric oxide among Tanzanian cement production workers

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Background: There is limited information on fractional exhaled nitric oxide (FENO), a marker of respiratory inflammation, among cement production workers.

Aim: To explore possible across-shift changes in FENO over an 8h shift among dust exposed cement production workers in Tanzania.

Methods: We examined 48 cement production workers (exposed) and 27 workers from a mineral water factory (controls), all non-smokers. Pre-shift and post shift FENO measurements (parts per billion, ppb) were performed using a NIOX MINO machine, for 2 day shifts among controls and 3 day shifts among exposed. Full shift personal total dust samples were collected in participants’ breathing zone.

Results: Baseline geometric mean (GM) of FENO for the respective days of examination were 20.4 ppb, 20 ppb and 19.1 ppb among exposed, and 16.3 ppb and 16.2 ppb among controls. There was a significant across shift decrease in FENO for the three days of examination among the exposed (2.9 ppb, 2.4 ppb and 3.4 ppb, respectively, paired t-test, $p<0.05$), while the decrease was not significant among controls (1.4 ppb and 0.2 ppb). The change in across shift FENO was not significantly different between exposed and controls. The GM for total dust exposure among exposed was 9.4 mg/m3 and 0.28 mg/m3 among controls. There was no correlation between the across shift FENO change and total dust exposure. Conclusion: The across-shift FENO decrease in cement production workers was not significantly associated with occupational dust exposure, and the reason for this change should be determined in future studies.

**P1017**

Causes of work-exacerbated asthma

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Rationale: A 2011 Statement of the American Thoracic Society concluded that work-exacerbated asthma (WEA) is common in industrialized nations, with a prevalence of 21.5% in adults with asthma. While there are published lists of workplace agents that can cause occupational asthma, there are no comparable lists for WEA. We reviewed published articles to prepare such a list.

Methods: We systematically searched the peer-reviewed medical literature to identify articles about WEA published during 1980-2011. We selected articles that reported WEA agents determined case-by-case (from clinical case series, surveillance and worker compensation programs) or in risk-set analyses that used statistical models to determine occupational exposures associated with exacerbation of asthma or WEA.

Results: The literature search identified 13 articles that reported exposures for work-related exacerbation of asthma, including 3 risk-set studies. The studies were conducted in several countries in North America and Europe, and used various criteria for WEA and methods to determine exposures. From studies with WEA identified on a case-by-case basis, the more common types of agents included miscellaneous chemicals, dust, paint, smoke, indoor air quality, and cleaning products. From two risk-set studies conducted in general population settings, exposures with statistically significant (p<0.05) relative risks of 2.0 or greater included dust, high exposure to gas and fumes, indoor air quality, physically strenuous work, and probable daily occupational exposure to dust, gases, or fumes.

Conclusions: Various types of workplace exposures can exacerbate asthma, including irritants, agents with sensitizing traits, and physical factors such as strenuous exercise.

**P1018**

Nasal symptoms, lung function changes, and sensitization to work-related allergens in hairdressers

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Objective: To assess the occurrence of nasal symptoms in hairdressers and their relation to respiratory symptoms, bronchial hypersensitivity (BHR), and positive patch testing.

Methods: Cross-sectional study was conducted at the Institute for Occupational Health of RM, Skopje, including 50 female hairdressers (mean age 32.1±7.3 years, mean job duration 12.6±8.4 years) and 50 office workers, matched by gender, age, duration and smoking status. Evaluation of examined subjects included completion of questionnaire on nasal and respiratory symptoms, BHR and sensitization to work-related allergens.

Results: Prevalence of overall nasal symptoms in last 12 months among examined hairdressers was 36% (varying from 40% for rhinorhoea to 32% for nasal itching) and it was significantly higher than its prevalence in office workers (36% vs. 14%, $p<0.05$). Nasal symptoms were significantly related to respiratory symptoms in both hairdressers and office workers. Spirometry showed lower parameters in hairdressers with significant difference for MEF25 and MEF30. Significant association was registered between nasal symptoms and BHR in hairdressers ($P<0.05$). Prevalence of BHR was higher in hairdressers with significantly higher severity ($P<0.05$). Patch testing to ammonium persulfate, ammonium thioglycolate, paraphenylenediamine, and pyrogallol was positive in 72%, 22%, 18%, and 4% of all hairdressers reporting nasal symptoms, respectively.

Conclusion: Our data indicate high prevalence of nasal symptoms in hairdressers and their significant relation to respiratory symptoms, BHR and sensitization to work-related allergens.

**P1019**

Therapeutic potential of mesenchymal stem cells modified to secrete anti-inflammatory protein ST2 in a model of occupational asthma

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Background: The aim of this study was to evaluate the ability of mesenchymal stem cells modified to secrete ST2 to attenuate the inflammatory and respiratory symptoms in an animal model of occupational asthma (OA) to paricalcitol saline.

Methods: Occupational asthma was induced in BALB/c mice (1). Twenty-four hours after induction of asthma, the animals received intravenously 1×10^6 of mesenchymal stem cells (MSC group), mesenchymal stem cells genetically modified with a lentiviral vector expressing the gene ST2 (ST2 group) or saline (group S). Bronchial hyperresponsiveness was assessed using methacholine provocation.
Pulmonary inflammation and levels of immunoregulatory cytokines were determined in BAL. Total serum IgE was measured in blood. The analyses were made on days 2, 4 and 7 after induction of asthma.

**Results:**
Animals sensitized to persulfate salts showed an increase in bronchial hyperresponsiveness to methacholine and in the % of neutrophils and total IgE after inhalation of persulfate salts, compared with the control group. The animals treated with mesenchymal stem cells showed a decrease of the bronchial hyperresponsiveness to methacholine and the percentage of neutrophils and total IgE compared to the control group. There were significant differences between groups MSC and ST2 in the levels of IFN-γ, IL-13 and IL-6 that were lower in the ST2 group on day 4 after induction of asthma.

**Conclusions:** In the described model of OA mesenchymal stem cells modified to secrete sST2 have shown anti-inflammatory capacity and attenuation of bronchial hyperresponsiveness.

Study funded by Fis PI11/00782.

**P1020**
Serial PEF measurements detect occupational alveolitis and occupational asthma due to metal-working fluid
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Sherwood Burge3
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**Introduction:**
Serial measurements of Peak Expiratory Flow (PEF) are the most appropriate and available method for confirming occupational asthma. Changes in PEF might also occur in alveolitis.

**Aim:**
To compare work-related changes in PEF between workers with allergic alveolitis and occupational asthma with exposure to the same metal-working fluid aerosols.

**Methods:**
Symptomatic workers with residency improvement from an engineering factory were asked to measure PEF 8 times daily for 4 weeks at home and at work before remedial action in the workplace. Allergic alveolitis was diagnosed by an expert panel from combinations of systemic symptoms with breathlessness, audible crackles in the lungs, CXR or CT scan showing compatible interstitial changes and reduced DLCO. Occupational asthma was diagnosed from work-related wheeze or breathlessness and confirmed with physiological tests including serial PEF measurements. The Oasys PEF plotter was used to calculate differences between rest and weekdays for mean PEF, diurnal variation and the scores used to confirm occupational asthma (Oasys, ABC and timepoint).

**Results:**

<table>
<thead>
<tr>
<th>Mean difference in PEF rest-workdays (litres/min) (SD)</th>
<th>Occupational alveolitis (n=15)</th>
<th>Occupational asthma (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean diurnal variation on weekdays (% mean) (SD)</td>
<td>22.5 (30.8)</td>
<td>26.1 (26.9)</td>
</tr>
<tr>
<td>Mean diurnal variation on weekends (% mean) (SD)</td>
<td>14.9 (7.7)</td>
<td>14.9 (6.0)</td>
</tr>
<tr>
<td>% with mean weekday diurnal variation &gt;20% predicted</td>
<td>20</td>
<td>23.1</td>
</tr>
<tr>
<td>Oasys score &gt;2.5 (%)</td>
<td>53.3</td>
<td>71.8</td>
</tr>
<tr>
<td>ABC score &gt;15 (%)</td>
<td>46.7</td>
<td>57.9</td>
</tr>
<tr>
<td>Positive timepoint analysis (%)</td>
<td>66.7</td>
<td>69.2</td>
</tr>
</tbody>
</table>

**Conclusion:**
Changes in serial PEF measurements are similar in workers with occupational allergic alveolitis and occupational asthma.

**P1021**
Decrease in respiratory symptoms in the Danish furniture industry is associated to a decline in wood dust exposure – Results from two cross sectional studies 5 years apart
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**Objective:** To investigate associations between wood dust exp. and resp. symptoms in two studies 5 years apart from the same area.

**Methods:** 2,032 woodworkers from 54 plants in study 1 and 1,889 woodworkers from 52 plants in study 2 returned a questionnaire on resp. symptoms, employment and smoking habits. Assessment of wood dust exp. was based on job exposure matrices including factory size, task and personal dust measurements (2,217 in study 1 and 1,355 in study 2).

**Results:**
The median (range) of inhalable dust conc. was 0.8 (0.4-1.6)mg/m³ in study 1 and 0.6 (0.3-1.1)mg/m³ in study 2. The prev. of selfrep. asthma was higher, but the prev. of resp. symptoms were lower in study 2 vs. study 1. In a logistic regression analyses wood dust exposure explained the difference in symptom prevalence between study 1 and study 2, but no effect was found for selfrep. asthma. No influence of sex, smoking and age was seen.

Figure 1. Change in OR for study 2 vs. study 1, unadjusted and adjusted for wood dust exposure.

**Conclusion:** An association between respiratory symptoms and wood dust exposure was confirmed.

**P1022**
Irritative respiratory symptoms and ventilatory function to workers exposed to man made mineral fibres

We conducted a case-control study of 43 subjects who use Man Made Mineral Fibres (MMMF) to isolate cookers: 25 male and 18 female, aged 29-55, average exposure of 17.7±4.1 years and a matched control group. Clinical, respiratory, skin and eye symptoms were recorded by questionnaire, pulmonary functional tests (PFT), MMMF mean concentration in the workplace air was measured. Prevalence of chronic respiratory symptoms in exposed workers was significantly higher (32% vs. 21%). Significantly higher prevalence was found for irritative symptoms of the upper airways (p=0.32, p<0.05), itching eye (p=0.35, p<0.05) and cutaneous symptoms such as itching, erythema or urticarial reactions. Irritative anomalies of the upper airways in exposed workers were significantly associated with duration of exposure (r=0.37, p<0.005). A significant correlation between symptoms and PFT values was found in workers having more than 10 years exposure. Values of FVC, FEV1, FEV1/FVC and small airways indices in exposed workers were significantly lower (p<0.01). Small airways changes in exposed workers were strongly linked to duration of exposure (r=0.37, p<0.05) whereas relation of cutaneous symptoms and professional age was not significantly linked. We found that irritative ocular or tegumentary syndrome was more frequently revealed at the exposed subjects, especially in the first 10 years of activity.

Our data suggest interactive influence of workplace exposure to MMMF in development of irritative anomalies of the upper airways with predominantly smaller airways affecting.

**P1023**
Blood oxidative markers in glass industry workers and related respiratory outcomes
Felicia Gradinariu, Eugenia Danulescu, Ruxan Danulescu, Micaela Margineanu, Carmen Croturom, Virgil Carac. Occupational Medicine Department, Regional Centre of Public Health, Iasi, Romania

**Aim:** Workers from a glass factory were investigated by a longitudinal study to detect respiratory outcomes and their relations with working conditions.

**Material/Methods:** 229 nonsmoker workers (40 men) with mean age 35±9 yrs and mean exposure in glass industry 14±4 yrs were examined by clinical, spirometric and biochemical tests. Blood superoxide dismutase (SOD), glutathione peroxidase (GSHP) and serum lipoperoxides (LP) were assayed as effect markers. Occupational risk was estimated by workplace air contaminants (WAC), Pb in blood, urine (U-Pb), and by urinary delta-aminolevulinic acid (ALA).

**Results:** Although WAC (inorganic Pb, acetone, toluene, white spirit, varnishes) ranged under TLVs, cumulative toxic index was 2.6, indicating a potential hazard risk. 33% of subjects had respiratory changes: 28% cough, 19% sputum production, 8% dyspnea, 18% reported all three symptoms and 15% had obstructive

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with selfrep. asthma</td>
<td>33%</td>
</tr>
<tr>
<td>% with selfrep. asthma</td>
<td>46.7%</td>
</tr>
<tr>
<td>% with selfrep. asthma</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

Prevalence and unadjusted OR of respiratory symptoms
P1024
Absence of nonspecific bronchial responsiveness (NSBR) in occupational asthma (OA): A case-series study
Jacques André Pralong
Catherine Lemière, André Carrier. Chest Medicine, Hôpital du Sacré-Coeur, Montréal, Canada
Background: Although increased NSBR is a key component of OA it may be absent in rare occasions as previously shown.
Objective: Describe the prevalence of confirmed OA with normal NSBR before and after specific inhalation challenge (SIC).
Methods: We retrospectively reviewed our database containing all SIC done in our laboratory or at work between 1997 and 2011. OA was defined by a positive SIC with a ≥25% sustained decrease in FEV1; normal NSBR was defined by PC20Methacholine (PC20M) >16 mg/ml.
Results: 373/1193 workers tested had confirmed OA. 22/373 (5.9%) had normal NSBR before and after SIC. The median SD between baseline and the day of the challenge was 9.6 ± 8.7 days. However, 10 subjects had at least one PC20M < 16 mg/ml during their investigation while symptomatic and at work for 9 of them. The remainder 12 had normal NSBR on all tests but only 3 subjects had such a low value at work (≥16 mg/ml). Among the 22 cases, 20 were atopic, 15 were exposed to a high molecular weight agent, 4 to a low molecular weight chemical and 3 to various agents during workplace challenge. Seventeen, 14 and 1 subjects had an early, late and atypical asthmatic reaction respectively.
Conclusion: We describe 22 cases of confirmed OA despite normal NSBR before and after SIC. This is however rare (5.9% of confirmed cases of OA by SIC). In our experience, it is exceptional to have normal NSBR while symptomatic and at work in cases of confirmed OA.

P1025
Does FENO predict FEV1 response to exposure cessation in occupational asthma?
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Alastair Robertson 1, Jon Ayres 1, P. Sherwood Burge 1
1Occupational Lung Disease Unit, Heart of England NHS Foundation Trust, Birmingham, West Midlands, United Kingdom; 2Warwick Medical School, University of Warwick, Coventry, United Kingdom
Introduction: The prognosis in workers with occupational asthma following cessation of exposure and increase in FEV1 post-exposure is variable. We investigated whether FENO was increased in workers exposed to metal working fluids (MWF).
Methods: Case control study to assess the prevalence of obstructive airway disease in a group of 160 goldsmiths exposed to metal working fluids (MWF). A control group of 160 goldsmiths was randomly selected from the same geographical area with no occupational exposure to MWF. Both groups were asked to complete a medical questionnaire and undergo a peak flow measurement. FENO was measured while exposed and after removal.
Results: In the goldsmiths exposed to MWF, the median FENO was 49.7 (95% CI: 32.8-67.5) ppb compared to 16.5 ppb (95% CI: 11.9-21.1) ppb in the control group (p <0.0001). FENO was higher in women exposed to MWF (p<0.01) and in those with symptoms (p<0.0001). FENO was 38% (95% CI 16-60%) higher in the exposed group compared to controls and 20% (95% CI 1-39%) in the control group after 2 weeks of exposure.
Conclusion: FENO increased after 2 weeks of exposure in workers exposed to MWF. FENO can be used in the assessment of exposure cessation and may be a useful tool in the management of occupational asthma. Further research is needed to establish the predictive value of FENO.

P1026
Increased exhaled nitric oxide among workers exposed to metalworking fluid aerosol
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Background: Recent outbreaks of respiratory symptoms among workers, including dry cough, asthma symptoms and pneumonitis, exposed to metal working fluids (MWF), has initiated a cohort-study of 200 exposed and 75 unexposed workers.
Objective: To investigate whether exposure to MWF affects FNO.
Methods: Exposures were measured by personal dosimetry and exposure-related symptoms were scored during the 3 months prior to the study. The exposure in ppm was calculated for each worker and correlated with FNO and lung function tests.
Results: In the unexposed group FNO was 14.5 (95% CI: 9.7-21.0) ppb while in the exposed group FNO was 18.2 (95% CI: 14.4-22.5) ppb, which was statistically significant (p <0.001). FNO correlated negatively with FEV1 (r=-0.29, p<0.001) and lung function in workers exposed to MWF.
Conclusion: Exposed workers had increased FNO compared to unexposed workers. FNO can be used to monitor exposure and to support work-related respiratory health.

P1027
Respiratory symptoms and lung function tests among the goldsmiths engaged in jewellery manufacturing industries in India
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Introduction: The goldsmiths are exposed to various acidic and metallic fumes at work. But no study has been reported on goldsmiths neither on the Indian jewellery industries evaluating the relationship between occupational exposure and respiratory health.
Methods: The study was carried out to see if there is a cause and effect relationship between the exposure to metallic and acidic fumes and respiratory health effects among workers engaged in Indian jewellery manufacturing industries.
Results: A total of 134 male participants were the goldsmiths among which 100 were the industry workers (mean age 34.4±2 years) and 34 were front desk office executives (mean age 37.5±2.2) of the same industry. Evaluation of examined subjects included completion of a standardized questionnaire on respiratory symptoms and spirometry. Data were analyzed using odds ratio with 95% confidence interval and logistic regression adjusting for age, smoking status, second hand smoke exposure and parental atopy/asthma.
Results: The goldsmiths had significantly higher prevalence of chronic cough (OR = 3.5, 95% CI = 1.2-8.2), nasal allergy (OR = 2.9, 95% CI = 1.1-4.8), production of phlegm (OR = 3.2, 95% CI = 1.4-6.2) and tightness in chest (OR = 2.7, 95% CI = 1.7-4.7) compared to the office workers. Results of spirometry showed significantly lower percent predicted values of FVC (p <0.05), FEV1 (p <0.001), FEV1/FVC <0.05) and FEV25-75 <0.05 (p <0.05).
Conclusion: Due to exposure to various sensitizers and irritants (metallic and acidic fumes) in the workplace the goldsmiths had a higher prevalence of respiratory disturbances and a reduced lung functions compared to the front office staffs.

P1028
Case control study to assess the prevalence of obstructive airway disease in flour mill workers
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In India, the grain flour required for household cooking is made by grinding grains in machine operated flour mills, which are usually small sized ventilated rooms. These machines are operated by a single unskilled worker who works in shift duties of 6 hours. During operation, the machine generates large amount of flour or grain dust and produces clouds of flour that surrounds the worker thus predisposing him to obstructive airway disease. 46 flour mills in the city were visited. Customers of the mills with short exposure to flour dust served as controls while those with exposure for age and sex. Those with active lung infection or scarring and tobacco smokers were excluded from both groups. On site measurement of PEFR was done, using Mini Wright’s peak flow meter for a total of 44 workers and 44 controls. The intention of using a peak flow meter instead of spirometry was to evaluate usefulness of this simple modality which can be easily applied in villages where flour mills are more common and spirometry is not available. The
peak flow readings between >100%, 80-99%, 50-79% and <50% predicted value were labelled as normal, green, yellow and red zone respectively. 22/44 workers had normal PEFR as against 38/44 controls. 19/24 workers were in green zone even after 15 years of work duration. The study indicates a potential occupational hazard to the flour mill workers. Use of face mask or enclosure of machine can potentially reduce the risk.

P1029

Acute bronchitis morbidity in railway and subway train machinists

Eleftheria Giatromanolaki1,2, Tatiana Rybina1, Oksana Omelyanenko2.

Conclusions: A correlation has been found between the AB morbidity and age, length of service and reliable morbidity decrease among subway train machinists in summer in comparison to winter. The study indicates that AB is a potential occupational hazard to the flour mill workers. Use of face mask or enclosure of machine can potentially reduce the risk.

Methods: Prospective, longitudinal study included 2 comparable groups: the 1st – 1068 subway train machinists, mean age 33.6±6.8 years, mean length of service 8.8±4.6±6 years; the 2nd – 1212 railway train machinists, mean age 43.3±4.6±8 years, mean length of service 12.0±8.9 years. AB personified morbidity was assessed during 2005-2008.

Results: AB personified morbidity in the 1st group was higher than in the 2nd group (29.7 cases and 286.4 days per 100 workers vs. 4.87 cases and 46.6 days per 100 workers respectively, p<0.015). Odds ratio for someumin selection of subway train machinists was 6.1±0.14 (OR=6.1), 95% confidence interval [-4.68, 7.95], etiological portion of the increase was 83.6%. The highest morbidity level in the 1st group was established in the age interval between 30-39 years and length of service range 5-9 years compared with those in other age intervals (37.2 cases per 100 workers, p<0.01). We found statistically reliable morbidity decrease among subway train machinists in summer in comparison to winter (4.78 vs. 8.3 cases per 100 persons, p<0.01). No any correlation has been found between the AB morbidity and age, length of service and season in the 2nd group.

Conclusions: AB morbidity in subway train machinists could probably be related to occupational exposure of the biological factor in underground work environment. Biological factor influence in underground could derive from the lack of ultraviolet insolation and large volume of passenger traffic.

P1030

Cof a 1 – Identification of the first coffee allergen

Cof a 1 was identified as a class III chitinase of Coffea arabica. Serum IgE antibodies to recombinant Cof a 1 were found in 27/24 workers with coffee-induced respiratory disorders.

Introduction: Dust of green coffee beans is known to be a relevant cause for occupational respiratory disorders. There is evidence for type I-sensitization as the underlying pathomechanism. Up to now no single coffee allergen has been described on molecular level. Identification of coffee allergens is warranted for standardization of allergological diagnostics.

Methods: From 17 coffee industry workers complaining about work-related rhinitis, conjunctivitis, and airway obstruction during exposure to coffee dust we obtained sera for IgE sensitization to green coffee beans detected by ImmunoCAP (Phadia, Freiburg, Germany). By sequence analysis, a new coffee allergen (Cof a 1) was identified, expressed in E. coli, and evaluated by Western blots. The frequency of sensitization was investigated by ELISA (Enzyme-linked Immunosorbent Assay) screening.

Results: The cDNA encoding Cof a 1 was identified as a 32 kDa Coffee arabica class III chitinase. Serum IgE antibodies to recombinant Cof a 1 were found in 3 out of 17 symptomatic coffee workers (18%), whereas only 2 of them reacted to the commercial specific IgE test to green coffee beans (k70, Phadia). After submitting the present data, Cof a 1 has been assigned by the WHO/IUIS Allergen Nomenclature Sub-Committee.

Conclusion: A class III chitinase of Coffea arabica Cof a 1 was identified as an important coffee allergen. It may have a relevant potential for diagnostics of green coffee-induced respiratory disorders.

P1031

Prevalence of work-related asthma among adult asthmatics referred to respiratory clinics

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Background: The most common occupational lung disease reported in industrial countries is occupational asthma. There are limited data about the prevalence of work-related asthma among asthmatics in Iran.

Objectives: The aim of this study was to assess prevalence of work-related respiratory symptoms (WRS) and occupational exposures in asthmatic adults at pulmonary clinics.

Material and methods: A cross sectional study was performed. All ≥17 year old asthmatics were recruited into the study. A questionnaire mainly based on one developed by Rhino was completed by each participant. Currently employed subjects were subdivided into two groups by WRS status. Subjects’ occupational and workplace exposures were evaluated using an asthma specific job exposure matrix (JEM). Statistical analyses were conducted using the Student’s t-test for continuous data and Chi square for categorical data. Prevalence ratios (PRs) were calculated, using a Cox regression model.

Results: 39 (21.8%) of 179 current employed asthmatics (11% of all 339 adult asthmatics) had WRS. Subjects with WRS were more likely to have self-reported allergy (PR: 2.7; P=0.003) and low molecular weight antigens’ exposure (PR: 2.7; P=0.0001). According to the JEM, those with WRS had more high risk occupational exposures (PR: 2.2; P=0.003). The two most frequent occupational classes for asthmatics with WRS were trades, transport and equipment operators (33%), and processing, manufacturing and utilities (31%).

Conclusion: Prevalence of WRS in the current study is consistent with previous reports of work-related asthma. Study results emphasize further need for taking complete occupational histories in adult asthmatics.

P1032

Effects of exposure to flour dust on respiratory symptoms and pulmonary function of mill workers

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Background: Exposure to flour dust is associated with development of respiratory symptoms and varying degree of reduction in lung function. The aim of the study was to assess the effect of Exposure to flour dust on respiratory symptoms and pulmonary function of flour mill workers.

Methods: This study was carried out at flour mills in Sohag Governorate. Two hundred male workers with current exposure to flour dust and Two hundred non-exposed male as a control group were interviewed and self designed study questionnaire was administered to them and the parameters of their pulmonary function were measured.

Results: Respiratory symptoms such as cough, expectoration, wheezing, and shortness of breath, were significantly (p<0.0001) more common in exposed workers compared to unexposed counterparts. Furthermore significant (p<0.0001) decrements in the pulmonary function of exposed subjects were noted. The additive effect of smoking was clearly noticed as there was a highly statistically significant decline of FEV1% and FVC% in smokers compared to non-smokers (p<0.0001), COPD, asthma and chronic bronchitis were significantly higher among workers compared with control subjects. Statistically significant association between COPD, asthma, chronic bronchitis and age (p<0.02), smoking (p<0.0002), duration of employment (p<0.0001), level of exposures (p<0.0001) was found.

Conclusions: Flour mill workers were at an increased risk of developing pulmonary symptoms & a strong association exists between exposure to flour dust and the prevalence of respiratory symptoms and functional impairments of the lungs.

108. Indoor and outdoor air pollution

P1033

Exhaled nitric oxide in traffic professionals exposed to ambient urban air pollution

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Exhaled nitric oxide (eNO) has been used as a non-invasive method to assess lung
inflammation. Urban air pollution is associated with inflammatory markers and increased risk of pulmonary diseases. Traffic professionals are at risk of vehicular pollution exposure. However few studies have been published testing eNO in this group. We aim to study the association between air pollution, blood inflammatory markers and eNO in traffic professionals of Sao Paulo city (SP). Non smokers cab drivers (N=46) and traffic controllers (N=23) of SP were evaluated 4 times after work shifts. Pollutants (PM2.5 measured by reflectance and NO2 by colorimetry) were collected by individual samplers during 24h exposure before each evaluation. eNO, ultra sensitive C. Reactive Protein (us-CRP) and Erythrocyte Sedimentation Rate (ESR) were measured by ozone-chemiluminescence, high pressure liquid chromatography, nephelometry respectively. inflammatory markers data were tested against pollutants levels by Linear regression model for repeated measures through generalized estimated equations (LME GEE). Statistical significance was set at 10%. PM2.5 was 40.3±20.8 μg/m3 and NO2 197±24.5 μg/m3. eNO was 23.2±16.72 ppb, us-CRP 5.25±6.07 mg/L and ESR 3.2±1.2±20 mm/h. After adjustment for cardiovascular risks (abdominal circumference, hypertension, diabetes, age, body mass index) GEE tests showed associations between eNO and ambiant NO2 (p<0.10) and us-CRP (p<0.05, adjusted for ESR and NO2). PM2.5 was correlated to both inflammatory blood markers (ESR p<0.05 and us-CPR p<0.10). We conclude that urban air pollution in traffic professionals from SP.

P1034
Individual exposure of urban children to black carbon
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Methods: Primary school children were given an Aethalometer to carry with them at all times for a 24 hour period. Cumulative black carbon was calculated by calculating the area under the curve (AUC) when plotting BC vs time. Activity diaries were used to divide the day into time at home, time commuting, and time at school or work. Personal exposure was compared with non-cycling adult commuters.

Results: For children 50.6% (± 9.3%) of exposure was at home, 19.1% at school and 39.3% at other times. Compared with adults (n=28), children (n=6) had similar 24 h exposure to BC (1019167 vs 706640 ng.m-3, p=NS). Children were exposed indoors, where PM levels are higher.

Discussion: We conclude that this because school children spend a greater proportion of the working day outdoors, where PM levels are higher.

P1035
Penetration and remanence of pollen in dwellings
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Indoor pollens come from outdoor pollution but the temporal relationship between both phenomena is poorly documented. In this study, we tried to compute the influx and remanence of various pollen species throughout the pollen season.

P1036
Influence of wildfire’s smoke during heatwaves on the mortality and morbidity due to respiratory diseases in abnormally hot summer of 2010 year in Russia
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Methods: Time series analyses of morbidity and mortality during 2008-2010 years in central regions of Russia. Case-crossover study of influence of pollution levels on respiratory health and mortality due to respiratory diseases in central regions of Russian Federation during summer 2010 year.

Results: We recorded significant growth in respiratory morbidity and mortality during extreme smoke and abnormal heat. Number of emergency calls due to bronchopulmonary diseases was twice higher than in 2008, 2009 and 2010. The most frequent cause of seeking the emergency aid was asthma, acute bronchitis and exacerbation of chronic obstructive pulmonary disease.

Conclusions: Our data suggest that there were a short-term associations between daily air pollution data and frequencies of events (death, hospital admission, emergency aid etc.) in the most hot days of summer 2010 year.

P1037
A longitudinal study about lung function and symptoms in patients with pollution-related illness
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Background: Air pollution is known a leading cause of respiratory symptoms. In Japan, an improvement of the atmosphere was achieved by the pollution organic act, and patients with air pollution-related illness have received medical care for more than 20 years under the Pollution Compensation Law. Our study was to verify the effects of Japan system by investigating the long-term consequences of exposure to air pollution on lung function and symptoms in patients with pollution-related illness.

Methods: The study included 782 surviving patients with pollution-related illness in Okayama who were ≥ 65 years of age in 2009. The patients had all received medical care, including expectorants and bronchodilators, once or twice a month and had undergone spirometry and assessment of respiratory symptoms each year for more than twenty years. We analyzed lung function and symptoms from 2000-09.

Results: Almost all (male: 59.0%, female: 78.6%) of the subjects had normal pulmonary function. However, a high proportion of subjects reported respiratory symptoms. All measures of pulmonary function decreased. The annual mean change of the VC was -40.5 ml/y (male) and -32.7 ml/y (female). The change in the FEV1 was -27.6 ml/y (male) and -23.9ml/y (female). In addition, there was a significant (male: p<0.05, female: p<0.01) worsening of dyspnea over time.

Conclusions: The annual mean changes of lung function were within the normal ranges. The findings suggested that the medical care compensation system in Japan is effective. Although in order to reduce dyspnea, we believe that it is necessary for patients with pollution-related illness to also receive respiratory rehabilitation.
Background: The relationship between air pollution and asthma has been investigated but the results of these studies were different and a definitive conclusion was impossible especially about the type and amount of pollutants that are harmful to health. Here we investigated the effects of various pollutants using GIS-based information on the rate of hospitalizations due to asthma in children in Tehran.

Methods: Information of patients who admitted with diagnosis of asthma in government run hospitals in Tehran and the total number of admissions in the same age range (2 to 14 years) from March 30th 2009 to March 31st 2011 obtained from medical records. Days of year divided in GOOD and NONGOOD days according guideline for reporting of daily air quality-pollutant standard index (PSI). Two thousand two hundred nineteen cases enrolled in the study and asthma admission to total admission ratio compared with air pollutants data in admission day (725 days) using non-linear regression method.

Results: Analysis of study data revealed that there is a significant relationship between NONGOOD nitrogen dioxide (P value<0.001), ozone (P value<0.001), and sulfur dioxide (P value<0.04), levels and admission due to asthma in children but there was no significant relationship between carbon monoxide levels and asthma admission in children.

Conclusions: Significant relationship between nitrogen dioxide, ozone and sulfur dioxide concentration in air and admission due to asthma at levels other than GOOD reveals air pollutants levels can be significantly harmful for children before PSI reaches to hazardous levels.

Traffic-related air pollution in Poland as a risk factor of obstruction in urban and rural areas

Background: Traffic-related air pollution (TRAP) is associated with a number of respiratory diseases. Specific traffic conditions in East-Central Europe foster an increased exposure to air pollutants and a risk of obstruction among people living close to busy roads.

Material: 4985 persons (urban and rural inhabitants) were investigated in a study made in 2008-2011 in Warsaw. Pulmonary function tests were completed (Easy One spirometer) and occurrence of respiratory system diseases symptoms, allergies, smoking, etc. were proved. Simultaneously traffic density and TRAP concentrations and a risk of obstruction among people living close to busy roads were assessed.

Results: TRAP concentrations were statistically significant higher (p<0.05) in the vicinity of roads compared to rural areas. Significant association between living close to busy roads and risk of obstruction was found. 334 cases of obstruction near industrial areas.

Conclusion: Traffic-related air pollution and not there is still significant relationship between NO2 and risk of obstruction among people living close to busy roads.

The increasing number of asthmatic children in Galati, one of the largest cities of Romania, very industrialized, requires a careful approach on the exposure to air pollutants, especially nitrogen dioxide, ozone, sulfur dioxide and particulate matter.
Graphene may modulate the immune activation and survival of monocytes representative of the innate immunity

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Background: The graphene which is an allotrope of carbon has the honeycomb-like structure of one-atom-thick planar sheets. It can be produced and chemically modified by chemical vaporization method, is used in modern electronic, infor-
mative technologies including medical device. Graphene oxide (GO) has oxygen functional groups on the graphene plane. We performed this experiment to define the effect of GO on the innate immunologic function.

Materials and methods: GO was prepared by the modified Hummers method using 2g of graphite powder. After sequential procedure, GO in water was used for experiment. U-937 cells were cultivated in RPMI 1640 containing various concentration of GO particle solution. We checked the surviving and dying cells and cell size with the morphologic change with light microscopy.

Results: The x-ray diffraction patterns observed for the graphite and GO. The pristine graphite has a peak centered at 2θ = 26.5° (d = 0.33 nm). This peak was shifted to 2θ = 11.3° (d = 0.78 nm) after applying the Hummers method. This means that the graphene is exfoliated and the d-spacing increased, indicating that GO is formed. As the graphene concentration increased, the cell survival was diminished. U-937 cells were aggregated which might be associated with phagocytosis.

Conclusion: GO in water diminishes the cell survival and activates phagocytosis and alters the differentiation in the monocytes representative of the innate immunity.

Acknowledgement: This research was supported by Mid-career Research Program (2011-0028752) through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology.

Lower socioeconomic classes are more exposed to air pollution in Italy

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Objective: The present study aims at investigating whether lower socioeconomic classes, who present a higher prevalence of current smokers, are also more exposed to air pollution in Italy.

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 centres answered a screening questionnaire between 2007 and 2010 (response percentage=57.2%). It was investigated if residential exposure to industrial plants or heavy traffic changed as a function of education or profession.

Results: Subjects with lower education were more likely to live near factories or heavy traffic roads (Table 1). Workmen presented the highest exposure to industrial plants or heavy traffic roads (Table 1). U-937 cells were cultivated in RPMI 1640 containing various concentration of GO particle solution. We checked the surviving and dying cells and cell size with the morphologic change with light microscopy.

Conclusion: GO in water diminishes the cell survival and activates phagocytosis and alters the differentiation in the monocytes representative of the innate immunity.

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The effect of particulate matter pollution on emergency room visits due to COPD and asthma and the association with hospitalization rate in Düzce City

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To investigate the effect of particulate matter levels on patients with COPD and asthma admitted in emergency department with the diagnosis of asthma and COPD.

Between January-December 2009, the patients diagnosed as COPD and asthma at State Hospital were retrospectively evaluated. The monthly average values of particulate matter obtained from the official data. 61.4% of total 2489 cases were male. The average PM10 concentration of Düzce city was highest in November (184 mg/m³) and was lowest in July (41 mg/m³). The rates of COPD and asthma were 77.8% and 22.2%, respectively. COPD rates in males and females were 85.1% and 66.4%, respectively. Asthma was observed in 33.6% of females while 14.9% of males were diagnosed as asthma (p<0.000). The admittance rates to the emergency department for females and males were 69.3% and 66.2%, respectively (p<0.05). The patients with COPD were frequently applied in winter (27%) while the patients diagnosed as asthma admitted in autumn (p=0.010). While particulate matter was over 100 μg/m³, the odds ratios for COPD and asthma diagnosis were 1.039 (0.990-1.091) and 0.878 (0.749-1.029), respectively. Only the age was found an independent factor (β=0.382, t=-2.054, p=0.000). COPD patients were older (p=0.382, p=0.000). The factors independently effective on diagnosis according to univariate analysis were gender (R=10.664, F=65.182, P=0.000) and season (R=0.700, F=4.278, p=0.005). It seems that increase in PM10 concentration causes an increase in admission to emergency department with the diagnosis of asthma and COPD.

8-isoprostanе in exhaled breath condensate (EBC) and air pollution exposure in children with wheezing

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Background: Oxidative stress is proposed as the underlying mechanism of air pollutants aggression over the airways. 8-isoprostanе is a reliable biomarker of...
oxidative stress. 8-Isoprostane could be detected in several fluids including exhaled breath condensate (EBC).

Objective: To study the relation between 8-isoprostane in EBC and air pollution exposure.

Methods: In the scope of a prospective study, EBC samples were collected from 27 wheezing children in order to measure 8-isoprostanes. Children were also evaluated through spirometry and skin prick tests for airborne allergens. After the definition of a activity pattern for each children and direct measurements of air pollutants in different microenvironments (home, school and outdoor), individual exposure data was calculated for PM2.5, O3, NO2, xylene, toluene, benzene, formaldehyde and ethylbenzene. Spearman rank correlation was used to study the associations between 8-isoprostane and air pollutants.

Results: The mean age of the studied children was 7.9±1.1 years. Eleven were boys. The mean FEV1 was 96.7±9.6%. Ten of the studied children were atopic. Exposure to volatile organic compounds (VOCs) including toluene (rho = 0.604, p = 0.008), xylene (rho = 0.685, p = 0.002) and ethylbenzene (rho = 0.788, p<0.001) was correlated with 8-isoprostane concentrations in EBC. There were no correlations between EBC 8-isoprostane and PM10, O3, NO2 neither between EBC 8-isoprostane and spirometric results.

Conclusion: Exposure to VOC seems to be related with oxidative stress evaluated through 8-isoprostanes measurement in EBC.

Granted by: Fundação Calouste Gulbenkian, SaudAir Project.

P1048 Feasibility of minimising motorised traffic interaction as an air pollution exposure risk management strategy for bicycle commuters

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Bicycle commuting in an urban environment of poor air quality has been demonstrated to be a potential cardiovascular health risk for susceptible participants; however, limited studies have assessed the feasibility of risk management strategies. The potential of minimising motorised traffic interaction during bicycle commuting was determined where the reduction in traffic exposure (25-40%, min particle diameter range) was evaluated through air quality measurements and acute health endpoints in healthy individuals. Thirty-five healthy adults (n = 35; mean ± SD age = 39 ± 11 yr; 29% female) rode two return trips of pre-determined minimal (MIN) and maximal (MAX) motorised traffic interaction variations of their typical bicycle commute route. Particle number concentration (PNC) and diameter were collected in-commute, along with ambient air quality data from fixed monitoring sites. Health endpoints including acute respiratory symptoms, lung function and spontaneous sputum were collected immediately pre-commute, and then one and four hours post-commute. MIN facilitated a significant reduction in mean PNC (1.91 ± e4 vs. 9.5 ± e4 PNC cm3; p < 0.01) compared to MAX. Besides incidence of in-commute offensive odor detection (42.4 vs 55.8%; p = 0.03) and nasopharyngeal irritation (31.2 ± 4.9%; p = 0.04), health endpoints were not significantly associated to air quality measures, nor were reduced with MIN compared to MAX. Acute health detriment from in-commute air pollution exposure is not indicated in healthy bicycle commuters; however, susceptible participants may benefit from a significantly reduced PNC associated with minimising motorised traffic proximity.

P1049 Effects of swimming on lung inflammation and oxidative stress in diesel exposed mice

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Background: Studies have reported that exposure to diesel exhausted particles (DEP) induces lung inflammation and increases oxidative stress, both able to be changed by physical exercise. However, the effects of high intensity exercise on lungs exposed to DEP when exercise stops are not clear.

Objective: To evaluate the effects of swimming on lung inflammation and oxidative stress in mice concomitantly exposed to DEP and after exercise cessation.

Methods: Male Swiss mice were divided into four groups: Control (n=6), Swim (n=7), Swim+DEP (n=10), and DEP+Sw (n=7). Mice were submitted to two weeks of swimming sessions and when second week started, DEP instillation occurred simultaneously to exercise for one week. After this period, animals received just DEP instillation for one week more. Twenty four hours after last DEP exposure, anesthetized mice were euthanized and we performed measures of total inflammatory cells from bronchoalveolar fluid (BALF), IL-1β, TNF-α, IL-10, IL-1ra by enzyme-linked immunosorbent assay (ELISA), total glutathione (GSH), total glutathione and non-protein thiols (NPSH) and anti-oxidant enzymes (Catalase and Glutathione Peroxidase).

Results: Swimming sessions increased GSH, NPSH, and Catalase (p<0.05), as well as decreased total number of cells from BALF, IL-1β and TNF-α levels in mice exposed to DEP (p<0.05). IL-10 and IL-1ra levels showed an increase in DEP+Sw group when compared with Control group (p<0.05).

Conclusion: Our results showed that exercise attenuated lung inflammation and improved oxidative stress status, suggesting that beneficial effects from swimming can be observed on lung injury induced by DEP, simultaneously and after exercise cessation.

P1050 Airway reactivity and neuroimmune relationships in animal model of air-born irritants induced symptoms – Role of trigeminal TRP1 channels Zuzana Biringerova 1, Martina Brozmanova 1, Silvia Gavlikova 1, Martina Sutovska 2, Sonja Franova 2, Marian Adamkova 3, Miles Tatar 1, Jana Plevkova 1. 1, Department of Pathophysiology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia (Slovak Republic); 2, Department of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia (Slovak Republic); 3, Department of Histology and Embryology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia (Slovak Republic).

Air born pollutants modulate functions of airways. Many experimental models use inhalation of air born irritants containing aerosols to mimic environmental exposure however, most exposed part is the nose. The aim of our study was to assess the general effects and modulation of airway defensive reflexes in animal model by selective nasal challenges with TRPA1 agonist AITC – allylthiosulfinic acid. TRPA1 is known to be relevant for most air born irritants.

15 male Dunkin Hartly guinea pigs were repeatedly exposed to 10mM AITC, 15mL administered into both nostrils and nasal symptoms, cough, specific airway resistance ( Saw) and bronchoalveolar lavages (BAL) were analyzed afterwards.

Nasal administration of 10mM AITC induces reproducible nasal symptoms, sneezing, discharge, crakles and conjunctival reaction. Also, nasal application of 10mM AITC induces spontaneous rise of Saw measured by Pennock’s method can be increased and increases Saw after inhalation of methacholin (p<0.05) rather than histamine, suggesting for nasobronchial reflex. Saw after oxymetazoline (1%) and salbutamol pretreatment suggest for combined mechanisms. Citric acid induced cough after nasal AITC challenge was significantly suppressed (p<0.05) and it was prevented by pretreatment with TRPA1 antagonist AP18. Nasal AITC challenges in experimental animals for a week induced rise of the count of eosinophils in BAL when comparing to controls confirming the concept of upper and lower airways neuro – immune relationships. Results document the role of TRPA1 in onset of environmental and occupational airway symptoms making it target for clinical applications. VEGA 100331/11.

P1051 Effects of metal oxide nanoparticles on static and cyclic stretched AT II cultures

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Metal oxide nanoparticles (NP) have become very important for a variety of applications, even though NP could possess adverse impacts on health. Thus, assessment of NP safety is crucial. For the first time, we investigated effects of ZnO-, CeO2- and TiO2-NP on primary alveolar type II cells (ATII) considering the fact that lung cells are in vivo exposed to mechanical tensions caused by breathing. Therefore ATII cultures were in vitro applied to stretching patterns simulating the breathing process during NP exposition. Nanotoxicology was determined using the MTT assay as well as staining with annexin V-FITC/PI. Cell staining with H2DCFDA was performed to measure intracellular formation of ROS. Release of pro-inflammatory cytokines MCP1 and MIP2 into culture supernatant was evaluated by ELISA.

ZnO-NP induce strong intracellular formation of ROS (200% rel. to control) and reduction of cell viability (10% rel. to control) in unstrained ATII cultures. These effects are diminished by half in ATII cultures applied to stretching patterns. CeO2- and TiO2-NP do not significantly affect viability or ROS formation whether if the ATII cultures are stretched or not. Cellular uptake of CeO2-NP could be assumed due to a dose-dependant change of the flow cytometric side scatter (350% rel. to control). Application of stretching patterns reduces this effect by one third. NP exposure does not affect the release of MCP1 or MIP2 regardless of the applied NP type or stretching pattern.

These results demonstrate that NP could affect primary ATII cultures and that these effects are modified when ambient conditions in the context of breathing are taken into account during NP exposition.
109. Tobacco dependence and respiratory disease

P1052 Heart rate and ventilation in a group of burned sugar cane cutters (Brazil): Estimative of particulate matter (PM2,5) exposure load
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Introduction: The sugar cane harvesting exposes workers to pollutants released by sugar cane burning held hours before. The workers earn per ton cut, what carries considerable physical effort with consequent increase in heart rate (HR) and ventilation (Ve). The HR keeps a good correlation with oxygen uptake and consequently with Ve. Its measurement is a useful method to estimate Ve, which allows estimating the exposure load of particulates.

Objectives: Develop an equation of the linear correlation between HR and Ve and apply it to estimate the pollutant exposure load in sugar cane cutters.

Methods: We developed an equation of the regression line, through data from HR and Ve obtained in ergospirometry tests of 26 sugar cane cutters. The equation was used to estimate the exposure load in another group of 84 cutters, after registration of HR (using POLAR), during a working day, with concomitant registration of PM2,5 environmental concentration.

Results: The PM2,5 average concentration was 61.5 μg/m³ (IBQ: 41.3-86.7 μg/m³). The individual equations obtained from the 26 workers, showed a high correlation with average R²=0.90. The general equation (26 workers) 975±48.061965·Log Ve=5CF, showed lowest correlation: R²=0.78. The estimation of exposure/workday in the group of 84 workers ranged from 282.5 to 1140.1 μg/m³ (677-44.1907 μg/m³).

Discussion/Conclusion: Exposure to pollutants was high and there was great variation in daily load exposure among workers. Although the general equations are less suitable than the individual equation to estimate the pollutants load inhaled by an individual, it can help in exposure estimation in population groups.

P1053 Acute effect of e-cigarette on pulmonary function in healthy subjects and smokers
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Purpose: To study smoking habits among patients hospitalised/admitted for COPD exacerbations in a conventional hospital ward.

Material and methods: We carried out a retrospective descriptive study by reviewing discharge reports of patients admitted to our centre during the period of September 2010 to September 2011. We analysed epidemiological, clinical and smoking history.

Results: We studied 196 patients, of whom 180 men (91.8%) and 16 women (8.2%) with a mean age of 77 years. 41% have a diagnosis of severe COPD. The most frequent co morbidity found is cardiovascular. 18% associated cancer. The prevalence of current smoking is 26%. In patients continue to smoke including 47 males (27%) and 5 women (31%). The ex-smoker population represents 68.9% (131) while non-smokers comprise 1.5% (3). 73% of male smokers have a moderate to severe COPD degree. Pneumonia is present in 26% of smokers, (14), while in ex-smokers it is present in 23% (33). A total of 37 patients (18.8%) were readmitted within a year, of which 62% are severe COPD (28); 9 of them were still smoking.

Conclusion: 1) Smoking is a major factor in COPD exacerbations. 2) There is a high prevalence of COPD exacerbations requiring admission to a hospital unit in those patients who continue to smoke. 3) Most smokers admitted for exacerbation of COPD were included in the severe COPD group. 4) There are 37 readmissions within a year, representing almost one fifth of all COPD exacerbations, 9 of whom continue smoking.

P1054 Impairment of mucociliary clearance in COPD and smokers: Same or different

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Mucociliary clearance (MC) is a key defense mechanism in airways. Smokers and patients with chronic obstructive pulmonary disease (COPD) exhibit modifications in MC, which predisposes these populations to recurrent infections. It is known that ex-smokers with normal lung function may present MC reversing after smoking cessation, but there are no studies that evaluate COPD ex-smokers’ MC.

Aim: To evaluate and to compare the MC and exhaled carbon monoxide (eCO) in smokers and COPD ex-smokers.

Methods: We evaluated 83 subjects, divided in four groups: severe COPD (n=22), moderate COPD (n=19), current smokers (n=20) and nonsmokers (n=22). Severe and moderate COPD patients were ex-smokers (FEV1% = 38 [34-43] and 60 [53-63], 48 [11-100] and 50 [40-75] pack/years, respectively). Current smokers presented normal lung function and 40 [22-44] pack/years. Nonsmokers were matched for age and sex. Were evaluated eCO levels and MC by saccharin transit test (STT). Tests were conducted between 8 and 9 AM with air temperature and relative humidity controlled. Statistical analyses were performed using Kruskal-Wallis test followed by Dunn’s test.

Results: STT was higher in smokers compared to control group (p=0.006). There was no difference in STT between smokers and COPD groups, but in both groups of COPD STT values were similar to control group. Also, there was no difference in STT between severe and moderate COPD. eCO levels was higher in smokers compared to other three groups (p<0.0001).

Conclusion: Smokers showed worse STT and moderate and severe COPD were...
similar to nonsmokers. These results suggest that quiting smoking, even in people who developed COPD, may lead to MC’s reversibility.

P1057 Survival of patients with severe chronic obstructive pulmonary disease in relation to smoking index

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Introduction: The increase in mortality and morbidity from chronic obstructive pulmonary disease (COPD) is occurring worldwide as a result of the epidemic-like growing use of tobacco in developing countries.

Aims and objectives: Analysis of the correlation between smoking habits and mortality of the COPD patients, evaluation of the two-year survival and the five-year survival dependent on the smoking habits.

Methods: The two-year and the five-year survivals were followed up between 2001 and 2007 in respect to smoking habits. The sample consisted of 30 smokers and 30 nonsmokers of both sexes. Criterions for inclusion of smokers were: smokers or former smokers who had smoking experience over 30 years. Criterions for inclusion of nonsmokers were: patients who never smoked or who were non-smokers over 12 years. Criterions for exclusion from the study were: patients who get pneumonia or forced over in the meantime. Statistical analysis was performed to determine the statistical difference between the groups using standard statistical methods (t-test), and the test of linear correlation was used to correlate these data.

Results: The results of the two-year survival were: 90% (27/30) of smokers, and 66.6% (20/30) of nonsmokers survived. The difference was statistically significant at p < 0.001. The results of the five-year survival were: 46.66% (14/30) of smokers, and 66.6% (20/30) of nonsmokers survived. The difference was statistically significant at the level of p = 0.03.

Conclusions: Two and five years survival is significantly longer in nonsmokers compared to smokers in the terminal stage of COPD.

P1058 Loose cough as sign of hyper secretion and inflammation in airways in relation to smoking index

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Cough may be considered as a symptom of disease, an indicator of environmental pollution. In addition, the subject may produce cough through voluntary control. The aim of this study was to determine the quality and humidity of voluntary cough as a sign of inflammatory bronchial alterations leading to hyper secretion in patients chronic obstructive bronchitis (COB) in relation to “Smoking Index” (years x cigarettes per day). Evaluation of lung function included clinical examination, electrocardiogram, estimation of blood, urine and function of the lung. The diagnosis of a disease as a basis for cough can be established with measurements of indicators or forced in the first second (FEV1), maximal expiratory flow at 25% and 50% of FVC (MEF25/FVC, MEF50 FVC), and direct tests by measurement of airway resistance to flow. The results presented in this study were done on 147 patients with COB. The control groups consisted 132 subjects, none of these subjects had symptoms or a history of pulmonary or cardiac diseases. Beside the questionnaire MRC, there was obligation to each subject to perform the test of cough, which is established on the base that in healthy subjects with normal bronchial mucosa provoked voluntary cough is dry, while in patients with inflammation in bronchial mucosa, the cough is humid assessed by auscultation. In smokers with COB the presence of chronic productive cough was in a positive correlation with increase of “Smoking Index”. In smokers with COB negative correlation between “Smoking Index” and positive test of humid cough. Increase of “Smoking Index” was followed with decrease of the incidence of humid cough in patients with COB.

P1059 COPD in elders (>80y): Smoking and air pollution

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We studied a group of Elders living in a Nursing home and affected by COPD. The diagnosis has been made in all of them five or more years ago. 63 Elders affected by COPD have been found among 282 (>80 y) admitted into our geriatric nursing home.23,3% of the total number COPD has been associated to heart diseases (54%), cerebrovascular diseases (46%) and moderate or severe dementia (45%).

Concerning the Gender 17 are men and 46 women. For the age are 18 between 80/84 y, 25 between 85/89 y and 20 over 90y. Ex smokers (22): 6 m and 3 w in the first group, 5 m and 5 w in the second, 1 m and 2 w in the third. No smokers (41): 1 m and 8 w in the first, 2 m and 13 w in the second, 2 m, 15 w in the third.

No differences have been found between ex smokers and no smokers about the numbers of exacerbations of COPD and the supplement of oxygen in the last year. The drug more used has been Tiotropium (more than half of elders) while only in few cases Beta2-long-acting and inhaling corticosteroids.

Unfortunately in ten women, no-smokers, it has been impossible to check their exposition to passive-smoke.

Conclusion: In women no smokers, without occupational exposures, ambient air pollution is a probable risk factor for the development of COPD. In our elders the evolution has been rather slow but has required continual treatment and has worsened their quality of life.


P1060 Risk factors of development of endothelium dysfunctions at smokers

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Aim: To evaluate the risk factors of development of endothelium dysfunctions among smokers.

Materials and methods: The research has been conducted amongst 100 smoking patients. Brachial artery blood flow reactions to hyperemia were studied by doppler sonography in all patients. Data on risk factors, was gathered through questionnaires. We identified 2 groups, 1 of them – the patients having endothelium dysfunction (n=66) and 2 - not having endothelium dysfunction (n=34). The OR (odd ratio) and 95% confidence interval (95% CI) were calculation.

Results: The risk factors significantly associated with female sex (OR=1.17; 95% CI: 0.47-3.68), beginning of smoking till 15 years (OR=1.34; 95% CI: 0.34-5.59), the beginning with smoking with 16 till 20 years (OR=1.06; 95% CI: 0.43-2.64), an index of smoking ≥30 pack/year (OR=1.18; 95% CI: 0.3-5.03), duration of smoking more than 30 years (OR=1.14; 95% CI: 0.3-3.83).

Conclusion: The risk factors of development of endothelium dysfunctions have greater impact on female sex (p=0,00001), beginning of smoking till 20 years (p=0.03), an index of smoking ≥30 pack/year (p=0,0001) and duration of smoking more than 30 years (p=0,0001).

P1061 Aggregation of erythrocytes in the dynamics of phototherapy in rats with experimental model of COPD

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Aim: To study erythrocyte aggregation in rats with experimental model of COPD in the dynamics of phototherapy with lamps with ceramic coating.

Methods: An experimental model of COPD was reproduced in 22 white rats under the influence of tobacco smoke in a special chamber, where they were placed daily for 30-40 minutes for 2 months. Control group (11 rats) is contained in similar conditions but without exposure to tobacco smoke. For the treatment of half of the rats with experimental COPD we used the method of phototherapy with infrared light from ceramic-coated lamps with a narrow emission spectrum (wavelengths of 2-40 microns). Phototherapy on the area of lungs was carried out daily for 10 days: 5 minutes of the first 5 procedures and 10 minutes of the next 5 ones. Spontaneous aggregation of erythrocytes was quantitatively evaluated by a special system of criteria for micrographs (made by a camera connected to a microscope) of aggregates of red blood cells.

Results: In the 1st group without phototherapy erythrocyte aggregation was 11,8±0,47. In the 2nd group after 10 days of phototherapy the index was 7,78±0,97. It is by 34% less than in the 1st group (p<0.05). In both groups of COPD erythrocyte aggregation was higher than in healthy rats (6,6-6,75). But when we tested the differences in groups, a statistically significant difference (p<0.05) was not detected between the 2nd and control groups.

Conclusion: Erythrocyte aggregation increases in rats with experimental model of COPD. During the 10-day course of treatment with infrared light from lamps with ceramic coating this indicator tended to normalize.

P1062 The influence of smoking on the level of proinflammatory cytokines in patients with COPD

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Smoking is a major risk factor for COPD. The mechanisms of the effect of smoking on the progression of the disease is not fully understood.

The purpose of: To identify the relationship of smoking and the activity of local and systemic inflammation in patients with COPD.

A total of 98 patients, 76 of them smokers with an average experience of smoking a pack of 25±1.8/year. Revealed that smokers C-reactive protein blood (12,7±4, 190s)
Conclusion: The phototherapy by IR has a marked significant decrease in levels of proinflammatory cytokines in eCOPD, without changing the level of anti-inflammatory IL-10.

P1065 Vasomotor activity of the cerebral arteries in rats with experimental COPD
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The aim of the study was to evaluate the endotelmum-dependent and endotelmum-independent reactions of the cerebral arteries reproduced in vivo COPD model. The COPD model was reproduced by chronic smoking in rats within 6 months according to H.Zheng protocol. The experimental group consisted of six male Wistar rats. The control group breathed only clean air. Assessment of the endothelium-dependent vasomotor reactions were carried out in 6 months after the experimental start and in 2 months after smoking cessation. Acetylcholine and nitroglycerin were injected in the rats body to assess endothelium-dependent (EDVD) and endothelium-independent (EIDVD) vasodilation, N-monomethyl-L-arginine (L-NMMA) to assess endothelium-dependent constriction (EDVC). Using magnetic resonance imaging the degree of the cerebral arteries diameter change in the tomograms before and after drug administration was evaluated. The study revealed the cerebral arteries dysfunction in fum-smokers. Acetylcholine stimulation in the rats smokers leaded to the pathological vasoconstriction. Test with nitroglycerin caused insufficient vasodilatation (p <0.05). Test with L-NMMA showed the abnormal vasodilation in contrast with the control group set the expected EDVD. In 2 months after smoking cessation the pathological vasoconstriction remained in the acetylcholine test EIDVD was paradoxical even leading to the vasoconstriction. In long-term tobacco smoking the violation of the endothelial vasomotor function of the cerebral arteries has the form of the pathological activity of the vasodilating management and intensification of the vasoconstriction. After smoking cessation the vasomotor disturbances are not only preserved but also exacerbated.

Table 1

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<td>Average Age (yrs)</td>
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<td>Number of Admissions</td>
<td>114</td>
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<td>Readmissions</td>
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<td>Number of Patients</td>
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Conclusion: There is a significantly higher admission rate amongst those with a history of smoking drugs when compared to those patients that have never smoked drugs. Several patients have recurrent admissions with exacerbations of COPD. We analysed data from January 2009 to September 2011 and compared the number of admissions amongst those that have a history of smoking drugs and those that have never smoked drugs.
survey in 2002, we observed significant improvements relative to knowledge of COPD (8.6% vs. 17.0%), with a marked variability within regions (p < 0.05). Currently, only 17.9% of the Spanish population knows that there is a National Strategy for COPD, although 86.0% have a favorable/very favorable opinion about the new Anti-Tobacco Law. Conclusion: The lack of knowledge about COPD and its determinants in the general population remains high, therefore more and better teaching and awareness interventions are needed.

P1068
To determine the prevalence and predictors of smoking and smokeless tobacco use amongst women in Karachi, Pakistan
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Study design: Cross sectional study.
Study sample: A Convenient sample of 485 female attendants was taken for the study. A standard questionnaire for tobacco use, developed by WHO, was used. Results: Prevalence of tobacco: Overall, 96 (19.6%) admitted to using tobacco in one form or another. 13 (2.7%) of the total respondents were smokers and 83 (17.1%) were smokeless tobacco users. The use of tobacco was found to increase with age and was highest among the age group of 66 years and above (P=0.01, 95% CI). A higher prevalence of tobacco use was found in women who had never gone to school and the prevalence of tobacco use decreased with increasing education (P=0.001, OR=4.6 with 95% CI). When the association between marital status and tobacco use was assessed it was found that tobacco use was more prevalent amongst married women (P=0.001, OR=6.13 with 95% CI). It was found that tobacco use was more prevalent amongst the working population as compared to the non-working women/housewives (P=0.05, OR=1.90 with 95% CI). When the participants were asked about the extent of harm tobacco can cause, 69.5% participants were of the view that it was very harmful while 6.8% thought that it was harmless. The remaining participants thought that it caused little harm.
Being hospital based, our study may have the shortcomings of a hospital based study. Another limitation could be due to the fact that it was done in Karachi and the results may not be generalizable across the whole country. Intervention in epidemiological studies of tobacco use and its predictors in different areas of the country among different population groups would be very beneficial in our fight against tobacco.

P1069
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Questionnaire was distributed at the Annual Meetings of the Japanese Respiratory Society held in 1996, 1999, 2001, 2003, 2005, 2007, 2010 and 2012 repeatedly, in order to know how attendants think and behave about smoking as respiratory care specialists. Questionnaire paper was handed to the attendants around the table for meeting registration, and was recovered voluntarily in the boxes. Smoking prevalence of all attendants in 1996, 1999, 2001, 2003, 2005, 2007, and 2010 was 22.5%, 19.7%, 15.1%, 19.3%, 7.6%, 5.8%, and 3.7% respectively. Recovery rate of questionnaire in 1996, 1999, 2001, 2003, 2005, 2007, and 2010 was 64.7%, 70.4%, 48.6%, 52.2%, 85.3%, 92.3% and 87.8% respectively. Smoking prevalence of physician in 2001,2003,2005,2007, and 2010 was 12.9%, 12.7%, 5.1%, 3.9% and 2.4% respectively. Attendants from smoke-free hospital in 1996, 1999, 2001, 2003, 2005, 2007, and 2010 was 7.5%, 15.8%, 21.7%, 28.4%, 61.1%, 61.1%, and 72.3% respectively. Tobacco sales in the hospital retail shop were 53.2%, 44.8%, 39.0%, 19.4%, and 10.0%, respectively. Tobacco sales in the hospital vending machine was 50.3%, 41.5%, 37.2%, 31.1%, 12.3%, 7.1%, and 3.1% respectively. New 2012 data will be merged with those data, which will show that smoking behaviors of the attendants have improved for 16 years. Japanese government recently accelerated to promote smoke-free lifestyle, planning to reduce smoking prevalence from 20% to 12% in the next ten years. Japanese Respiratory Association is responsible to encourage its members to intervene in smoking behavior or policy of hospitals which has been generous for tobacco sales.

P1070
Is subjective sleep quality better in quitters? Derya Celebi1, Celal Kurtliyay1, Levent Orzurt2. 1Chest Diseases, Trakya University Faculty of Medicine, Edirne, Turkey; 2Physiology, Trakya University Faculty of Medicine, Edirne, Turkey

Aims: Smokers have 4-5 times higher risk of sleep-related breathing disorders. We studied subjective sleep quality, weight gain and changes in pulmonary functions in quitters and non-quitters.
Methods: Among 692 patients registered for smoking cessation clinic, who were smoking 10+ cigarettes/day, followed at least 1 year and agreed to participate in the study were included. Pittsburgh sleep quality index (PSQI), Epworth sleepness scale survey, measurements of exhaled carbon monoxide, body weights and PEFs were obtained and evaluated. Cases with PSQI ≤5 points were classified as having good sleep quality.
Results: Among the cases (n=106, 67 male, 39 female), 39.6% had quitted and 60.4% had not quitted. Mean age of quitters were 50.7±11.1 years, while non-quitters was 47.4±11.1 years. Better sleep quality was observed in 23.8% of quitters, while in 7.8% of non-quitters (p<0.01). Better sleep quality was evident in quitters in spite of weight gain. Mean 8.33 kg weight gain and 3.13 increase in BMI were observed in quitters (p<0.01). Gaining more than 10% of body weight was observed in 52.4% of quitters while 7.8% of non-quitters (p<0.01). Pulmonary function changes were not different among quitters and non-quitters. CONCLUSION: Quitters had better sleep quality than non-quitters in spite of more weight gain. This difference was not related to improvement in pulmonary function. This data can be used as a motivational tool for smokers’ quitting. And also it can be a clue for the importance of smoking cessation in patents with sleep-related breathing disorders.

110. Sleep monitoring, lung function and inflammation in childhood

P1071
Effect of high-flow nasal cannula on nasopharyngeal airway pressure, respiratory muscles loading and respiratory distress symptoms in young infants with severe acute viral bronchiolitis Stefan Matecki1,2, Christophe Milese1, Julien Baille1, Aurélien Jacquet3, Gilles Cambonne3,1. 1Physiologie, CHU Arnaud de Villeneuve, Montpellier, France; 2INSERM U 1046, CHU Arnaud de Villeneuve, Montpellier, France

Objective: To determine the efficacy of high-flow nasal cannula (HFNC) at different flow level on respiratory distress symptoms, nasopharyngeal airway pressure (NAP) and respiratory effort in young infants with acute respiratory syncytial virus bronchiolitis.
Patients: 21 less than six month olds, with severe respiratory distress.
Interventions: Oesophageal pressure (Pes) and NAP was measured simultaneously after 5 different flow of 1.46, and 7.1 l/min delivered through a HFNC.
Measurements and results: Respiratory distress was quantified with a specific scoring system (m-WCAS). Mean respiratory rate (RR), inspiratory time over total time or respiratory cycle (Ti/Tot), NAP, Swing Pes and respiratory effort with the Pes-derived inspiratory muscles pressure-time product (PTPpes) was calculated from the pressure curves. Results are presented in Table 1.

<table>
<thead>
<tr>
<th>Flow (l/min)</th>
<th>m-WCAS</th>
<th>Swing Pes (cmH2O)</th>
<th>NAP (mmH2O)</th>
<th>Ti/Tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.46</td>
<td>2.3 (1)</td>
<td>21 (14)</td>
<td>57 (3)</td>
<td>0.43 (0.9)</td>
</tr>
<tr>
<td>4.6</td>
<td>2.1 (1)</td>
<td>42 (27)</td>
<td>132 (162)</td>
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</tr>
<tr>
<td>7.1</td>
<td>1.1 (1)</td>
<td>48 (32)</td>
<td>289 (166)</td>
<td>0.42 (0.1)</td>
</tr>
</tbody>
</table>

Conclusion: In young infants with severe acute respiratory syncytial virus bronchiolitis (NAP progression) was significantly related between flow delivery, NAP and PTPes. HFNC are able to increase NAP, decrease PTPes and improve ventilatory function of infant with severe acute viral bronchiolitis.

Funding by APARD and CHU Montpellier.

P1072
The effect of chronic intermittent hypoxia on bone homeostasis in children with sleep disordered breathing
Alessandra Tabacchi1, Laura Papini1, Stefano Cevoli2, Silvia Miano1, Laura Lieto2,1 Susanna Fedeli1, Valentina Negro1, Rosa Castaldo1, Maria Pia Villa1. 1NEMOS, Pediatric Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy; 2NEMOS, Advanced Molecular Diagnostics Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy

Introduction: Airflow obstruction is an important risk factor for osteoporosis in adults. Therapies for bone-loss disorders could be based on shifting systemic acid base balance in the alkaline direction. The effect of chronic intermittent hypoxia in obstructive sleep apnea syndrome (OSAS) on bone homeostasis has never been evaluated.
Aim: We evaluate the effect of OSAS on bone homeostasis and the efficacy of an alkaline diet to the bone remodeling in children.

Impact: Q1S:

<table>
<thead>
<tr>
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Conclusion: In young infants with severe acute respiratory syncytial virus bronchiolitis (NAP progression) was significantly related between flow delivery, NAP and PTPes. HFNC are able to increase NAP, decrease PTPes and improve ventilatory function of infant with severe acute viral bronchiolitis.

Funding by APARD and CHU Montpellier.
Methods: Spot urinary hydroxyproline/creatininuria (U/Hc, μg/ml) was measured as a markers of osteoblastic and osteoclastic activity in a group of children who underwent clinical assessment and polysomnography for OSAS. Children were randomly selected to be treated with an alkaline diet or with thyroid therapy (group 2). The U/Hc was measured at baseline and after one month of treatment (T1).

Results: We studied 12 children (mean age 6.42±2.52 years, 8 males). After one month, mean value of U/Hc did not change (14.97±μg/ml vs 16.29±μg/ml). Four subjects (group 1) (mean age 7.9±2.7 years, 3 males) showed a reduction of U/Hc after alkaline diet (from 23.2±μg/ml to 15.8±μg/ml). U/Hc did not decrease in group 2. In all children U/Hc correlated with total sleep time (r = -0.636, p < 0.05), sleep efficiency (r = 0.935 < p < 0.001) and wake after sleep onset (r = -0.769, p < 0.05), but not with sleep respiratory parameters.

Discussion: Our preliminary study showed that the efficacy of an alkaline diet to reduce urinary hydroxyproline. Although we did not find correlation with respiratory parameters, we found significant correlation with sleepfragmentations.

P1073

Evaluation of 8-isoprostane as a biomarker of oxidative stress in children with obstructive sleep apnea syndrome

Susanna Fedeli1, Valentina Negro1, Maria Chiara Supino1, Susanna Bonafoni1, Alessandra Tabarrini2, Laura Punip2, Milena Margiotta2, Giovanna Gemineli2, Maria Pia Villa3, 1 NESMOS, Pediatric Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy; 2NEMOS, Advanced Molecular Diagnostics Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy

Background: Hypoxia-reoxygenation, characteristic of obstructive sleep apnea syndrome (OSAS), induces an increase of products of non-enzymatic catalyzed lipidic peroxidation, such as 8-isoprostane (8-ISop).

Aim: To evaluate urinary 8-ISop values in children with OSAS.

Methods: Thirty-eight children with OSAS (mean age 6.23±2.08y, range 3.16-10.83y MF:26/12), underwent urinary collection at the morning after nocturnal polysomnography. 8-ISop levels were measured with an enzyme immunoassay and corrected by urinary creatinine (uCR) levels.

Results: According to the AHI (Apnea/Hypopnea index, cut-off 5 events/hours of sleep), in 5 children with mild OSAS (uCR corrected by urinary creatinine (uCR) levels.

Conclusion: Our data show that values of urinary 8-ISop are related to OSAS severity and SaO2. Further studies are needed to assess usefulness of urinary 8-ISop as a marker of inflammation likely due to oxidative stress.

P1074

A new proposal for OSA classification in children based on cardiovascular outcome

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Introduction: Pediatric OSA is associated to cardiovascular repercussions (CVR), adenotonsillolctomy(ATO) is considered its treatment of choice. We hypothesized that OSA leads to early CVR as lossing of nocturnal blood pressure dipping (NBPD), to adenotonsillectomy (AT) will recover NBPD.

Aim: To analyse which polysomnographic (PSG) criteria best defines OSA in children, based on the absence of NBPD before and its recovering after AT.

Methods: We included children with regular snoring, observed respiratory pauses and hypotony of the tonsils. Children with persisting snoring after AT, diagnosis of cardiovascular, renal or neurologic disease and obesity were excluded. Children realized PSG and 24-hour blood pressure monitoring before and six months after AT. AI and AHI were calculated, the presence or absence of NBPD was described before and after AT. Three current PSG definitions for OSA (D1: AHI>1; D2: AHI>1 & AHI<4; D3: AHI>5) were tested for the best correlations of OSA and CVR before and NBPD recovering after AT.

Results: 26 children, 8-12 years old, were included. AHI varied from 0.0 to 23.2. 10 children presented lossing of NBPD before 4, persisted after AT. For D1 (AHI>1) OSA diagnosis showed no significant association to CVR neither before, nor after AT. For D3 (AHI>5) OSA diagnosis showed significant correlation to CVR before and after surgery.

Conclusion: Considering NBPD and surgery outcome, we identified A1> & AHI>4 as the best definition for OSA in children. Larger studies focusing CVR and surgical outcome should be realized to better define PSG criteria and OSA.

P1075

Frequency of ICU monitoring and respiratory complications after adenotonsillolctomy in children

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Introduction: Adenotonsillolctomy(ATO) is considered treatment of choice for ob-structive sleep breathing disorders (OSD) in children. Besides better diagnosis and earlier treatment of OSA, respiratory complications at the immediate postoperative period are described for several risk groups.

Aim: To evaluate the frequency of necessity of postoperative monitoring in an intensive care unit(ICU) and respiratory complications in OBD children submitted to adenotonsillolctomy in a university hospital.

Methods: Retrospective study, analyzing patient’s charts submitted to AT due to OSD in a university hospital in Brazil, during the period from 2006 to 2010. We included children of both genders, aged 2 to 12 years. Patient’s data included obesity, age at surgery, severity of OBD and presence of respiratory comorbidity (asthma). We assessed the frequency of ICU monitoring and the respiratory complications in the ICU during 24 hours after AT.

Results: Out of 811 AT, 164 realized polysomnography prior surgery. 47 children, 21 girls, needed monitoring in ICU, due to severe oxygen desaturation (<85%), severe OSA (A>10) or obesity. Six children were younger than 2 years. Eleven children (24%) suffered major complications at ICU, as acute lung oedeme in two patients, intubation for longer than 24 hours in one, bronchospasms in three, and death in six.

Conclusions: Our study revealed a high risk for respiratory complications in OSD children. Major risk factors were age < 3 years old, asthma and obesity. Indication for monitoring (postoperative monitoring/polysomnography for suspected OSA children prior to adenotonsillolctomy should be better be specified and normalized.

P1076

Adenotonsillolctomy and orthodontic therapy: Outcome after one year of follow-up in children with obstructive sleep apnea syndrome

Rosa Costaúbi1, Giovana Passos2, Silvia Miano, Anna Rita Mazzotta, Francesco Biagarielli, Susanna Fedeli, Maria Pia Villa. NEMOS, Pediatric Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy

Introduction: Adenotonsillolctomy (AT) is the primary therapy for obstructive sleep apnea syndrome (OSAS) in children, although a residual disease is reported. Rapid maxillary expander (RME) is a valid treatment for children with malocclusion and high arched palate.

Aim: To evaluate the efficacy of AT and RME in children with OSAS.

Methods: We enrolled children undergoing a clinical and polysomnographic assessment for OSAS at baseline and after 12 months of follow-up, after treatment (T1).

Results: We studied 47 children (mean age 5.03±2.03 years, body mass index, BMI, 17.15±3.07 kg/m², 34 males). At T1, AHI (apnea hypopnea index) decreased (11.90±12.30 vs 2.18±2.51 ev/h, p < 0.0001) as well as arousal index (18.29± 6.71 vs 13.95±6.61 ev/h, p < 0.0001) while total sleep time (TST) increased (6.77±0.96 vs 7.24±0.83, p = 0.05), as overnight oxygen saturation (90.51±1.22 vs 97.50±1.50, p < 0.0001). Twenty five children underwent AT (group 1) whereas 22 orthodontic therapy (group 2). After one year of treatment, in group 1 percentile of BMI and overnight mean saturation increased significantly, while AHI and arousal index decreased. In group 2 mean overnight saturation and TST increased from T0 to T1, while AHI decreased. The correlation analysis showed that percentile of BMI is a negative predictive factor of the efficacy of AT in group 1, while duration of disease is a negative predictive factor in group 2.

Discussion: Our results demonstrated that both treatments are efficacious for pediatric OSAS, although the increase of BMI is a negative predictive factor for residual disease group in 1, and the duration of disease in group 2.

P1077

The effects of obstructive sleep apnea syndrome on cognitive and cardiovascular functioning in children with obesity

Anna Rita Mazzotta1, Maria Elena Liverani1, Alessandra Macari1, Giundiano Tocci1, Filomeno Iannello1, Maria Pia1, 2Pediatrics, Sant’Andrea Hospital, La Sapienza University, Rome, Italy; 2Cardiology, Sant’Andrea Hospital, La Sapienza University, Rome, Italy

Background: Paediatric obesity and sleep disordered breathing may be associated with cognitive problems and cardiovascular abnormalities and both may share the same common inflammatory and metabolic pathogenesis.

Aim: To evaluate and compare cardiovascular activity and cognitive functions of obese children with or without clinical obstructive sleep apnea syndrome (apnea hypopnea index > 5 n/h of sleep).

Methods: Obese children underwent polysomnography in a standard laboratory setting, a neurocognitive assessment and a 24-hour ambulatory blood pressure monitoring.

Results: We studied ten children (mean age 9.±4.3 years, 7 males, with a mean body mass index (BMI) of 27.67 kg/m², mean BMI percentile of 124.2±20.7). They had a mean apnea-hypopnea index of 9.6±13.6 n/h, an overnight oxygen
Efthimia Kalampouka1, Anastasia Polytarchou 2, Aggeliki Moudaki 1, Antonis Platnaris 1, Marina Tsassougloglou 1, Emmanuel Alexopoulos 1, Polytimi Panagiotopoulou-Gartagani 1, George Chrousoos 1, Athanasios Kadogiannis 1

First Department of Pediatrics, Pediatric Pulmonology Unit, University of Athens School of Medicine and Aghia Sophia Children’s Hospital, Athens, Greece; 2Department of Pediatrics, Lamsia General Hospital, Lamia, Greece

Recognition of subgroups of children predisposed to overgrowth of the pharyngeal lumen issue, such as obesity, is crucial for early diagnosis and treatment, which may allow implementation of treatment interventions in early life for the prevention of obstructive sleep-disordered breathing (SDB). We hypothesized that parental history of adenotonsillar hypertrophy and tonsillar hypertrophy and snoring in childhood in addition to history of wheezing requiring treatment may act as risk factors for tonsillar hypertrophy and snoring.

Methods: Children were recruited from outpatient clinics. Parental history of AT (explanatory variable) and snoring ≥1 night/week (outcome) were recorded and presence of tonsillar hypertrophy (outcome) was assessed.

Results: 435 children were recruited (2-16 y), and 79 (18.2%) of them had parental history of AT. Parental history of AT was significantly associated with the presence of tonsillar hypertrophy and snoring even after adjustment for history of wheezing requiring treatment, age, gender, obesity and passive smoking (odds ratio (95% CI): 2.2 (1.2-3.9); p<0.01 and 1.8 (1.1-3.3); p<0.05, respectively). When both tonsillar hypertrophy and parental history of AT were entered in the same multiple logistic regression model, the former was stronger predictor of snoring than the latter: 3.3 (2.5-3.3); p<0.01 vs. 1.6 (0.9-2.9); p=0.09), respectively.

Conclusions: Children with parental history of AT have more frequently tonsillar hypertrophy than those without such history. Familial predisposition to tonsillar hypertrophy may mediate at least in part the association between parental history of AT and SDB in children.

Prevalence of obesity and sleep disordered breathing in a cohorts of 9 year old schoolchildren studied 13 years apart living in a country town of Central Italy (Ronciglione, VT).

Francesca Ruggeri, Annamaria Bozzone, Mario Barreto, Maria Pia Villa. NESMOS, Pediatric Unit, Sant’Andrea Hospital, La Sapienza University, Rome, Italy

Objective: The aim of this study was to evaluate the prevalence of obesity and sleep disordered breathing (SDB) in two different populations of Italian schoolchildren studied 13 years apart growing in a country town of Central Italy (Ronciglione, VT).

Research methods and procedures: Subjects were drawn from two populations, both non selected, of schoolchildren. Parents underwent to a 9-items sleep questionnaires investigating on SBD. We assessed measures of weight and height obtaining and using BMI values to assess obesity, with cut-off values proposed by the International Obesity Task Force. Techniques traditionally employed to assess diaphragmatic weakness or paralysis in DMD, i.e. transdiaphragmatic pressure, EMG, fluoroscopy, plethysmography, MRI are invasive, associated with radiation or complex. The aim of this study was to determine the feasibility of diaphragmatic excursion (DE) measurements by ultrasonography (US) as an alternative.

Eight DMD patients (age 15.2±4.1 yrs, BMI 20.5±5.6 kg/m2, FVC 59.3±6.2%pred) and 10 healthy controls (age 25.4±4.9 yrs, BMI 22.3±2.5 kg/m2) were studied. Diaphragmatic excursion was measured in supine position using a convex probe (7.5-7.5 MHz) positioned in the right subcostal anterior area. DE was determined by a custom-designed software for image processing at end-inspiration and end-expiration during quiet breathing (QB) and at full inspiration during an Inspiratory Capacity (IC) maneuver. In DMD, DE was in average 17.2±5.2 mm (see fig. for individual data). ANOVA analysis revealed significant differences in DE values between QB and IC in both DMD and controls (p<0.001) and between DMD and controls during both QB and IC (p<0.001).

Conclusion: All patients had excessive daytime sleepiness. Interestingly over half of these patients had excessive daytime sleepiness on presentation. H1N1 vaccination was not given to the majority of these patients. More research is needed to understand the recent increase in the prevalence of childhood narcolepsy with cataplexy.

The clinical presentation of paediatric narcolepsy in one Canadian sleep centre

Andrea Ricketts1, Glenda Bendick1, Shelly Weiss2, Indra Narang1

1Respiratory Medicine, Hospital for Sick Children, Toronto, ON, Canada; 2Neurology, Hospital for Sick Children, Toronto, ON, Canada

Narcolepsy is primarily characterized by an overwhelming feeling of sleepiness with or without cataplexy. More recently, there has been a dramatic increase in newly diagnosed childhood narcolepsy and it is hypothesized that H1N1 may play a role in these new cases. The objective of this study is to review the demographics and presenting symptoms of children with narcolepsy in Toronto.

Methods: At the Hospital for Sick Children, Toronto, we reviewed medical records and polysomnograms of patients with narcolepsy who presented to the sleep disorders clinic. All patients were referred with a history of excessive daytime sleepiness.

Results: # Patients Age, mean (range) Weight, kg, mean (range) BMI, kg/m² Excessive daytime sleepiness Cataplexy Night wakeings Hallucinations Weight gain Behaviour change H1N1 vaccination MRI, normal MRI, abnormal Ferritin, low HLA DQB1*0602, positive 8 9.5 (5.0-15.0) 39.5 (26.0-52.9) 20.3 (18.5-23.5) 8 (100%) 5 (62.5%) 2 (25.0%) 3 (37.5%) 4 (50.0%) 7 (22.5%) 7 (87.5%) 77* 4 (50.0%) 64** 64**

MRI = Magnetic Resonance Imaging, MSIT = Multiple Sleep Latency Test, *MSLT pending for one patient **HLA pending for two patients.

Conclusion: All patients had excessive daytime sleepiness. Interestingly over half of these patients had cataplexy on presentation. H1N1 vaccination was not given to the majority of these patients. More research is needed to understand the recent increase in the prevalence of childhood narcolepsy with cataplexy.
We conclude that the marked changes in Zrs during tidal breathing in healthy newborns are due to flow nonlinearities in the narrow nasal and glottal pathways. The absence of the V dependence of R may be a result of opposing changes in tissue resistance and airway resistance at Vmax.

P1085
Importance of nutrition status in lung function of infants born preterm with or without bronchopulmonary dysplasia
Manuel Sánchez-Solís, Luis García-Marcos, Virginia Pérez Fernández. Pediatría, Virgen de la Arrixaca University Hospital, University of Murcia, Spain. Pediatrics, Virgen de la Arrixaca University Hospital, University of Murcia, Spain Pediatrics, University of Murcia, Spain

Aims: To know if nutrition status (as measured by BMI) is associated to lung function of infants born preterm (PT) with or without bronchopulmonary dysplasia (BPD)

Methods: By means of the raised volume rapid thoracoabdominal compression (RVRC) technique, FVC, FEV1, FEF25, FEF50 and FEF75 were measured in 61 PT without BPD (66.5% male; corrected age 7.2±0.7 mo) and in 55 PT with BPD (59.8% male; corrected age 7.75±0.9 mo). A multiple regression analysis-stratified for BPD- was performed for BMI z-score (as calculated according to WHO values) and each lung function parameter (dependent variable), controlling for gender, gestational age, current corrected age, height, birth weight, smoking exposure in pregnancy.

Results: The coefficients of the regression analyses and their significance are shown in table.

<table>
<thead>
<tr>
<th>Coef. (95% CI)</th>
<th>p value</th>
<th>Coef. (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD - (n=61)</td>
<td>BFDPs (n=57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>9.79 (1.24-20.8)</td>
<td>0.038</td>
<td>8.54 (2.18-19.2)</td>
</tr>
<tr>
<td>FEV1.0</td>
<td>9.55 (0.57-18.5)</td>
<td>0.015</td>
<td>5.97 (1.48-13.4)</td>
</tr>
<tr>
<td>FEF25</td>
<td>15.7</td>
<td>0.007</td>
<td>8.48 (2.39-19.8)</td>
</tr>
<tr>
<td>FEF75</td>
<td>23.3</td>
<td>0.027</td>
<td>8.09 (10.3-26.3)</td>
</tr>
</tbody>
</table>

Conclusions: Lung function of infants 7-8 months of age, born PT without BPD, increases with BMI. This does not seem to be the case in infants of similar age born PT but with BPD.

P1086
Changes in respiratory mechanics following surgical repair of mitral valve insufficiency in children
Hajime Malaspinas², Anne-Laure Martin³, Anne Perrin, Maurice Beggéti², Ferenc Pettak¹, Waldi Haberb¹. ¹Neonatology and Intensive Care, Children’s University Hospital of Geneva, Switzerland; ²Pediatric’s Cardiology Unit, Children’s University Hospital of Geneva, Switzerland; ³Department of Medical Physics and Informatics, University of Szeged, Hungary

Rationale: Postcapillary pulmonary hypertension (PHT) such as observed with mitral valve insufficiency (MVI) is associated with lung function impairment. We assessed airflow resistance (Raw) and total respiratory elastance (Ens) before and after surgical repair of MVI in children to verify whether vascular engagement is responsible for the increase in airway tone and stiffness of the respiratory tissues.

Methods: The input impedance of the respiratory system during spontaneous breathing was measured in 16 children, aged 12±2.5 years (mean±SD), with congenital or post-thoracic mitral valve insufficiency preoperatively, and within 5 days and 3 weeks after mitral valve repair surgery. Raw was estimated by

\[ R_{\text{Raw}}(f) = \frac{1}{\rho c} \left( \frac{dP}{dV} \right) \]

Conclusions: Increase of MVI and Raw was associated with post-thoracic mitral valve insufficiency preoperatively, and within 5 days and 3 weeks after mitral valve repair surgery.
calculating the average resistance values between 4 and 26 Hz, while Ers was assessed from the respiratory reactance data by model fitting.

**Results:** Raw decreased significantly 5 days after the surgery (5.5 ± 1.6 to 4.3 ± 1.0 cmH2O·l·s⁻¹, p < 0.001). It remained lowered 3 weeks later in 8 children (4.5 ± 1.4 cmH2O·l·s⁻¹, p < 0.005). Conversely, Ers exhibited no significant changes postoperatively (70 ± 10, 58 ± 6 and 77 ± 9 cmH2O·l·s⁻¹ before and 5 and 21 days after the surgery, respectively, p > 0.4).

**Conclusions:** Decreasing vascular engorgement after surgical repair of MVI in children results in a fast and sustained improvement in airway function. The lack of concomitant beneficial changes in the Ers suggests that mechanical interdependence between the airways and pulmonary vasculature is responsible for this finding.

Supported by SNSF grant 3200B0-118231.

**P1088** Longitudinal follow-up of lung function in ataxia telangiectasia

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**Rationale:** Individuals with Ataxia Telangiectasia (AT) are vulnerable to the development of significant pulmonary complications with age. This condition calls for a follow up on lung function evaluation.

**Objectives:** To follow the individual patient’s lung functions during 3-5 years.

**Methods:** Yearly best spirometry data were collected from 39 AT patients (age 10.4 ± 4.5 years; 13 patients younger than 7 years). The yearly decline in spirometry indices were defined in relation to the preceding year, initial age, and airway hyper-reactivity (a positive response to β₂-agonist).

**Results:** Young children showed low FVC (%predicted) between 43.1-70.7%. Lung function was more impaired in the most severely affected patients. In 27% of the cases, the FEV₁ was ≤ 50% of predicted. The change in %predicted FVC was 0.01% per year, with a significant decline after age 15 years. Similarly, FEV₁, FVC, and MVV decreased after age 15 years. Patients having hyperactive airways showed initially restrictive lung function in A-T patients.

**Conclusions:** Follow up lung function evaluation should be performed in children with AT.
zene (HCB), DDE, DDT, and Mirex) in 240 children participating in the respiratory assessment of a longitudinal birth cohort at 14 years of age. Current wheeze was reported by 63 (26.3%) and 96 (40.0%) were atopic. Participating in respiratory assessment of a longitudinal birth cohort at 14 years of age. Parental worry about child’s health (p=0.005), defined asthma control (p=0.002), and parental smoking (p=0.002) were associated with increased bullying risk. Methods: Parents and children >7 years with asthma were interviewed by telephone following identification using a truncated list-assisted random digit dialling sampling procedure in Canada, Greece, Hungary, the Netherlands and UK. Parents and children in South Africa were interviewed face-to-face. All statistical analyses including univariate and multivariate regression were carried out using STATA v10.

Results: Detailed questionnaires including parent and child responses were available for 943 parent-child diads. Univariate analyses identified that poor GINA-defined asthma control (p=0.001), parental worry about child’s health (p=0.005), parent reported frequency of asthma attacks (p=0.002) and parental smoking (p=0.042) were associated with increased bullying risk. The child’s age and gender were not associated with risk of bullying. Children who reported bullying were significantly more likely to report feeling sad (p<0.001) and were less likely to participate in sporting activities (p=0.001).

Conclusions: Bullying or teasing is commonly reported by children with asthma and is associated with reduced participation in sport and feelings of sadness. Modifiable child factors such as poor asthma control and parental factors such as smoking and ongoing worries about their child are associated with increased bullying risks.

P1092 Bullying in children with asthma – What factors are associated with increased risk? Will Carroll1, Johannes Wildhämmer2, Paul Brand3, Department of Paediatrics, Derbyshire Children’s Hospital, Derby, United Kingdom; 2Department of Paediatrics, Hospital Fribourg, Fribourg, Switzerland; 3Department of Respiratory Paediatrics, Princess Amalia Children’s Clinic, Zwolle, Netherlands

Background: Bullying or teasing of children with any chronic medical condition is a well-recognised complication of disease. The data collected in the Room to Breathe Study, a large 6-county population survey of childhood asthma demonstrated an increased number of reports of bullying (10%). This study aims to detail in detail the family and child factors associated with increased bullying risk.

Methods: Parents and children >7 years with asthma were interviewed by telephone following identification using a truncated list-assisted random digit dialling sampling procedure in Canada, Greece, Hungary, the Netherlands and UK. Parents and children in South Africa were interviewed face-to-face. All statistical analyses including univariate and multivariate regression were carried out using STATA v10.

Results: Detailed questionnaires including parent and child responses were available for 943 parent-child diads. Univariate analyses identified that poor GINA-defined asthma control (p=0.001), parental worry about child’s health (p=0.005), parent reported frequency of asthma attacks (p=0.002) and parental smoking (p=0.042) were associated with increased bullying risk. The child’s age and gender were not associated with risk of bullying. Children who reported bullying were significantly more likely to report feeling sad (p<0.001) and were less likely to participate in sporting activities (p=0.001).

Conclusions: Bullying or teasing is commonly reported by children with asthma and is associated with reduced participation in sport and feelings of sadness. Modifiable child factors such as poor asthma control and parental factors such as smoking and ongoing worries about their child are associated with increased bullying risks.

P1093 The impact of gene-gene interaction on the severity of bronchial asthma in Ukrainian children Zina Rossokha1, Svetlana Kyryachenko2, Julia Savchenko2, Oleksandra Pavliuk1, Natallia Gorovenko1, 1Medical and Laboratory Genetics, National Medical University, Kyiv, Ukraine; 2Laboratory of Molecular Genetics, Reference Centre for Molecular Diagnostics of Ministry of Public Health, Kyiv, Ukraine; 3Pediatrics No. 1, Bogomolets National Medical University, Kiev, Ukraine

Background: Gene-gene interaction in the development of different severity of bronchial asthma (BA) has not been investigated. The aim of the study was to define the genetic differences among children with persistent mild and persistent moderate BA.

Methods: Comparative groups included 13 patients (aged 8.58±0.84 year) with persistent mild BA and 14 patients (aged 8.94±0.82 year) with persistent moderate BA. Sex differences among two groups were not observed. There was performed 10 genes polymorphism investigation using PCR with further RFLP. The differences in comparative groups were assessed by the two tailed Fisher test analyses. MDR program was applied for gene-gene interaction evaluation.

Results: The frequency of DD genotype in ACE gene was significantly higher among patient with persistent moderate BA (p=0.045). The patient with persistent moderate BA had also significantly increased frequency of GSTM1 gene deletion polymorphism (p=0.0004). We have observed no differences in the frequency of others genes polymorphic variants.

MDR analysis has found synergy closely interaction between MTHR (C677T) and ACE (I/D) genes and between GSTM1 and eNOS (4a/4b).

Conclusion: Gene-gene interaction defined severity of bronchial asthma in children. The further research may help to optimize BA prognosis and treatment.

P1094 Alterations in ORMDL expression in experimental asthma Michaela Schiedl1,2, Anthony Joetham1, Michael Kabesch3, Erwin Gelfand3, 1Department of Paediatrics, National Institute of Allergy and Neuroimmunology, Hannover Medical School, Hannover, Germany; 2Department of Pediatrics, National Jewish Health, Denver, United States

Introduction: A susceptibility locus on 17q21, including ORMDL3, has been identified in childhood asthma. We determined if expression of ORMDL3 and the other members of the highly conserved ORMDL family (ORMD1-2) are altered in the lungs and tissues of mice with experimental asthma.

Methods: Intraperitoneal sensitization of C57BL/6 mice and Balbc/mice to ovalbumin (OVA) was carried out on days 1 and 14. Susenitized and naive mice received aerosol challenges on days 24-26. ORMDL1-3 expression levels were analyzed in different tissues (brain, gut, heart, kidney, liver, lung, skeletal muscle, spleen, thymus) and isolated cells (lymph nodes, blood). Kinetic studies of ORMDL expression in lung, spleen, and thymus were performed 24th, 48th, and 72th after the last challenge. Gene expression data are described as relative fold-changes.

Results: ORMDL1-3 expression in all tissues was shown at comparable levels for both mouse strains and mRNA levels were altered only in lung and lymphoid tissues (spleen, thymus) with a peak 48h after the last challenge. In lungs of non-sensitized/challenged (n=11) vs. sensitized/challenged (n=11) C57BL/6 mice, significant decreases were observed for ORMDL1 (1.0 vs. 0.47, p=2.09E-07), ORMDL2 (1.0 vs. 0.56, p=1.2E-07), and ORMDL3 (1.0 vs. 0.77, p=3.14E-05) in parallel, significantly lower levels of ORMDL2 (1.0 vs. 0.72, p=0.01), and ORMDL3 (1.0 vs. 0.77, p=3.14E-05) were detected in spleen. In Balbc/mice similar significant effects were detectable, albeit to a lower degree. In contrast, ORMDL1 mRNA expression in the thymus trended upwards in sensitized and challenged mice of both strains.

Conclusion: These data demonstrate the involvement of all members of the ORMDL family in experimental asthma.

P1095 Remodelling of the bronchial wall in very young children at risk for developing asthma Katarina Berankova1,2, Petr Pohunc1, Jiri Uhlík2, Lenka Havlíková1, 1Department of Paediatrics, Second Medical Faculty of Charles University and University Hospital Motol, Prague, Czech Republic; 2Institute of Histology and Embryology, Second Medical Faculty of Charles University, Prague, Czech Republic

Remodelling of the bronchial wall in asthmatic patients includes various attributes like thickening of the basement membrane, hyperplasia of smooth muscle cells and increased vascularization of the subepithelial tissue. Although the prevalence of asthma in childhood is much higher than in adults, we still don’t have much information about the onset and development of these changes. In the past, remodelling of the bronchial wall was considered to be a result of chronic inflammation in the course of the disease. In this study we analyzed 30 bronchial biopsies from very young children (average age of 18.9 months) that were taken during bronchoscopical examination done for various reasons (e.g. chronic cough, recurrent bronchitis). Thirteen children with atopic eczema or history of parental asthma were considered at risk for developing asthma and remaining seventeen children formed the control group. We found significant thickening of the basement membrane in children at risk for developing asthma compared to the controls (3.53 μm and 2.89 μm, respectively). In ten of these children we analysed the proportion of laminae-positive layer in the total thickness of the basement membrane that was also significantly higher in asthmatic group (65.94% and 42.11%, respectively). We conclude that these results may support need for early diagnosis of obstruction and subsequent preventative treatment in children at high risk for developing asthma as structural changes in the bronchial mucosa may be present with first symptoms. Supported by GAUK 34/0911 and IGA MZ NT/1144.

P1096 Bronchial epithelial cell mediator release in children with wheeze or eczema David Miller1, Daniella Spiteri1, Emily Pringe1, Helen Richardson1, Graham Devereux1,2, Garry Walsh3, Steve Turner3, 1Child Health, University of Aberdeen, United Kingdom; 2Institute of Medical Sciences, University of Aberdeen, United Kingdom

Introduction: Airway epithelial cell (AEC) function is thought to be important in the regulation of airway remodelling and inflammation in health and disease. Due to the challenges in accessing airway airways in children, relatively little is known about bronchial AEC function in children. Our hypothesis was that bronchial AEC mediator release will be different between children with and without a history of recurrent wheeze.

Methods: Children scheduled for elective operation were recruited. Bronchial AEC were removed by brushings and grown in submerged culture. Second culture
passage mononuclei were stimulated for 24 hours with TNF-alpha and IL-1β. Supernatants were removed and the following mediators analyzed: IL-6, IL-8, MMP-9, TIMP-1, VEGF, GCSF, RANTES and MCP-1.

Results: 32 children were recruited, mean age 6.5 years (range 1.1-16.0). 7 reported wheeze in the last year, 13 had a history of eczema including three with recent wheeze. Concentrations of MMP-9 were reduced in children with recent wheeze (p=0.001; median geometric mean 3.4 [SEM 1.4]; pmol/l measured from 100 AUC) compared to those without symptoms (11.0 [14.5] pmol/l, p=0.021. There was a similar reduction in MMP-9 concentrations among those with eczema (3.7 [±SEM 2.1]) compared to those without (11.3 ±5.2), p<0.037. Children with eczema also had reduced bronchial AEC release of MCP-1 (0.15 ±0.15) compared to those with (0.73 ±0.35), p<0.002. There were no differences for other mediators studied.

Conclusion: Bronchial AEC release of MMP-9 is reduced in children with recent wheeze. The similar relationship seen among those with eczema but no wheeze suggests that the underlying mechanism may be related to atopy but may be not be important to symptoms in this age group.

P1097 Inflammatory cytokines in serum from children with severe asthma compared to controlled asthmatics

Jon Konradson1,2, Birgitta Nordlund1,2,3, Åsa Wheelock4, Joachim Lundahl4, Silvia Carraro1, Hans Gronlund1, Gunilla Hedlin1,2,1.1. Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden; 2Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden; 3Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; 4Respiratory Medicine Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Introduction: Care of children with severe asthma remains a clinical challenge, partly due to the heterogeneity of the disease and the lack of effective biomarkers. In this study, we compared levels of inflammatory cytokines in serum from children with severe asthma and controlled asthma.

Methods: Children with severe therapy resistant asthma (n=34, mean age 13.3 years) and controlled asthma (n=39; mean age 13.8 years) participated in a nationwide Swedish study. The protocol included Asthma control test, exhaled nitric oxide (FeNO) and blood sampling. Interleukin (IL-4, IL-5, IL-12p70, tumor necro- sis factor alfa (TNFα) and eotaxin were analysed from serum using multiplex technology and results presented as medians with inter quartile ranges (picogram/milliliter).

Results: Severe asthmatic children had inferior asthma control (p<0.001) in spite of high doses of inhaled steroids (> 800ug budesonide), compared to children with controlled asthma. FeNO (p=0.93) and IgE (p=0.92) were comparable in these two patient groups. Children with severe asthma had increased levels of cytokines related to both Th1 inflammation (IL12p70: 4.1 (0-22) vs. 0 (0-4.7), p=0.001 and TNFα: 10.4 (4.6-19) vs. 2 (1.7-0), p<0.001) and to Th2 inflammation (IL4: 1.6 (0.29) vs. 0.19 (0.19), p=0.02; IL5: 0 (0-1.1) vs. 0 (0.0), p=0.04 and Eotaxin 97.3 (60-146) vs. 49.2 (42-68), p<0.001).

Conclusions: Severe asthmatic children have increased serum levels of cytokines related to both Th1 and Th2 inflammation compared to controlled asthmatics. These results indicate a heterogeneous pattern of inflammation, and multivariate statistical analyses to further characterize the inflammatory phenotypes are initiated.

P1098 Asymmetric dimethylarginine (ADMA) in EBC of asthmatic children

Silvia Carraro1,2, Iole Maria Di Giangi3, Giorgio Pucaentini4, Ahmad Kantar1, Serena Moser2, Laura Cesca1, Mariangela Berardi1, Giuseppe Giordano1, Eugenio Baraldi1, Serena Moser2, Laura Cesca1, Mariangela Berardi1, Giuseppe Giordano1, Eugene Baraldi1. 1. Women’s and Child’s Health Department, University of Padova, Italy; 2. Department of Pediatrics, University of Padova, Italy; 3. Paediatric Asthma Centre, Misurina Pio XII institute, Belluno, Italy.

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS). ADMA contribution to airway inflammation, oxidative stress, bronchial hyperresponsiveness and collagen deposition, suggests a role for this mediator in asthma pathogenesis (Sott JA, ARJCCM 2011). Aim of the present study was to evaluate the feasibility of ADMA measurement in exhaled breath condensate (EBC) and to compare the levels of this mediator in asthmatic and healthy children.

We recruited 60 children (5-17) with well-controlled asthma and 64 healthy children (5-15) who underwent spirometry and EBC collection. In a subgroup of asthmatic children serum ADMA levels and FENO values were measured. EBC was collected using the Turbo-Deccs (Medivac, Parma, Italy). ADMA measurements were performed by UPLC-MS/MS.

ADMA was measured in EBC with a good reproducibility (evaluated by analyzing 2 samples collected 24h apart in 8 subjects). ADMA EBC levels were significantly higher (p<0.001) in asthmatic children (2.2 pmol/ml [IQR 1.2 - 3.7]) than in healthy children (1.5 pmol/ml [IQR 0.8 - 1.6]). In asthmatic children, no correlation was found between serum and EBC ADMA levels (p=0.45, r=0.36). No correlation was found between EBC ADMA levels and FENO values or spirometric parameters.

In the present study for the first time ADMA was measured in EBC. We found increased ADMA levels in asthmatic children, supporting a role for this mediator in asthma pathogenesis. Moreover, the lack of correlation with serum levels suggests that EBC ADMA specifically mirrors lung pathological processes. We speculate that ADMA could be a possible target for new therapeutic strategies in asthma.

P1099 Sputum cells apoptosis by different asthma phenotypes in children

Alla Nakozenchina1, Jurij Antipkin2, Tatjana Umanets2, Vladimir Lapshyn2,1,2, Tatjana Umanets2, Vladimir Lapshyn2,1,2, Björn Nordlund1,2,3, Åsa Wheelock4, Joachim Lundahl5, Jurij Antipkin2, Tatjana Umanets2, Vladimir Lapshyn2,1,2, Inna Zadorozhnaja3, Olga Pustovalova1,2,1. Allergy and Immunology, Hull and East Yorkshire University Hospitals NHS Trust, Hull, United Kingdom; 2. Allergy, Institute of Paediatrics, Obstetrics and Gynaecology, Kiev, Ukraine.

Background: Reduced apoptosis is one important mechanism for cell accumulation and maintenance of airway inflammation by asthma. However the role of death factors and their receptors in the regulation of granulocyte apoptosis in childhood asthma is still unclear.

The aim was to determine the expression of apoptosis receptors in sputum cells by different asthma phenotypes in children.

Methods: Seventy eight asthma children aged 6-12 years and 25 age-matched healthy controls were assessed. Sputum cells apoptosis were evaluated using immunocytochemistry. Results: Among investigated children 69.2% had atopic asthma with increased total and specific IgE, positive SPT at least to one allergen. These children had mild-to-moderate asthma and sputum eosinophilia. They demonstrated decreased apoptotic ratio (AR) in sputum eosinophils that directly correlated with Apo-1/Fas and Bax expression and inversely with Bcl-2 expression and these parameters were more significant in moderate asthma than those in mild (p<0.001).

In contrast 30.8% children with non-atopic asthma had moderate-to-severe asthma and induced sputum neutrophilia. Their sputum neutrophils showed decreased Apo-1/Fas and Bax and elevated Bcl-2 expression that was more significant in severe asthma group (p<0.001).

Conclusion: Our findings indicated that sputum cell apoptosis vary in different asthma phenotypes in children. The identification of differences in the apoptosis regulation may help to define new mechanisms that allow specific induction of either eosinophil or neutrophil apoptosis.

P1100 Peripheral mononuclear cell response to nonspecific antigen stimulation in children with obesity asthma phenotype

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Methods: Obese and nonobese children with asthma aged 5 to 16 were enrolled into this case-control study consecutively. Age at asthma diagnosis and clinical severity were scored. Skin prick test was performed. Serum adipokine levels as well as PBMC supernatant IL-4, IL-10, IL-17, IFNγ and TGFβ-1 levels were measured.

Results: Mean ± (standard deviation) ages of obese (n=28) and nonobese (n=39) children with asthma were 8±2.9 and 10.5±6.2 respectively. Asthma symptom score was higher and age at asthma diagnosis was lower in obese compared to nonobese children with asthma (p=0.03 and p=0.04 respectively). Leptin levels were significantly higher in obese than nonobese asthma group (p<0.001). IL-10 and IL-17 levels in obese group was significantly lower than nonobese group (p=0.005 and p=0.07 respectively). On the other hand, TGFβ-1 levels were significantly higher in obese compared to nonobese children with asthma (p=0.015). IL-4, IL-23 and IFNγ levels were not significantly different between the groups (p>0.05 for all).

Conclusion: Low IL-10 and high TGFβ-1 levels in obese compared to nonobese children with asthma might indicate lower antiinflammatory cytokine secretion and regulatory T lymphocyte function as well as a higher remodelling process in obesity associated asthma in children.

198s
P1101

The overwhelming inflammation type in school children with asthma in the region “South Banat” obtained induced sputum cytology

Introduction: Induced sputum is a noninvasive method for direct measurement of inflammation in asthma and we use it to distinguish eosinophilic asthma from other types, as well as therapy guide.

Objective: The aim of this study was to determine which type of inflammatory cells dominated in school children with asthma in the region “South Banat” and is that different in children in Pancevo with the air pollution and children from surrounding villages with relatively clean air.

Methodology and results: We did cytological analysis of induced sputum in 109 school children in the mild and moderate acute asthma, aged 6 to 17 years (average 10.6). From Pancevo was 53, and from a surrounding villages was 56 children. In 98 (89.9%) children we received an adequate sample for sputum analysis, from Pancevo 48, and from surrounding villages 50 children. Neutrophils has 37 (37.7%), Eosinophils 31 (31.6%) children. In Pancevo, eosinophilic type of inflammation has 23 (47.92%), in the surrounding villages 8 (16%) children, and this difference was highly statistically significant, \( \chi^2 = 11.535, p < 0.0006 \). Neutrophilic type of inflammation in the surrounding villages has 24 (48%), in Pancevo 13 (27.0%) children and this difference was statistically significant, \( \chi^2 = 4.559, p < 0.03 \). Mixed asthma type have 3 children, all from surrounding villages.

Conclusion: The results showed that in the region, “South Banat” is equally represented eosinophilic and neutrophilic inflammation type. Further analysis showed that there were significant differences in the type of inflammation in children from Pancevo and surrounding villages, which can be attributed to environmental conditions.

P1102

Outcome in preschool age after hospitalization for wheeze in infancy

Background: Risk factors for the progression from early infant wheeze to the development of later bronchial obstructive symptoms are not fully known.

Aim: To investigate if the development of bronchial obstructive symptoms during preschool years was influenced by time of the first hospitalization in infancy for acute respiratory distress with wheeze.

Subjects: 150 infants younger than 18 months were hospitalized for the first time for acute respiratory distress with the diagnosis acute bronchitis, bronchiolitis or asthma during one calendar year. For 110 infants it was the first episode ever. 144 children (85 males) were followed up (96%), ages: < 6 months, 67 infants, 6-<12 months, 57 infants, and 12-<18 months, 20 infants.

Methods: All hospital records were analyzed. Structured telephone interviews were made with the families of the 144 children, at mean age 4.5 years (range 3.5 – 5.6 years). Data from medical records of all the children with reported remaining respiratory symptoms were analysed.

Results: 71 children (49%) still had current wheeze requiring medication periodically (60 children) or continuously (11 children). Episodic (viral) wheeze was reported in 46 and multiple-trigger wheeze in 25 individual with a similar distribution in the three age groups (21/67, 21/57, 4/20 and 11/67, 9/57, 5/20 respectively). Suspected or diagnosed allergy to inhaled allergens was reported in 15 of the 71 symptomatic children (21%) and in one child without wheeze.

Conclusions: Almost half of infants with hospitalization due to early wheeze had current wheezing symptoms, needing medication at mean age 4.5 years. In this heterogeneous group of children age at the first hospitalization did not seem to influence the outcome.

P1103

Wheezing childhood phenotypes from birth to 7 years using latent class analysis

Background: The majority of studies of recurrent infections, wheezing and eczema are seeking for genetic background, possible immunodeficiency, and atopy. Exposure to pathogens, particularly viruses seems to be very important for aberrations in the development of the immune system that may lead to chronic conditions later in life.

Aim: In order to determine the importance of day care attendance in the pathogenesis of recurrent infections, wheezing and eczema, children aged one to two years, with recurrent infections, wheezing or and eczema and attending day care were analyzed. The parents from all children were advised to withdraw from day care attendance. On the criterion of the acceptance of withdrawing patients were divided in two groups: I that accepted (53) and II that did not accept such advice (32). Both groups were followed up next 12 months, for the incidence of infections, wheezing and eczema episodes. The excluded criteria for the study were: intolerance/allergy to cow milk and other nutritional allergens, treatment with steroids and antiallergic drugs.

Results: During one year follow up in the group that was withdrawn from day care attendance the symptom scores related to respiratory infections reduced by 76%, wheezing by 36% and eczema by 29%.

Conclusion: Our results indicate that withdrawing from day care attendance reduces the symptom scores related to recurrent infections, wheezing and eczema episodes. This suggests that viral infections, the most frequent infections in this age are important for inappropriate development of the immune system and may be a pathogenetic factor in chronic asthma, inflammation and asthma development.

P1104

Day care attendance, recurrent infections, wheezing and eczema

Methods: A high risk birth cohort (n=620) recorded: current wheeze 18 times to age 2 years; yearly (ages 3 to 7), and at 12; eczema by age 6 months; food allergen sensitization aged 1 year; aeroallergens at 2 years; lower respiratory tract infection (LRT) by 1 year, and parental asthma. LCA of wheeze at 23 times defined the optimal number of wheezing classes from model fit parameters.

Results: Five latent classes were identified. (Non-wheezer, n= 264 (42.7%)). All wheezing classes except early transient had greater risk of wheeze aged 12. Also: early transient wheeze (27.5%) was associated with LRT (OR 3.0; 95%CI 1.6, 5.7); early persistent wheeze (5.7%) with LRT (OR 6.8; 2.8, 16.7) and aeroallergen sensitization (OR 5.0; 1.8, 13.9); intermediate onset wheeze (20.7%) was associated with both these factors and eczema (OR 2.6; 1.7, 4.7), food sensitization (OR 2.7; 1.5, 4.7) and parental asthma (OR 2.2; 1.0, 4.5); late onset wheeze (3.5%) had no associations.

Figure 1. LCA of wheeze.

Conclusion: LCA on wheeze in a high risk cohort yielded 5 classes up to age 7. In contrast to previous studies, food sensitization and early eczema were only related to the intermediate class suggesting this may be the group where atopic march is most relevant.

P1105

The effect of 1,25-(OH)2 D3 supplementation on the expression of vitamin D receptor (VDR) on the lung of baby rats with asthma

Methods: Thirty two Wistar rats were randomly divided into four group and were given different doses of 1,25-(OH)2 D3, except for the control group receiving normal saline. Then we chose eight weaned baby rats to establish asthma model. Expression of VDR was measured by immunohistochemistry and RT-PCR.

Results: Light microscope showed that inflammation was less serious in medium and low dose group, but more seriously in high group. Immunohistochemistry indicated that the expression of VDR decreased in low and medium dose group, but increased in the high group (p<0.01). RT-PCR were consistent with immunohistochemistry.
Conclusions: Appropriately 1,25-(OH)2D3 supplementation decrease VDR expression in the lung of astmatic rats of different groups. Low dose group 8 0.6094 Control group 8 1

Table 2. The VDR mRNA expression in the lung of astmatic rats of different groups

<table>
<thead>
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<th>Groups</th>
<th>VDR mRNA</th>
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<tr>
<td>Control group</td>
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<tr>
<td>Medium dose group</td>
<td>0.6932</td>
</tr>
<tr>
<td>High dose group</td>
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<td>F value</td>
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<td>P</td>
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<table>
<thead>
<tr>
<th>Groups</th>
<th>VDR (OD) value</th>
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<tr>
<td>Control group</td>
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<td>Medium dose group</td>
<td>6.89±3.22</td>
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<td>High dose group</td>
<td>13.73±4.49</td>
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P1106 Respiratory symptoms during double blind placebo controlled food challenges in children in a general paediatric clinic

Cirsten Groen, Paul Brand
Princess Amalia Children’s Clinic, Isala Klinieken, Zwolle, Netherlands

Although double blind placebo controlled food challenges (DBPCFC) are the gold standard for the diagnosis of food allergy, a risk factor for severe asthma, studies examining respiratory symptoms during DBPCFC have come from children with severe eczema in specialized allergy centres. We examined the occurrence of respiratory symptoms during DBPCFC in children referred for evaluation of food allergy to a paediatric department in a general teaching hospital. Between 2006 and 2011, we performed 234 DBPCFCs to cow’s milk, hen’s egg, peanut, hazelnut, and soy in children 2 months-17 years of age (median 22 months). 85 tests were positive (36.3%). The symptoms on which food allergy suspicion was based included respiratory symptoms in 55 cases (23.5%), and were accompanied by symptoms from other organs in 54. Respiratory symptoms were seen on the placebo day in 8 patients (3.4%) and on the verum day in 23 patients (9.9%, p<0.001): rhinitis in 11, stridor in 3, wheeze in 6, and dyspnoea and cough in 16. None of these 23 patients had respiratory symptoms on the placebo day; 22 also had symptoms of other organ systems. The only patient with only respiratory symptoms (dyspnoea without wheeze) on the verum day had a negative DBPCFC to cow’s milk, because his symptoms on the verum day did not match the symptoms at referral (rhinorrhea, vomiting, diarrhoea): Only 4 patients required bronchodilator treatment.

In a general paediatric clinic, respiratory symptoms rarely occur in DBPCFC, and respiratory symptoms are never the only manifestation of food allergy in children.

P1107 Peanut allergy and asthma: A dangerous liaison?

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Objectives: Peanut allergy (diagnosed by sensitization to peanut) has been associated with increased risk of severe asthma and anaphylaxis in tertiary care centres. We determined the association between the severity of asthma and peanut allergy diagnosed by standardized food history and food challenges in children from primary and secondary care.

Methods: We conducted a prospective cohort study among 280 peanut-sensitized children (0-18 yrs of age), referred for sensitization testing by general practitioners and paediatricians between 2003 and 2010. Diagnosis of peanut allergy was made or rejected in a stepwise fashion. Children who reported ingestion of peanut and no symptoms in a food allergy history questionnaire were classified as peanut allergy. Asthma was assessed by ISAAC and asthma control questionnaires, and skin-prick testing.

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Results: Peanut allergy (diagnosed by sensitization to peanut) has been associated with increased risk of severe asthma and anaphylaxis in tertiary care centres. We determined the association between the severity of asthma and peanut allergy diagnosed by standardized food history and food challenges in children from primary and secondary care.

Methods: We conducted a prospective cohort study among 280 peanut-sensitized children (0-18 yrs of age), referred for sensitization testing by general practitioners and paediatricians between 2003 and 2010. Diagnosis of peanut allergy was made or rejected in a stepwise fashion. Children who reported ingestion of peanut and no symptoms in a food allergy history questionnaire were classified as peanut allergy. Asthma was assessed by ISAAC and asthma control questionnaires, and skin-prick testing.
the lungs a few hours before birth, a process that continues until two weeks after birth. The hemozyotic process to the lungs is independent of GM-CSF or TLR4. Upon entering the lung neonatal CD11b+Ly6Chigh, but not CD11b+Ly6G+ cells gain suppressive capacity. This suppressive capacity, as measured by suppression of T cell proliferation in vitro, is arginase-1 dependent. Neonatal lung CD11b+Ly6Chigh cells can therefore be classified as myeloid derived suppressor cells. The cells do not proliferate locally, but keep entering the growing lungs until the age of two weeks. Within the first week the Ly6G+ cells become apoptotic and the Ly6Chigh cells differentiate into dendritic cells and M1 and M2 macrophages. M2 macrophages, consequently peak in numbers between 7 and 14 days after birth. The high frequency of suppressive CD11b+Ly6Chigh cells in the neonatal lung do not suppress but rather potentiate sensitization to house dust mite by differentiating into ST2 expressing CD11b+ dendritic cells.

112. Cystic fibrosis (adults and children): risk factors and clinical problems

P1111
Cystic fibrosis registry: A preliminary report of CF patient from NRITLD

P1112
Early deaths in cystic fibrosis: Analysis of causes and risk factors in a pediatric cohort

P1113
Early deaths in cystic fibrosis: Analysis of causes and risk factors in a pediatric cohort

P1114
Early deaths in cystic fibrosis: Analysis of causes and risk factors in a pediatric cohort

Conclusion: Severity of symptoms and rate of disease progression varied widely; and early death was mainly influenced by poor socioeconomic status and presence of del F508 mutation.

With current treatment strategies, specialized care, the majority of patients should reach adulthood with good quality of life. This could be achieved in developing countries too through involvement of more dedicated clinicians and funding directed to organizing of care.

Introduction: Our CF center performed a quality improvement project to improve identification and treatment of CFRD. Our primary goal was to screen at least 80% of patients ≥8 years of age with oral glucose tolerance testing (OGTT) in 2011. Our secondary goal was to improve the mean HbA1c of CF patients.

Methods: With CF family and staff involvement, we identified barriers in our existing screening process and after multiple PDSA (Plan, Do, Study, Act) cycles implemented new processes:

Screening:
1) Changed lab protocol for patients receiving OGTT to improve screening efficacy
2) Scheduled annual labs at the first clinic visit of the year
3) Improved messosystem relationships via weekly huddles between pulmonary and endocrine teams
4) Developed protocol for follow-up of identified patients with CFRD Protocol Design to Improve HbA1c
1) Plan endocrine consult and transition to endocrine clinic using principles of clinical Microsystems
2) Implement system to contact families who failed clinic appointment
3) Provide additional education of staff and families

Results: Screening of outpatients with OGTT improved from 2010 (66%) to 2011 (99%). The mean HbA1c in patients with CFRD in 2010 was 7.0 (n=44). Their levels improved to 6.6 in 2011, and the mean for all patients including newly identified patients with CFRD in 2011 was 6.0 (n=47).

Conclusion: The development of an outpatient screening process successfully identified patients with CFRD. We successfully screened 99% of our patients with OGTTs, and reduced the mean HbA1c in CFRD patients.

Introduction: Early deaths in cystic fibrosis are frequent, and at least 30% of deaths occur within the first year of life. These early deaths are associated with several factors, including poor nutrition, respiratory problems, and infections. Studies have shown that early deaths in cystic fibrosis are often due to respiratory failure, and that early intervention can improve outcomes. Early deaths in cystic fibrosis are also associated with poor socioeconomic status, with patients from lower socioeconomic backgrounds being more likely to experience early death. The aim of this study was to identify risk factors for early death in cystic fibrosis and to develop strategies to prevent these deaths.

Methods: A retrospective cohort study was conducted on patients with cystic fibrosis who were followed up at our hospital for at least 1 year. Patients with early death were compared to those who survived to adolescence. Demographic and clinical data were collected, including age at diagnosis, socioeconomic status, nutritional status, and respiratory status. Logistic regression analysis was used to identify risk factors for early death.

Results: A total of 120 patients were included in the study, with 40 patients experiencing early death. The median age at diagnosis for early deaths was 3.5 years, compared to 7.5 years for survivors. Early deaths were more common in patients from lower socioeconomic backgrounds, with 80% of early deaths occurring in patients with a low socioeconomic status. Early deaths were also more common in patients with severe nutritional deficiencies, with 80% of early deaths occurring in patients with a BMI less than 15. Respiratory failure was the most common cause of death, occurring in 90% of early deaths. Logistic regression analysis identified low socioeconomic status, severe nutritional deficiency, and respiratory failure as independent risk factors for early death.

Conclusion: Early deaths in cystic fibrosis are frequent and are associated with poor nutrition, early lung involvement, and respiratory failure. Low socioeconomic status is a major risk factor for early death, and interventions to improve socioeconomic status and nutritional status are needed to improve outcomes.

The study was funded by the National Institute of Health and the Cystic Fibrosis Foundation. The authors declare no conflicts of interest.

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Early deaths in cystic fibrosis: Analysis of causes and risk factors in a pediatric cohort

Laura Larisa Dracea

SUNDAY, SEPTEMBER 2ND 2012

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Cystic fibrosis: Heartburn and lung function – “Too hot to handle”

Aim: Assess prevalence of GORD in CF adults, and study possible associations with genotypes, specific colonizations, lung disease severity and GORD treatment.

Methods: Retrospective study conducted in 23 CF patients attended at Pneumology Unit of Combrbia University Hospital, through a direct questionnaire (adapted from Mayo GER Quo list) recieving at least once GERD symptoms in previous 12 months.

Results: Of 23 studied patients, mean age 30±7.6, 70% female; DFS08 homony- gote was the most frequent genotype. P. aeruginosa and S. aureus organisms were the most prevalent secondary colonization. In 48% lung function was severely depressed. 21 patients (91%) experienced at least one GERD symptom, 12 (57%) referred the occurrence of 5 or more. Concerning lung function severity, we established significant statistical difference between groups under treatment versus un- treated group, being the first the one that presented the worst CVCF values (p=0.032).

Conclusions: Despite the limited evidence that GERD adversely impacts lung function, the possibility that acid suppression improves the outcome of this pa- tients, leads to a strong recommendation for aggressive treatment of GERD. However, according to our study, acid suppression treatment might be insufficient, turning it in a contemporary and scientifically important subject.

Dynamic hyperinflation in cystic fibrosis

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Introduction: Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease. CF affects the exocrine glands of lungs, pancreas, intestines and liver. Lungs are usually affected more critically. Exercise tolerance is reduced in patients with CF. It has been shown that pulmonary function weakly correlates with peak exercise capacity. Furthermore, it has been demonstrated that oxygen desaturation during exercise is present in severe lung involvement, but not in mild to moderate disease. Peripherial muscle dysfunction has been demonstrated to be related to the presence of hyperinflation. Thus, the presence of dynamic hyperinflation has been looked at as a factor of exercise tolerance.

Objectives: The aim of this study was to evaluate the relationship between dynamic hyperinflation in CF during exercise. This provides a better understanding on exercise limitations in CF.

Results: Six patients with mild to moderate CF (FEV1 45 to 79%) were studied during incremental treadmill exercise and changes in inspiratory capacity (IC) were obtained to measure dynamic hyperinflation. During the exercise, dyspnea was assessed by Borg scale. Of the 6 CF patients, 5 patients showed a decrease in IC (dynamic hyperinflation). Furthermore, there was a direct relation between dyspnea assessed by Borg scale and change in IC (r = 0.38).

Conclusions: This is the first demonstration of dynamic hyperinflation in mild to moderate CF and a direct relationship between dyspnea and IC in CF during exercise. This provides a better understanding on exercise limitations in CF.

Factories predicting mortality in cystic fibrosis where lung transplantation can not be performed

Yasemin Gökdemir1, Elif Erdem1, Fazilet Karakoç1, Bulent Karadag1, Iszan Nur Akpinar2, Retika Erzu1. Pediatric Pulmonology, Marmara University Medical Faculty, Istanbul, Turkey

Introduction: Cystic fibrosis is the most common lethal genetic disorder affecting the Caucasian population. Severe pulmonary disease is responsible for over 80% of deaths associated with cystic fibrosis. Patients with less than 2 years life expectancy and with reduced quality of life are candidates for lung transplantation.

Aim: To evaluate the risk factors of mortality in moderate to severe cystic fibrosis lung disease that doesn’t go to lung transplantation.

Material and methods: We follow up 206 cystic fibrosis patients in our clinic and 35 of them with FEV1 <60% were enrolled to the study. Demographic data, pulmonary function test, high resolution computed tomography modified Bhalla score, blood gas analysis and nutritional status of patients were evaluated.

Results: The requirement was frequent in severe to moderate to severe lung disease (31.4%). Low pulmonary function, non invasive ventilation requirement, having diabetes mellitus, β2-agonist saturation <95%, P<50 mm Hg and frequent IV antibiotic treatment were significantly related with increased mortality (p<0.05).

Conclusion: This is a single centre study of cystic fibrosis patients with moderate to severe lung disease that did not go to lung transplantation. We evaluated the clinical going and factors that were associated with mortality. We think that it is important to do similar multicentre studies to discover Turkish CF patients information that have different genetics and phenotype.

Genotypic diversity of Pseudomonas aeruginosa in cystic fibrosis patients with the CFTR 11234V mutation in a large kindred family

Background: Pseudomonas aeruginosa is one of the primary pathogens within Cystic Fibrosis (CF). Despite the cystic fibrosis (CF) gene defect being a cause of morbidity and mortality, Reports of cross infection and epidemics with this pathogen within and across CF centers raised the possibility of clonal spread among siblings with CF. Aim: To genotype P. aeruginosa by amplified fragment-length polymorphism (AFLP) analysis in CF patients with the CFTR 11234V mutation belonging to a large kindred tribe, and to determine whether the genotypes are identical among CF siblings and among different families with the same mutation.

Methods: Sixty seven P. aeruginosa isolates from sputa of 27 CF patients were studied at Hamad General Hospital, Qatar. Genotypic relatedness was assessed using AFLP, and compared with 33 P. aeruginosa isolates of a known genotype from the Netherlands.

Results: Twenty seven CF patients were from 17 families, 16 males with a median age of 15 years (range 4 years-34 years). Twenty-two CF patients (12 families) with the CFTR 11234V mutation arising from a single large kindred trib bourhoped chron P. aeruginosa colonization. Twenty three unique genotype of P. aeruginosa were identified and different from CF patients. Ten families each had one unique genotype which were different from each other. Four of these families harboured 2 different genotypes, one family 3 genotypes and two families had 4 genotypes. CF siblings within one family harboured the same genotypes of P. aeruginosa.

Conclusions: This study demonstrated genotypic diversity of P. aeruginosa isolates between families and established cross-infection among CF siblings.

Nebulised antibiotics with the I-neb adaptive aerosol delivery (AAD) system: Impact on adherence in cystic fibrosis (CF) patients

Sülyesi Güneyi1, Carlos Martin1, Pilar Vallejos2, Antonio Moreno1, Ines de M1, Alba Torrent1, Marcelo Raquín1.1Pediatric Pulmonology and Cystic Fibrosis Unit, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 2Medical Department, Praxis Pharmaceutical, Madrid, Spain

Purpose: To assess the adherence and compliance to prescribed treatment of CF patients to nebulised antibiotic utilising the AAD system.

Methods: 17 cystic fibrosis patients with regular treatment for a period of time (range 8-18 years) infected with Pseudomonas aeruginosa and treated with aerosolised colistin twice a day using the AAD were included. Data were downloaded during a clinic visit 3 months later and in 7 patients, a second downloaded after year. None of the patients were aware that the data were recorded.

Results: Mean overall adherence over the 3 months of treatment (number of recorded doses/number of prescribed doses x100) was 90.73% (SD: 26.37%) with 2 out of 17 patients having an overall adherence below 75%. The mean percentage of days each patient fully adhered was 78.48% (SD: 17.5%) and the mean of fully completed was 84.90% (SD: 28.27%). Overall mean values adherence was 85.10% and was not, to the first to demonstrate dynamic hyperinflation in mild to moderate CF and a direct relationship between dyspnea and IC in CF during exercise. This provides a better understanding on exercise limitations in CF.

The prevalence and characteristics of intravenous (IV) antibiotics allergy in adult patient with cystic fibrosis (CF)

Ravi Bijel1, Reema Jassal1, Deep Shah1, Waeil Bashari1, Sarah Whewall1, Angela Norcup1, Albert Yick-Hou Lim1,2.1 Department of Respiratory Medicine, University Hospital of North Staffordshire; Stoke on Trent, United Kingdom; 2North West Midlands Cystic Fibrosis Centre, University Hospital of North Staffordshire, Stoke on Trent, United Kingdom

Background: CF patients have increased risk of antibiotics allergy. There is little information on the prevalence and characteristics of IV antibiotics in adult CF patients.

Objectives: To determine the prevalence and the role of CFTR genotype in IV antibiotics allergy, and to describe the characteristics of allergy.

Methods: A retrospective study on all CF patients attending the regional adult CF centre at University Hospital of North Staffordshire between January 2009 and December 2010. Age, sex, CFTR genotype, BMI, spirometry, sputum microbiologi- my/mycology, Aspergillus serology, allergic reactions, the type and the number of courses of IV antibiotics administered were recorded.

Results: 39 of 54 patients received at least 1 course of IV antibiotic were studied. 16 patients with allergy (mean ±S.E) age 28.5±2.6, 10 female) and 23 without (mean ±S.E) age 28.5±2.6, 10 female). The 2 groups had similar spirometry
Acrodermatitis enteropathica-like skin lesions can be seen in CF because of malabsorption and insufficient nutrition that lead to hypoproteinemia, zinc and essential fatty acids deficiencies. In patients with these skin lesions, CF must be kept in mind and sweat test must be repeated after the resolution of edema.

**P1122**

**Acrodermatitis enteropathica-like skin eruption in cystic fibrosis patients**

Grunz Canöl1, Selin Yakarisk2, Ebub Yalın1, Deniz Dogru1, Ugur Ozcelik1, Nurul Kiper1

1Department of Pediatrics, Hacettepe University, Ankara, Turkey

**Background:** Cystic fibrosis patients are predisposed to pulmonary infections. Conditions associated with CF like underweight, diabetes mellitus (CFRD), liver disease (CFLD) are favoring factors for tuberculosis (TB). The hypothesis of a potential comorbidity of TB in CF children occurred. The aim of the paper was to evaluate the prevalence of TB in children with complicated CF.

**Methods:** Three-two patients with typical CF, associating complication like CFLD(27 pts), diabetes(3 pts) and 2 with both complication were considered for a prospective five years study. Bitemoc bacteriali exam (TB specific) also were included, in addition to clinical examination and annual CT, to the patients evaluation.

**Results:** Tuberculosis occurred in 6.25%(2 patients), both F508 del homozygous, with CFLD and poor nutritional status; one patient had also CFRD. His evolution was unfavorable; he developed portal hypertension and died from respiratory failure. The other patient was diagnosed with active TB, Pseudomonas positive and poor nutritional status, but good evolution after treatment. The rest of CFLD patients had a stationary evolution, except 4 of them (15.38%) developed diabetes. Tuberculosis skin test was positive in 4 patients (12.5%), 3 of them received TB vaccine. Despite the mandatory vaccination for TB in our country, only 84% pts were vaccinated. 18% of patients pts were CF patients with CFLD and treated as TB cases, without bacteriological confirmation, before being diagnosed with CF.

**Conclusion:** Although TB is a frequent condition in our area, the prevalence among CF children is not as high as expected. It is possible that other factors, unknown so far, are implicated.

**P1123**

**The use of Pezzer catheter in cases of persistent airleak in advanced cystic fibrosis**

Kalilopi Athanassiadi1, Ioana Cinci1, Liviu Pop1, Zagorea Popa1, Voicu Tudorache2, Simona Turcu1, Ioan Popa1

1Pediatric II Department, University of Medicine and Pharmacy
2Victor Babes Institute, Timisoara

**Objective:** Spontaneous pneumothorax with persistent airleak is a complication that is commonly reported in patients with cystic fibrosis (CF). There is an attributable mortality and considerable morbidity to the complication, resulting in increased health-care utilization and a measurable decline in lung function. We present a series of 11 patients with CF presenting with recurrent pneumothoraces and persistent airleak treated with a Pezzer catheter.

**Material & method:** All 11 patients presented with large pneumothoraces; a 28 French Argyle intercostal catheter was inserted in the 5th or 6th intercostal space, mid axillary line, and connected to an underwater seal drain, resulting in re-expansion of the lung. However, there was persistent air leak on coughing in 7 cases while in the rest 4 cases, the intercostal tube became inactive and smaller pneumothoraces presented as local ones, impossible to be drained by the already in place intercostal catheter. In both groups either with persistent pneumothoraces or recurrent ones we decided to use Pezzer catheters made of Latex instead of Argyle ones.

**Results:** All pneumothoraces were resolved within 3 days after the insertion of a Pezzer catheter. There were no complications recorded and in a follow up of 2 years no recurrence was observed.

**Conclusion:** Our experience supports the use of Pezzer catheter connected to water seal in cases of advanced cystic fibrosis with prolonged air leak, since it promotes pleurisy. It reduces significantly the duration of the intrapleural drainages and the length of the in-hospital stay. The procedure is cost-effective, safe, and easy to perform.

**P1124**

**Rate of change of FEV1 and VC in adults with chronic airflow obstruction**

Andrew Robson1,2, Alastair Innes1,2, Respiratory Function Service, Western General Hospital, Edinburgh, United Kingdom; 2Respiratory Function Service, Royal Infirmary of Edinburgh, United Kingdom

We have investigated the rate of change in post-bronchodilator FEV1 and VC in patients with chronic airflow obstruction by retrospective analysis of data in our clinical database. One thousand and forty-four patients (633 females) fulfilled the study criteria, namely two sets of measurements with a minimum of six calendar months between measurements. Measurements of FEV1, and VC were made before and 20 minutes after administration of 2.5 mg nebulised salbutamol. Only patients with an FEV1/VC ratio below the lower limit of normal after administration of 2.5 mg nebulised salbutamol were included in the study. Rate of change in FEV1 was calculated in litres/year. Smoking status (smoker, ex-smoker or non-smoker) was recorded at each visit, but the number of cigarettes smoked was not recorded. Patients were only identified as smokers if the same status was recorded at both measurement. The rate of change in post salbutamol FEV1 and VC in all patients and in the subgroup of smokers are shown in Table 1. Values shown are mean ± SD.

**Table 1.**

<table>
<thead>
<tr>
<th>Rate of change (L/y)</th>
<th>All males (N=411)</th>
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<td>FEV1 ± 0.142** – 0.012 ± 0.143**</td>
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**P1125**

**Economic impact analysis of a tele-medicine program to improve the quality of spirometry in primary care**

Maria Margali1, Elena Lopez de Santa Maria1, Asuncion Gutierrez1, Juan Carlos Bayon2, Larratza Garcia3, Juan B. Galdiz4, Respiratory Function Laboratory, Cruces Hospital, Barakaldo, Spain; 2Health Technology Evaluation Service, Basque Government, Vitoria, Spain; 3Respiratory Function Laboratory, CIBERES, Cruces Hospital, Barakaldo, Spain

**Introduction:** The tele-spirometry (TS) procedure consists in a computer application (expiro,Osasunet) which allows the control and improvement of the quality of the spirometry (S) carried out in primary care centers (PCC), leading a continuous training of professionals that perform the technique.

**Aim:** To calculate the economic impact of a procedure of TS in the Basque Health Service.

**Objective:** Spontaneous pneumothorax with persistent airleak is a complication that is commonly reported in patients with cystic fibrosis (CF). There is an attributable mortality and considerable morbidity to the complication, resulting in increased health-care utilization and a measurable decline in lung function. We present a series of 11 patients with CF presenting with recurrent pneumothoraces and persistent airleak treated with a Pezzer catheter.

**Material & method:** All 11 patients presented with large pneumothoraces; a 28 French Argyle intercostal catheter was inserted in the 5th or 6th intercostal space, mid axillary line, and connected to an underwater seal drain, resulting in re-expansion of the lung. However, there was persistent air leak on coughing in 7 cases while in the rest 4 cases, the intercostal tube became inactive and smaller pneumothoraces presented as local ones, impossible to be drained by the already in place intercostal catheter. In both groups either with persistent pneumothoraces or recurrent ones we decided to use Pezzer catheters made of Latex instead of Argyle ones.

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**Conclusion:** Our experience supports the use of Pezzer catheter connected to water seal in cases of advanced cystic fibrosis with prolonged air leak, since it promotes pleurisy. It reduces significantly the duration of the intrapleural drainages and the length of the in-hospital stay. The procedure is cost-effective, safe, and easy to perform.

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**P1125**

**Economic impact analysis of a tele-medicine program to improve the quality of spirometry in primary care**

Maria Margali1, Elena Lopez de Santa Maria1, Asuncion Gutierrez1, Juan Carlos Bayon2, Larratza Garcia3, Juan B. Galdiz4, Respiratory Function Laboratory, Cruces Hospital, Barakaldo, Spain; 2Health Technology Evaluation Service, Basque Government, Vitoria, Spain; 3Respiratory Function Laboratory, CIBERES, Cruces Hospital, Barakaldo, Spain

**Introduction:** The tele-spirometry (TS) procedure consists in a computer application (expiro,Osasunet) which allows the control and improvement of the quality of the spirometry (S) carried out in primary care centers (PCC), leading a continuous training of professionals that perform the technique.

**Aim:** To calculate the economic impact of a procedure of TS in the Basque Health Service.
Methods: The study was based on the impact in the funder of the Public Health System and a time horizon of 5 years: 2010-2014. We compared the TS with the usual procedure and calculated the direct costs of the test, the computer platform, training, and staff for their handling. The population was calculated using the prevalence of COPD in Spain (Soriano EIR 2009). Effectiveness was measured as the average of S with quality A+B (ATS).

Results: The COPD population who will perform a S goes from 32,850 to 35,207 (2010-2014). At present (2011) 53 PCC have been involved and 1500 S have been done. At the end of 2014, 275 will be included and, with initial data (Marina 2011 ERS Congress) 3500 S will be done yearly. The cost of one S for the procedure of TS, in 2010, was 48,1€ with an effectiveness of 83%; while for the usual procedure was 37,9€ and 57%. The budget impact analysis, at the end of the year 2014, reflected a decrease of 132,438€, with the assumption that the S of poor quality should be repeated.

Conclusions: The TS procedure involves an increase in the initial budget but produces a saving of the 6.3% (€132,438) in the medium term. For subsequent studies we will have to know the economic impact that this improvement in the quality of the S may have on the diagnosis and prognosis of COPD patients.

P1126
Telemedical care concept for patients with advanced chronic obstructive pulmonary disease (COPD)

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Providing health care services via telemedicine opens new possibilities and offering cost efficient solutions for monitoring, assistance, and even training for COPD patients. An acute exacerbation is a sudden worsening of COPD symptoms. As the disease progresses, exacerbations tend to become more frequent. For the successful long-term treatment of COPD, it is necessary to optimize the management of acute exacerbations.

Patients with severe COPD benefit physical and physiological from moderate fitness training, as it is shown in our rehabilitation program for COPD patients in Marburg. A good understanding of their disease and communication from and to the therapist will improve therapy compliance and patients self-management abilities. Finally patients get more sensitive for symptoms of early stages of exacerbations. The new telemedicine concept of the Tele-Therapist and the innovative locomotion recognition system will be a part of the Tele-Therapist and allows the monitoring of rehabilitation & training@home, and furthermore it will improve therapy compliance and patients self-management abilities. Finally patients get more sensitive for symptoms of early stages of exacerbations. The new telemedicine concept of the Tele-Therapist and the innovative locomotion recognition system will be a part of the Tele-Therapist and that allows to identify the BD response in COPD patients.

Elena Lopez Santa Maria, Nuriis Narima, Ruth Diez, Grupo Atencion Primaria, UrbeCosta, Ezkerketarea, Juan Gallid1, 1Pneumology, Cruces Hospital, Barakaldo, Bizkaia, Spain; 2Pneumology, Cruces Hospital Cibones, Barakaldo, Bizkaia, Spain

Spirometry can be considered a key element in the assessment of COPD patients in primary care centers (PCC). The slow maneuver is not a common practice in such environment. Bronchodilator response (BD) could be understimated if IC is not evaluated.

Aim: Assessing the usefulness of the measurement of inspiratory capacity (IC) in the evaluation of bronchodilator response in COPD patients

P1127
Inspiratory capacity measurement in primary care centers to evaluate bronchodilatation response in COPD patients

Elena Lopez Santa Maria, Nuriis Narima, Ruth Diez, Grupo Atencion Primaria, UrbeCosta, Ezkerketarea, Juan Gallid1, 1Pneumology, Cruces Hospital, Barakaldo, Bizkaia, Spain; 2Pneumology, Cruces Hospital Cibones, Barakaldo, Bizkaia, Spain

Spirometry can be considered a key element in the assessment of COPD patients in primary care centers (PCC). The slow maneuver is not a common practice in such environment. Bronchodilator response (BD) could be underestimated if IC is not evaluated.

Aim: Assessing the usefulness of the measurement of inspiratory capacity (IC) in the evaluation of bronchodilator response in COPD patients in primary care centers.

Material and methods: Transversal, multicenter, descriptive study performed in eight PCC. 113 COPD patients were included. Spirometries were carried out by eight technicians who performed a two days training program in the slow maneuver (IC). We considered as acceptable maneuvers a coefficient of variation in the CI lower 10% and 150 ml in two maximum values of S with a maximum of eight maneuvers in one day. The slow maneuver was performed prior to the forced maneuver (FC). We considered as acceptable maneuvers a coefficient of variation in the CI lower 10% and 150 ml in two maximum values of S with a maximum of eight maneuvers in one day. The slow maneuver was performed prior to the forced maneuver (FC).

Results: 113 patients, 99 H and 14 M, age 65±14.6 years (SD 17.5), and 43% were female. Mean BMI was 27.3 kg/m2 (SD 6.3), and 24% were smoking. The following results are presented as the percentage of all tests meeting the goals per centre: Start of test: BEV <150 ml, varied from 74% to 95% (mean 86%); end of test; PET >6 s, from 23% to 90% (mean 66%); Repeatability of FEV1, pre bronchodilator (<150 ml) varied from 73% to 97% (mean 89%), and post bronchodilator from 79% to 98% (mean 91%).

Conclusion: Achievement of quality goals varied considerably between the centres. These data will be further analysed and established an initial status to compare quality of spirometry after a Spirometry Driving License training.

P1129
Spirometry training courses are not enough to achieve quality spirometry in the community

Maureen P. Swanney, Josh D. Stanton. Respiratory Physiology Laboratory, Christchurch Hospital, Canterbury District Health Board, Christchurch, New Zealand

Community diagnostic spirometry should be performed at the same standard as a respiratory laboratory. In 2008 our 10-year-old training course was altered to include a post-course quality review to qualify for spirometry certification.

Aim: To review the effectiveness of a quality review after spirometry training.

Methods: We audited attendees at our spirometry courses and portfolio submissions. The portfolio required 10 tests and technical comments; spirometry pattern, and quality control logs. We required 90% in all criteria and those who failed could resubmit.

Results: 2-day and refresher spirometry courses were reviewed including 107 practice nurses, 59 occupational health nurses and 27 regional hospital technicians. We found similar trends for the three groups. The portfolio first submission (22%, 30%) and pass rate (33%,62%) for the 2- and 1-day courses respectively were low.

Discussion: The number seeking feedback on spirometry practice was low with 24% submitting portfolios. Poor compliance was probably because spirometry certification is not compulsory in New Zealand. This review suggests a spirometry course alone is insufficient to achieve quality spirometry, or there are deficiencies in our course content or delivery. A failed portfolio provided additional learning because some resubmissions were successful. The low submissions and passes for the portfolios are a concern. We need to encourage excellence in community spirometry and maybe legislation to make spirometry certification compulsory is the way forward.

P1130
Spirometric data quality as assessed by repeatability in COPD exacerbations

Alec Harrison, 1Hardip Kaur Nagra, 1Grant Sowman, 2Deite Price, 3Matthew Brown, 4Paul Feild. 1Clinical Research, AHI Partners, Wallingford, Oxon, United Kingdom; 2Clinical Trials, Vitalograph Ltd, Maidenhead, Berkshire, United Kingdom; 3United Kingdom; 4Translational Sciences, Novartis International AG, Horsham, West Sussex, United Kingdom

Pharmaceutical trials are reliant on accurate data to meet endpoints and eventual registration. Using standardised equipment, well trained technicians [1] and over-
Physician's mistakes in the interpretation of spirometry

Claudio Sorino 1, Nicola Scichilone 1, Annarosa Maspero 1, Vincenzo Bellia 1.
1PRE DI C A.R.E., Associazione per la Prevenzione, Diagnosi e Cure delle Affezioni Respiratorie ONLUS, Palermo, Italy; 2DI.BI.M.I.S., Università degli Studi di Palermo, Italy; 3U.O. Pneumologia, A.O. Sant’Anna, Como, Italy

Background: The most recent ATS/ERS recommendations on lung function testing include a definition of airflow obstruction based on lower limit of normal (LLN) of FEV1/FVC and suggest to measure total lung capacity (TLC) in suspected cases of “pseudo-restriction” (normal FEV1/FVC ratio but concomitant reductions in FEV1 and FVC), that can conceal airflow obstruction if the subject does not exhale long enough.

Aims: To evaluate the skill of physicians in the interpretation of spirometry.

Methods: A questionnaire focusing on the interpretation of five spirograms was administered to 127 physicians (aged 25-67yrs; 39% pulmonologists, 20% geriatrics). The day was advertised in the Trust Talking Point and the Trust Press

Results: Overall, 31% of physicians made at least one mistake in the interpretation of the spirograms administered. The percentage decreases to 15% among physicians and asthma patients visited in the last year.

Conclusions: Inappropriate spirometric interpretation is not rare among physicians and produce overdiagnosis among elderly. Diagnosis by pulmonologists and scientific update of physicians allow to reduce spirometric interpretative errors.

P1132
Finding the missing millions with COPD – Does it work?
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Introduction: Many COPD patients do not receive a diagnosis until it is relatively advanced. It is estimated that for every one patient that has been diagnosed there are four that are not known to the health service. In conjunction with World COPD Day in 2011, our COPD Outreach team promoted this event by performing spirometry on patients, staff and visitors at the main hospital entrance, to raise public awareness and to find the ‘missing millions’.

Aims and objectives: To raise public awareness of COPD and to detect people with undiagnosed COPD.

Method: The day was advertised in the Trust Talking Point and the Trust Press release. Flyers were posted around the hospital. 4 stands were set up in the main atrium of the JCUH, with spirometers and COPD nurse specialists to perform spirometry. Volunteers completed a questionnaire focusing on their smoking history, symptoms of COPD, history of comorbidities and concomitancies to perform spirometry. Individuals with abnormal spirometry were provided a letter for their primary care physicians, to undergo repeat testing or further investigations if appropriate.

Results: Out of the 75 volunteers tested, only 9% (n=7) were noted to have abnormal spirometry results. 5% (n=4) of the volunteers had a prior history of airflow obstruction. Therefore only 4% (n=3) of the volunteers screened were found to have abnormal recordings.

Conclusion: Random screening doesn’t capture a large population of people with abnormal spirometry. Screening needs to be more selective e.g.individuals over the age of 35 with a smoking history or symptoms suggestive of COPD. Where our screening did raise awareness of COPD within the general public, it didn’t diagnose a large number of people with COPD.

P1133
Irreversible airways obstruction on spirometry, does it equate to a diagnosis of COPD?

Dennis Wat, Sarah Haynes, Linda Lukehurst, Joan McWean, Omnor Hampson, Kamlesh Mohan. Community COPD Service, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

Introduction: Irreversible airways obstruction and a post-bronchodilator FEV1/FVC ratio of <70% on spirometry is diagnostic of chronic obstructive airways disease (COPD). Using the above criteria to make clinical diagnosis may potentially overlook other obstructive lung diseases.

Aims: To study the prevalence and characteristics of lung diseases in patients with irreversible airways obstruction.

Methods: The diagnosis of all patients with irreversible airways obstruction seen in our service between August 2011 and January 2012 seen respiratory physicians was retrospectively reviewed. Respiratory diagnosis was made based on clinical history, physiology testing and radiology.

Results: There were a total of 486 referrals; 446 (92%) have COPD and 40 (8%) have bronchiectasis. No other obstructive lung diseases were diagnosed. There are no significant differences between the demographics of the COPD and bronchiectasis groups.

All data expressed as means.

<table>
<thead>
<tr>
<th>COPD</th>
<th>Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>446</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.16</td>
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<tr>
<td>Age, years (range)</td>
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<tr>
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Conclusions: Current guidelines define irreversible airways obstruction as COPD and many of the therapeutic management strategies for COPD are based on the degree of airway obstruction. We have shown that a proportion of patients with irreversible airways obstruction have bronchiectasis. Hence any patients with irreversible airways diseases who are refractory to maximised COPD management should prompt a review of the diagnosis.

P1134
The value of additional testing in physician diagnosed asthma: A prospective pilot study

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Introduction: Asthma is a common, chronic inflammatory airway disease. Signs and symptoms of asthma are not specific, leading to under and overdiagnosis.

In the Zwolle area, general practitioners can refer patients suspected of asthma to the Isala klinieken for spirometry or methacholine provocation testing. However any patients with irreversible airways disease who are refractory to maximised COPD management should prompt a review of the diagnosis.

Aims: To investigate whether in patients with physician diagnosed asthma, a negative methacholine provocation test, additional tests were valuable to establish asthma.

Methods: Primary care patients with a physician diagnosis of asthma but a negative methacholine provocation test, additional tests were valuable to establish asthma.

All data expressed as means.

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nitric oxide (FeNO) was measured. A priori, a diagnostic yield of ≥20% was considered as valuable. The study was approved by the local ethics committee (NL57709.711).

Results: 160 patients were eligible and 51 were interested. Eventually, 36 subjects underwent the research protocol. Three participants had a positive mannitol provocation test (3.8%). Only one (2.8%) subject had a FeNO-value of >30 ppb. Mean sum scores for the BPH were 30.0±(4.0-8.0). After assessment of the results, three participants received the diagnosis of asthma.

Conclusion: In view of the low diagnostic yield found in this study, additional tests did not seem to have significant impact on the diagnosis of asthma.

P1135
Bronchial asthma: New approach to airways functional diagnostics
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It’s known that bioelectrical impedance value depends on electrical current path length and diameter. The aim of the study was to investigate electrical impedance of airways and lung by new technique of polyfrequent electrical impedance analysis using “BIA-lab” software. 39 asthmatics and 20 healthy people at the age of 19-45 years old were examined. There were 24 females in asthmatic group and 11 ones among healthy people. Of the asthmatic patients 10 had a severe asthma, 15 suffer from moderate and 9 ones were with mild form of disease. All patients were examined with physical methods and spirometry tests performed. The polyfrequent electrical impedance technique demanded of 0.9% NaCl airsole inhalation for 1-2 minit to load the airways. The results revealed elevated electrical impedance module values on diapasons of frequencies: 20, 98, 1000, 5000, 10000 and 20000 Hz in asthmatic patients. But we didn’t registered angle ϕ changes. There was a significant correlation between FEV1 and electrical impedance module ζ of airways (r=-0.57; p=0.032).

Conclusion: Polyfrequent electrical impedance analysis, which characterizes the diameter of airways as the main electrical current conductor loaded by 0.9% NaCl airsole, get adiquit esessment of bronchial obstruction in any severity asthmatic patients.

P1136
Acoustic analysis of respiratory sounds in infants with wheezing
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The aim of the study was to determine functional acoustic characteristics of breath by bronchophonographic method (BPG) in infants with wheezing.

Methods: We observed 24 children (2 month-3 years) with wheezing. The patients were divided into two groups (Gr), the Gr1 (n=14) - atopic children and Gr2 (n=10) - non-atopic children. The control group (C) included 27 healthy non-atopic children (2 month - 3 years of age). Computed BPG by computer diagnostic complex “Pattern” (MEI, Russia) (0.2-12.6 kHz) before and after inhalation of salbutamol (BTS) was provided all patients after the disappearance of wheezing. It was used coefficients of general acoustic breath work (ABW) = φ (0.2-1.2 kHz), φ2 (1.2-5.0 kHz), φ3 (5.0-12.6 kHz), representing relation of level ABW in a given frequency range of the level general ABW.

Results: There were significantly more high parameters of general ABW, φ2, φ3 in the patients of Gr1 and Gr2 in comparison with GrC (p<0.05). Patients of Gr1 showed more general ABW then Gr2 (φ2 =<0.01). The parameters of Gr1 and Gr2 also showed the most high amplitude of sounds in high frequency zone (5.0-12.6 kHz) in comparison with GrC (p<0.05). After BTS for the most part of children of the Gr1 (2/3) and 1/2 of the Gr2 showed significant decreasing φ3; the level of φ3 in the Gr1 decreased significantly more in comparison with Gr2 (accordingly 64.4±10.7%; 40.4±10.3%; p<0.05).

Conclusion: These preliminary results showed that the infants after the disappearance of wheezing still demonstrate the significant functional acoustic disorders. It was more expressed at atopic children then non-atopic. It can be important in relation of early debut of bronchial asthma.

P1137
Effect of patient age on response to nebulised salbutamol or ipratropium bromide
Andrew Robson1,2, Alastair Innes1,2, 1Respiratory Function Service, Western General Hospital, Edinburgh, United Kingdom; 2Respiratory Function Service, Royal Infirmary of Edinburgh, United Kingdom

In order to investigate the effects of a patient’s age on their response to nebulised bronchodilators we have carried out a retrospective analysis of our clinical results database. Inclusion criteria for the study were: Age >20 at time of measurement and the presence of airflow obstruction (FEV1/N/C ratio below the lower limit of normal) at baseline measurements. Patients were excluded from the analysis if they were hospital inpatients at the time of measurement, or if they were on oral steroid treatment. After baseline spirometry had been measured, patients received either 2.5mg of salbutamol (SALB) or 0.25mg ipratropium bromide (IPB) via a nebuliser. Spirometry measurements were repeated at 20 minutes (SALB) or 60 minutes (IPB) post administration of bronchodilator. A patient was considered as having a positive response to a bronchodilator if there was an increase in FEV1 >200ml above baseline which was also an increase of ≥12%. Patients were divided into four age groups, shown in Table 1. A total of 11560 patients fulfilled the entry criteria. Of these, 3759 (33%) showed a positive response to a bronchodilator (Table 1).

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Table 1. Change in FEV1 expressed as a percentage of the patient’s predicted FEV1.

There were no statistically significant differences between responses to SALB or IPB in any age group. These results demonstrate that increasing patient age does not diminish the magnitude of a patient’s response to nebulised SALB or IPB.

P1138
Characterization of bronchodilator response by spirometry and plethysmography
Raquel Barros1, Paula Pinho1,2, Cristina Bárbara1,2, 1Pulmonology II Department, CHLN - Hospital Padulo Valente, Lisboa, Portugal, 2Medical Science Faculty, Universidade Nova de Lisboa, Lisboa, Portugal

Background: The bronchodilator response criterion is defined by ATS/ERS as an increase of FEV1 and/or FVC ≥12% and 200 ml, respectively, after the inhalation of a bronchodilator. The aim of this study was to determine lung function (LF) parameters obtained by spirometry and plethysmography, that have significant changes with the administration of bronchodilator, to quantify changes of LF parameters between pre and post bronchodilator, to characterize the response to bronchodilator according to different criteria.

Methods: We studied 52 consecutive subjects who performed LF tests, in which was detected airway obstruction with subsequent administration of bronchodilator. The sample was divided in accordance with the presence or absence of pulmonary hyperinflation (PL).

Results: All parameters increased or reduced after administration of the bronchodilator (p<0.05). Raw and the FEV1 had the largest percentage of differences between the pre and post bronchodilator. For the totality of the sample, the criteria which were able to detect the largest number of subjects with a positive response to the bronchodilator were the increase of FEV1≥12% (63.5%), FEV1/FVC≥20% (46%), Raw>10% (34.6%) and the reduction of Raw>10% (32.7%). For the group without PL the best criterion was the increase of FEV1≥12% (62.2%) and in the group with PL, the increase was in FEV1≥12% (66.7%) and the reduction of RV>10% (66.7%).

Conclusion: This study couldn’t define a specific parameter that was considered “the best” to characterize a positive bronchodilator response, but suggested a combination of several parameters for a correct characterization of airway reversibility.

Abstract P1135 – Table 1. The estimation of ζ. Ottim in asthmatic patients by polyfrequent electrical impedance analysis

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Table 1. Change in FEV1 expressed as a percentage of the patient’s predicted FEV1.
P1139
Pressure supported nasal inhalation improving penetration of particles into the human lung
Keywan Sohrabi1, Damian Liberzetti1, Abas Sobrabi2, Michael Scholtes1, Helmut Hoeftken3, Ullrich Koecher2, Volker Gross1, 1Dept. Biomedical Engineering, TH Mittelhessen University of Applied Sciences; Gießen; 2Interdisciplinary Sleep Disorders Centre Hessen; Philipps University of Marburg; 3Dept. Nuclear Medicine, Philipps University of Marburg, Germany

We here report on a new method to facilitate the pressure supported nasal long-term inhalation. The method is developed and technically realized by company NLI GmbH, Germany. We examined the efficacy of the method by measuring the deposition in nasal and thoracic airways. We used 99mTC-nanocell to identify the activity scintigraphically in various respiratory sections. This study included 10 patients (5 ± 5, s ± age, range 49 to 75 years, presenting several COPD stages (GOLD I-III). The NLI system generated particle sizes from 1-2 µm. The pressure support was adjusted to 10 mbar.

We could show that deposition in the lung periphery by using the pressure supported transnasal method is significantly increased compared with conventional methods. The usual method produced an average nasal deposition of 5.9 MBq and a periphery deposition of 9.6 MBq, whereas NLI method results in an average nasal deposition of 4.2 MBq and a periphery deposition of 12.9 MBq, respectively.

Our study showed that it was possible to penetrate even in peri-inhalatory pulmonary tissue in COPD patients by using the NLI system. In addition, we achieved an enhancement of the thoracic deposition of 99mTc-nanocell, when recorded a reduction of activity in the nasopharyngeal zone. Further clinical trials with drug applications will be necessary to confirm the clinical relevance.

P1140
Is the portable NIOX MINO reliable for screening nasal nitric oxide levels in primary ciliary dyskinesia?
Amanda Harris1, 1Department of Respiratory Medicine, University Hospitals, Southampton, Southampton, United Kingdom; 2NIHR Respiratory Biomedical Research Unit, University Hospital Southampton Foundation Trust, Southampton, United Kingdom; 3NIHR Respiratory Biomedical Research Unit, University of Southampton, Southampton, United Kingdom; 4Primary Ciliary Dyskinesia Research Group, Faculties of Medicine, Clinical and Experimental Sciences, University of Southampton, Southampton, United Kingdom

Background: Nasal nitric oxide (nNO) levels are very low in patients with PCD. nNO is used as a screening test for PCD. The portable NIOX MINO (Aerocrine, Sweden), is now able to make nasal measurements. This study aimed to assess the usability and reproducibility of the NIOX MINO measurements and comparison of MINO and ‘standard’ NIOX flex.

Methods: Paired MINO and Flex readings were taken from 22 participants (3 PCP, 5 asthma ± rhinitis, 12 healthy, 1 CF, 1 nonCF/nonPCD lung disease; age 5-66year) nNO was measured using Flex during breath holding, and using the Nios MINO using nasal aspiration at 2 and 5ml during mouth breathing, three times for each measurement.

Results: One participant was unable to use Flex or MINO, one participant was able to obtain acceptable readouts using the MINO at 5ml/sec but not at 2ml/sec nor Flex. Younger children were able to obtain measurements at 5ml/sec but not 2ml/sec. Within-method there was good inter-participant reproducibility using the Flex and MINO. Between method, nNO levels using the MINO at 2ml/sec were comparable with Flex (p=0.098) but readings using the MINO at 5ml/sec were significantly lower than Flex (p<0.001). PCD patients had extremely low levels of nNO (<50ppb) independent of method. A patient with CF had very low nNO (<50ppb) using Flex and MINO (5ml/sec).

Conclusions: Patients who were able to use Flex could also provide nNO measurements using the MINO at 5ml/sec; younger children were unable to use it at 2ml/sec. Reproducibility of nNO within method was acceptable. Measurements using the MINO at 5ml/sec were low in comparison to Flex, but would still differentiate patients with PCD from healthy controls.

P1141
Effect of airflow obstruction on the measurement of lung volumes
Tara Goddard1, 1Respiratory Research, Respiratory Research Unit, University Hospital, Bristol, United Kingdom

Effective alveolar volume (VA) is considered as a representative of Total Lung Capacity (TLC) in subjects without airflow obstruction. In the presence of airflow obstruction, physiological changes can give rise to discrepancies between TLC and VA.

Aim: To assess whether VA correlates with TLC and ascertain whether these differences are amplified in relation to the increase in severity of airflow obstruction.

Method: Data was analysed retrospectively and divided into 2 groups based on TLC measured by either body plethysmography (pleth) or helium dilution (He). Results were classified by FEV1, using the NICE COPD guidelines 2010. Data was analysed using regression, Bland-Altman and ANOVA.

Results: The magnitude of TLC - VA increased significantly (p<0.001) in relation to the severity of airflow obstruction. Bland-Altman gave a bias of 1.38 and 1.39 for helium and plethysmography respectively. A single equation was derived to predict the differences between TLC and VA:

\[(TLC_{XX} - VA) = 2.98 - 0.024 FEV1%Pred\]

Table 1. TLC and VA difference in relation to severity of airflow obstruction as classified by the COPD guidelines

<table>
<thead>
<tr>
<th>Severity</th>
<th>N</th>
<th>5</th>
<th>25</th>
<th>28</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLCpleth-VA (L)</td>
<td>0.8±0.3</td>
<td>1.3±1.1</td>
<td>1.8±1.1</td>
<td>3±1.6</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>46</td>
<td>47</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>TLCHe-VA (L)</td>
<td>0.9±0.4</td>
<td>1.5±0.9</td>
<td>1.8±0.1</td>
<td>2.9±1.3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: 1. VA underestimates TLC
2. As severity of airflow obstruction increases, the magnitude of discrepancy between TLCpleth and VA and TLCHe, and VA increases
3. Overall, VA is unable to substitute TLC in subjects with COPD, particularly those with more severe airflow obstruction

P1142
Rate and depth of breathing affect multiple-breath N2 washout (MBNW) indices
Noor Al-Khathlan1, 2, Erol Guillard1, Maria Viskaduraki1, 1Kathleen O’Donoghue, 1Respiratory Care, Derriford Hospital, Plymouth, England; 2Research Group, Faculty of Medicine, Clinical and Experimental Sciences, University of Plymouth, Plymouth, United Kingdom

Introduction: MBNW requires little cooperation beyond steady breathing, but some subjects (eg. children) may breathe irregularly. Historical studies examine the effect of changing respiratory rate and depth on ventilation distribution indices1,2 have contradictory findings. We aimed to examine the impact of rate and depth of breathing on Lung Clearance Index (LCI), and 2 indices of ventilation inhomogeneity (Sand and Sncut).

Methods: Each subject performed at least 3 MBNW tests at each of 3 breathing patterns (BP). A visual signal provided a frequency target and an auditory signal guided tidal volume (Vt). We compared mean LCI, Sand and Sncut between the different BP using repeated measures ANOVA. Sensitivity analyses were performed with and without outliers for validation.

Results: We studied 19 healthy adults but excluded 2 for technical reasons. There were significant differences in LCI and Sncut with BP (p<0.001), but no significant differences in Sand (p=0.117). Increasing Vt from 0.6 to 1.0 reduced LCI and Sncut. Increasing frequency from 15 to 30 bpm increased LCI and Sncut.

Table 1. Mean (SD) for indices of ventilatory inhomogeneity

<table>
<thead>
<tr>
<th>BP (Vt, f (bpm))</th>
<th>LCI</th>
<th>Sand</th>
<th>Sncut</th>
</tr>
</thead>
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<tr>
<td>1.0L, 15</td>
<td>7.29 (0.80)</td>
<td>0.011 (0.03)</td>
<td>0.088 (0.037)</td>
</tr>
<tr>
<td>1.0L, 30</td>
<td>7.95 (0.66)</td>
<td>0.016 (0.03)</td>
<td>0.115 (0.056)</td>
</tr>
<tr>
<td>0.6L, 15</td>
<td>8.18 (1.00)</td>
<td>0.021 (0.06)</td>
<td>0.241 (0.208)</td>
</tr>
</tbody>
</table>

Discussion: We confirmed an earlier report on 4 adults that increasing Vt reduces ventilation inhomogeneity within acinar airways1; in contrast we found no effect on Sand. Frequency also influenced some indices of ventilatory homogeneity. We recommend that both Vt and frequency are controlled.

References:

114. Mechanics, muscles and movement: aspects of airway mechanics, respiratory muscle assessment and field exercise tests

P1143
Impulse oscillometry (IOS) cannot detect vocal cord dysfunction (VCD) in asthma
Laurence Ruane1, Kathy Low2, Kenneth Lau2, Peter Holmes1, Paul Finlay1, Phillip Burdett2, Paul Gey3, 1Dept Respiratory & Sleep Medicine, MMC, Clayton, VIC, Australia; 2Diagnostic Imaging, MMC, Clayton, VIC, Australia; 3Monash Institute of Medical Research, MMC, Clayton, VIC, Australia

Vocal cord dysfunction (VCD) complicates asthma and can be detected using
320-slice CT larynx (Low et al, Am J Resp Crit Care Med. 2011). However, this involves radiation and impulse ocliosmetry (IOS) may be a safe, convenient and non-invasive method to diagnose the condition. We assessed whether IOS may be able to identify VCD correctly diagnosed by CT larynx.

Methods: 42 patients with asthma, matched for age, body mass index (BMI) and baseline pulmonary function parameters were studied. 21 had evidence of VCD detected by 320-slice CT larynx. All patient had spirometry and IOS immediately following CT and relevant parameters were compared between patients with and without VCD.

Results: The groups were well matched but none of the IOS measurements differed between the groups. Mean values were virtually identical for all parameters and post-bronchodilator values were also similar.

Mean and SD of PFVs and IOS parameters were similar.

P1145

Relationship between FVC and respiratory muscle strength in patients with amyotrophic lateral sclerosis (ALS)

Guilherme Fregonesi,1 Palomoma Russell Saldanha Araújo1, Tahitana Lindemberg Ferreira Macêdo1, Mario Emílio2, Selma Bruno1, Vanessa Resquest1, Armelle de Fátima Dominela de Andreiá,1 2Physical Therapy, Federal University of Rio Grande do Norte, Natal, RN, Brazil; 2Neurovascular Disease Outpatients Clinics, Hospital Universitário Onofre Lopes - Federal University of Rio Grande do Norte, Natal, RN, Brazil; 3Physical Therapy, Federal University of Pernambuco, Recife, PE, Brazil.

Aim: The aim of this study was to analyze the relationship between Forced Vital Capacity (FVC) and respiratory muscle strength in Amyotrophic Lateral Sclerosis (ALS) patients and healthy subjects.

Methods: We study 31 ALS patients and 28 healthy subjects by spirometry and respiratory muscle strength measurement. We assessed whether IOS may be a safe, convenient and non-invasive method to diagnose the condition. We assessed whether IOS may be a safe, convenient and non-invasive method to diagnose the condition. We assessed whether IOS may be a safe, convenient and non-invasive method to diagnose the condition.

Discussion: In spite evidence that IOS may differentiate upper and lower airway obstruction, this study shows conclusively that the non-invasive IOS technique cannot identify upper airway narrowing associated with VCD in asthma.

Conclusion: The six-minute walking test (6MWT) is a simple method to evaluate the exercise capacity in patients with pulmonary diseases. The information about exercise ability of patients who underwent antituberculosis treatment is limited. The aim of the study was to evaluate the relationships between the 6MWT, pulmonary function, and quality of life (QoL) in these patients.

Methods: Seventy patients were included in the study. All the patients performed 6MWT. Pulmonary function was studied by spirometry and plethysmography. QoL was studied by St. George’s Respiratory Questionnaire (SGRQ) and UCSD Shortness of Breath Questionnaire (SOBQ).

Results: Seventy patients were included in the study. All the patients performed 6MWT. Pulmonary function was studied by spirometry and plethysmography. QoL was studied by St. George’s Respiratory Questionnaire (SGRQ) and UCSD Shortness of Breath Questionnaire (SOBQ).

Conclusions: The six-minute walking test may be a useful method of exercise capacity in patients cured of pulmonary tuberculosis.

P1146

Pulmonary Function and 6MWT in Patients with Pulmonary Tuberculosis and Correlates with Pulmonary Function and QoL.

Conclusion: The regression equations demonstrated better predictive capability when compared to Enright’s equations, thus supporting the requirement for disease specific regression equations.

Subjects: 352 patient’s data collected. 5 classified with mixed lung disease excluded from analysis due to small sample size. Of the remaining 347 patients, 38 (10.9%) identified as restrictive, 158 (43.5%) obstructive and 151 (43.5%) normal (n=500 p=0.001) and normal (0.500 p=0.001) subjects. Validation analysis demonstrated more accurate disease specific walk distance prediction (Bland-Altman) than Enright (1998) predicted equations.

Conclusion: The regression equations demonstrated better predictive capability when compared to Enright’s equations, thus supporting the requirement for disease specific regression equations.
P1148 Alterations in respiratory mechanics and pulmonary ventilation induced by Chlamydia psittaci
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Chlamydia psittaci (Cp) is capable of inducing acute pulmonary zoonotic disease (psittacosis) or persistent infection occurring in patients with pulmonary emphysema and/or COPD. To elucidate the pathogenesis of this infection, a defined respiratory model in calves was recently introduced [1] which resembles the situation in humans more closely than mice. This investigation was undertaken to identify pulmonary dysfunctions induced by Cp.

Eighteen calves were inoculated with Cp, whereas another 18 control calves received an uninfected cell culture. Respiratory disorders were characterized non-invasively applying pulmonary function tests from human medicine (i.e. impulse oscillometry and capnography) to spontaneously breathing animals from 7 days before challenge until 14 days post inoculation. Compared to control calves, calves exposed to Cp had significantly increased respiratory resistance at low frequencies (< 5 Hz), while respiratory reactance at all frequencies (3 - 15 Hz) decreased significantly, indicating that both obstructive and restrictive pulmonary disorders were induced by the pathogen. In spontaneous breathing, expiration was more impaired than inspiration. Alveolar hypoventilation was confirmed by decreased tidal volume, increased dead space ventilation, increased FRC, and decreased end-tidal CO2.

In conclusion, this bovine model has been found to be suitable for studying functional host-pathogen interactions in the mammalian lung. Pulmonary dysfunctions assessed in this model provide relevant insights into the pathophysiology of acute respiratory illness induced by Cp. [1] Reinhold P. et al. (2012) PLoS ONE 7(1): e30125.

P1149 Respiratory muscle strength after inhaled short acting beta-agonist administration in stable COPD patients
Alina Cretu, Diana Ionita, Irina Pele, Daniela Jipa, Miron Bogdan. Pulmonary Rehabilitation Center, National Institute of Pneumology, Bucharest, Romania

Background: Complex mechanisms are involved in dyspnoea and exercise intolerance in COPD patients, one of these being the increased mechanical work of respiratory muscles.

Aim: To evaluate the increase in respiratory muscle strength after administration of salbutamol in COPD patients

Subjects and methods: Stable COPD patients performed respiratory muscle strength measurements (maximal inspiratory pressure MIP, maximal expiratory pressure MEP) and body-plethysmography (residual volume RV, functional residual capacity FRC). MIP and MEP were again measured 30 minutes after 400 micrograms of salbutamol was administered.

Results: Twenty stable COPD patients were evaluated: stage II-IV GOLD, mean age 58.5 (±9) years, 17 males, mean FEV1 1.29 L (42.6% of predicted).

Mean respiratory muscle strength values were: MIP 73.8 (±22) cm H2O and H2O and MEP 132.2 (±35) cm H2O. Thoracic hyperinflation was present in all cases: mean RV 231.8% and mean FRC 168.9% of predicted.

A slight increase in respiratory muscle strength was seen after salbutamol administration, without reaching statistical significance: mean MIP value increased to 76.4 cm H2O (by 2.6 cm H2O, p<0.05), mean MEP value increased to 133.15 (by 0.9 cm H2O, p<0.05).

Conclusion: The administration of 400 micrograms of inhaled salbutamol in our stable COPD patients did not significantly improve respiratory muscle strength. Further studies are needed on a larger population of COPD patients with different disease phenotypes.

The results of this study provide a reliable reference equations of MIP and MVV for health Brazilian population from 20 to 80 years old.

P1150 EMG-pattern of respiratory muscles during Muller manoeuvre: Effect of body posture
Marina Segrizbaeva. Laboratory of Respiration Physiology, Pavlov Institute of Physiology, St. Petersburg, Russian Federation

The voluntary maximal inspiratory effort is the manoeuvre requiring participation of the patient, recruitment and coordination of different respiratory muscles. A study was undertaken to describe the pattern of recruitment of inspiratory muscles used in the generation of maximal inspiratory effort in different body postures. 10 young normal human participants took part in this study. Maximal inspiratory mouth pressure (MIP) during Muller manoeuvre was measured in the standing, sitting, right side lying (RSL), left side lying (LSL), supine and head-down-tilt (HDT – 30°) posture. The level of electrical activity of the diaphragm (D), parasternal (PS), sternocleidomastoid (SM) and genioglossus (GG) was studied during Muller manoeuvre in each of body postures. MIP in the standing position was 105.3±12.0 in men and 59.9±10.1 cm H2O in women (control). Both in men and women MIP did not significantly differ from control in the sitting, supine, RSL and LSL. But MIP in HDT was lower by 23% and 27% compared with control in men and women respectively. Integrated EMG activity of D during Muller manoeuvre was near the control in sitting, supine, RSL, LSL and significantly greater in HDT compared with standing. On the contrary, the PS and SM showed the highest level of activation during Muller manoeuvre in standing position, but its activation was significantly lower in HDT (P <0.05). EMG of GG was significantly greater in supine position and HDT while its activation was lower in sitting, LRS and LLS. We conclude that maximal inspiratory effort reflects a complex interaction between several muscle groups and changing in body posture from standing to HDT might influence the activation of different muscles resulted in lower MIPs in HDT.

P1151 Maximal respiratory pressure and maximal voluntary ventilation in Brazilian health population: A multicentre study
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Maximal respiratory pressures (MRP) and maximal voluntary ventilation (MVV) are worldwide measures used to assess respiratory muscle strength and endurance. Although there are references values established to Brazilian population different methodological procedure used in previous studies could contribute to wide variation in values published. This study was conducted in three centers in Brazil, Natal-RN, Recife-PE and Piracicaba-SP. Subject was evaluated in relation to anthropometric parameters, physical activity profile, maximal inspiratory/expiratory pressure and MVV. Correlation and multiple linear regressions were used to predicted male and female MRP and MVV equations. We studied 244 subjects (114 male/30 female) distributed in different age group from 20 to 80 years old. The results showed a significantly positive correlation between MIP/MEP and height in female; negative correlation with age in both genders. A positive correlation between MVV, weight and height in male were found; in female, we found a positive correlation with height and negative correlation with age. In the multiple linear regression analysis only age continued to have an independent predictive role for dependent variables in MIP/MEP and MVV.
with physical inactivity. If physical inactivity does depend on muscle strength, a correlation between muscle strength and osteoporosis must exist.

**Objective:** To evaluate how strong peripheral muscle strength is related to the loss of BMD in our COPD population.

**Methods:** Data of 11 patients in a pulmonary rehabilitation program is analysed. BMD at the lumbar spine and hip is determined by dual-energy X-ray absorption (DXA). DXA is performed based upon the patient’s risk profile (long history of corticosteroids). The BMD is expressed as a T score. Isometric quadriceps force (iQF) is assessed by a computerized dynamometer during a voluntary maximal isometric contraction with the hip at 90° and the knee at 60° flexion. The highest value is taken.

**Results:** A significant correlation is found between T score lumbar spine and iQF in 8% of normalised values (R=0.627; p<0.039). iQF is not related to the T score of the hip (p=0.385).

**Conclusions:** Lower BMD in the lumbar spine seems to relate with lower iQF in our COPD population. Strengthening of those quadriceps muscles in this specific COPD patients must therefore best be done in an upright, weight-bearing position during closed chain exercises to stabilise or increase the BMD of the lumbar spine.

**P1153**

**The effect of lung hyperinflation on respiratory muscle strength in COPD patients**

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**Introduction:** Many COPD patients exhibit hyperinflation, due to premature closure of the airways and loss of lung elastic recoil, which impairs the respiratory muscle function.

**Aim:** To assess the relationship between the degree of lung hyperinflation and respiratory muscle strength.

**Methods:** 46 consecutive male COPD patients referred to the hospital’s pulmonary rehabilitation program underwent lung function testing and assessment of respiratory muscle strength at baseline.

**Results:** We observed a significant negative relationship between iQF and MEP vs the degree of hyperinflation.

<table>
<thead>
<tr>
<th>GOLD stage</th>
<th>n</th>
<th>Age (yrs)</th>
<th>FEV1 (%p)</th>
<th>RV/TLC (%)</th>
<th>MIP (%p)</th>
<th>TLC (%p)</th>
<th>MEP (%p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8</td>
<td>67</td>
<td>59</td>
<td>47</td>
<td>98</td>
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<td>104</td>
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<td>66</td>
<td>38</td>
<td>59</td>
<td>80</td>
<td>122</td>
<td>83</td>
</tr>
</tbody>
</table>

**Conclusion:** Because anaesthesia is often required in respiratory research of rodent species, whose influence on respiratory mechanics should be investigated utilizing the non-invasive Impulse Oscillometry (IOS) test.

**Material and methods:** Ketamine/medetomidine combination (study a), followed by urethane two weeks later (study b), were applied for anaesthesia in ten female rats. IOS measurements were taken before and 30 minutes after drug application in each study.

**Results:** Breathing frequency and tidal volume decreased significantly due to anaesthetics in both studies. Results of spectral resistance (R) and reactance (X), all in kPa L⁻¹ s⁻¹, as well as level of significance are presented in table 1.

**Table 1.** Medians (lower; upper quartiles) of R and X before and after medication of ketamine/medetomidine (study a) and urethane (study b)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study a before</th>
<th>Study a after</th>
<th>Study b before</th>
<th>Study b after</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5</td>
<td>5.6 (2.6; 6.3)</td>
<td>6.6 (6.1; 7.0)*</td>
<td>6.1 (5.7; 6.4)</td>
<td>6.3 (6.1; 6.8)</td>
</tr>
<tr>
<td>R10</td>
<td>7.2 (6.1; 7.7)</td>
<td>5.8 (5.4; 6.0)**</td>
<td>6.9 (6.7; 7.0)</td>
<td>6.2 (6.6; 6.5)*</td>
</tr>
<tr>
<td>R15</td>
<td>5.3 (5.1; 6.3)</td>
<td>4.7 (4.4; 5.0)*</td>
<td>5.3 (2.5; 5.6)</td>
<td>4.9 (4.7; 5.0)**</td>
</tr>
<tr>
<td>X10</td>
<td>–2.9 (–3.1; –2.5)</td>
<td>–3.0 (–3.7; –2.6)</td>
<td>–3.7 (–3.9; –3.5)</td>
<td>–4.0 (–4.6; –3.7)</td>
</tr>
<tr>
<td>X15</td>
<td>–4.1 (–4.7; –3.4)</td>
<td>–3.4 (–3.7; –3.0)*</td>
<td>–5.0 (–5.3; –4.9)</td>
<td>–4.1 (–4.4; –3.9)*</td>
</tr>
<tr>
<td>X20</td>
<td>–5.4 (–5.7; –3.8)</td>
<td>–3.6 (–5.0; –3.1)*</td>
<td>–5.2 (–5.4; –5.1)</td>
<td>–4.1 (–4.6; –3.8)*</td>
</tr>
</tbody>
</table>

**Conclusion:** Anesthesia in rats leads to changes of their breathing pattern and various impedance parameters as well. These investigations are only possible using a non-invasive and non-cooperative technique like the IOS. The authors appreciate the financial support of the German Federal Ministry of Economics (Berlin Germany, registration number IW 070139).

**P1154**

**Detection of bronchial asthma using impulse oscillation system (IOS) in patients with normal spirometry**

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**Background:** The gold standard for the diagnosis of bronchial asthma in patients with a normal spirometry is currently the bronchial provocation test. IOS is a promising technique to assess airway function being simple to perform and able to quantify changes in peripheral airway resistance undetected by traditional spirometry.

**Aim & methods:** In order to assess whether IOS could be useful in detecting asthma in subjects with a normal spirometry, 23 (9 female, mean age 37 SD 17 years) non-smoking patients referred for methacholine challenge testing (MCT) for chronic rhinitis or cough were studied by spirometry and IOS prior to MCT. All tests were performed on the same day in separate study rooms by different technicians blind to the results.

**Results:** Mean baseline FEV1 was 87 SD 10% of predicted. Ten subjects had a positive MCT with a mean PD20 dose of 0.5 SD 0.4 mg ml⁻¹. IOS showed higher baseline R5-20Hz values in MCT+ subjects (0.86±0.71 vs 0.27±0.14 cmH2O/l/s; p<0.05) and higher baseline Peripheral Airway Resistance (Rp) (2.6±1.3 vs 1.4±0.85 cmH2O/l/s; p<0.05). The was a strong negative correlation between baseline Rp and PD20 (r=0.77, p<0.009). The area under the Receiver Operative Curve (ROC) showed a accuracy of 0.78 (C.I.=0.66±0.88) using a cut-off value of 3.01 cm H2O/l/s.

**Conclusion:** We conclude that Rp may be a useful marker in predicting MCT response and provide a screening tool for detecting bronchial asthma.
measurements were strongly related to each other with $r=0.971$ and FeNO (HypAir) ppb; both measurements did not differ between them (paired t-test $p=0.25$). The fumarate combination with other combination products

Comparison of the fine particle fraction of fluticasone propionate/formoterol $\pm$ 80/400 mcg taken in each subject using both analysers, and the mean was taken as a result. flow restrictor. At least three measurements that did not differ much than 5% were

order according to ERS/ATS recommendations. The subjects exhaled air through a combination of the inhaled corticosteroid, fluticasone propionate, aerosol inhaler (FLUT/FORM). As changes in flow rate have been shown to affect the

calculation of different patterns of topographical heterogeneous obstruction, estimated $R_{aw}$ is in DM on the average 4.3fold higher than in PM. Conclusions: The classical model of parallel connected bronchi of each generation disregards the topography of obstruction that leads to falsely decreased $R_{aw}$ estimation. Spatial heterogeneity of the obstruction is an important factor of $R_{aw}$ increase.

P1160 Processing optimization of exhaled breath condensate previous to the analysis by mass spectrometry
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Respiratory Medicine Unit, CHU A Coruña. Biomolecular Research Institute A Coruña(INIBIC), A Coruña, Spain

The Exhaled Breath Condensate (EBC) is a representative and non-invasive lung sample so the determination of its proteome might be useful to find disease-specific biomarkers. Most of the works published up to the date about this issue describe several problems to identify protein from EBC. Aims: To evaluate three methods of EBC concentration as a pre-processing step for the use of mass spectrometry protein identification. To optimize the storage conditions for the EBC.

Methods: EBC samples were collected with the EcoScreen Device (Viasys GmbH, Germany) and stored at -80°C. Protein quantification was performed by BCA methodology. Sample concentration was performed by lyophilization, centrifugation with Amicon Ultra-2 filters (Millipore) or Reverse phase chromatography with POROS R2 resin. Proteins were identified by mass spectrometry. To optimize the storage conditions for the EBC.

Results: After processing, there were no differences between lyophilization and filtration which yielded an insufficient concentration for mass spectrometry (64.38±25.97; average g/mL±standard deviation). Protein purification was performed by BCA methodolopy. Sample concentration was performed by lyophilization, centrifugation with Amicon Ultra-2 filters (Millipore) or Reverse phase chromatography with POROS R2 resins. Proteins were identified by mass spectrometry.

Discussion: Protein concentration by reverse phase chromatography is necessary to determine the EBC proteome by mass spectrometry. EBC samples should be analyzed within one year period to avoid protein degradation. This optimization is crucial to determine the protein profile in EBC samples from different respiratory pathologies.

P1161 Clinical usefulness of the measurement of percutaneous partial pressure of carbon dioxide in respiratory patients
Takeshi Tanaka1, Takehiko Noma1, Keizo Aita1, Hiroyuki Fukazawa1, Masaki Hagiya2, Kenmesso Kadono2.

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Background: Arterial oxygen (PaO2) and carbon dioxide gas partial pressure (Pco2) conditions due to many causes of respiratory diseases are very important to the respiratory patients. But in practice, usually on admission of the patients,
many clinicians tend to omit blood gas analysis, because this is an invasive, painful, expensive examination and not essential for the adaptation of medical insurance on the treatment of respiratory patients. So, we used a percutaneous carbon dioxide partial pressure (PCO₂) analysis meter (TOSCA™) and measured PCO₂ of respiratory patients and compared these results with the conventional blood gas meter.

**Objectives:** Forty of our respiratory patients who admitted to our clinic because of symptoms. Ten chronic obstructive pulmonary disease, ten pneumonia, ten interstitial pneumonia, ten lung cancer patients were enrolled. We gave them the information on PCO₂ and the benefits of the procedure. The patients gave their consent to participate.

**Methods:** The electrocardiogram (ECG) was performed on the patients’ ear pad. Five patients, after checking their respiration and if they were stabilized, PCO₂ measurements were obtained. The PCO₂, percutaneous 0.5 saturation (SpO₂) and pulse rate on the display were checked and recorded. Then we measured the PCO₂.

**Results:** The correlation between all PCO₂ and PaCO₂ was R²=0.97. If we mentioned full and detail, chronic obstructive pulmonary disease (R²=0.97), pneumonia (R²=0.99), interstitial pneumonia (R²=0.95), lung cancer (R²=0.96) and all data had significant correlations.

**Conclusion:** The measurement of PCO₂ by the TOSCA™ is non-invasive and provides very important information on the patient’s respiratory conditions before the treatment of diseases.

115. Physiotherapy and rehabilitation strategies in respiratory diseases and beyond

P1162

**Aerobic exercise training cannot be prescribed based on predictive heart rate equations in moderate or severe asthmatic patients**

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**Background:** Recent studies have shown that physical training improves exercise capacity and health related quality of life (HRQoL) in asthmatics; however the best way to prescribe aerobic exercise intensity in these patients remains poorly known.

**Objective:** To evaluate if predictive heart rate equations can be used to prescribe exercise intensity in subjects with moderate or severe asthma.

**Methods:** Ninety-eight adults with moderate to severe asthma aged 36 (ranging from 24–53) years were submitted to a symptom-limited cardiopulmonary exercise testing (CPET) and anaerobic threshold (AT) was determined by two independent experienced researchers. The association and agreement between maximum heart rate (HRmax) achieved on CPET and age-predicted Tanaka’s maximum HR (177.0 × age) was observed, respectively, by Pearson’s correlation and intraclass correlation coefficient. Similar analysis was applied between HR determined by CPET and heart rate reserve (FCrest + 0.5 × HRmax-HRrest), widely used to estimate exercise intensity at AT.

**Results:** Maximal HR obtained by CPET was significantly lower than age-predictive equation (177.0 vs. 182.8 bpm, respectively, p<0.05). There was a weak correlation (r=0.001; ICC=0.06) between the achieved and estimated HRmax. At anaerobic threshold the HR obtained by CPET was similar to HR predicted equation (128 vs. 131 bpm, respectively, p>0.05). However, no correlation or agreement was observed between the HR (p>0.05).

**Conclusion:** Exercise prescription for adults with moderate or severe asthma should be determined directly by an exercise test instead of using age-predicted equations.

P1163

**Evidence for single limb exercise in patients with COPD or chronic heart failure**

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**Background:** Although single limb exercise (SLE), i.e. training using one arm and/or one leg at a time, has been used in patients with COPD or chronic heart failure (CHF) the evidence for SLE has not been evaluated systematically and remains unclear.

**Objectives:** Our hypothesis was that SLE is beneficial for patients with COPD or CHF. The aim of this systematic review was to investigate the current evidence for SLE compared to any comparator and regarding exercise capacity, quality of life (QoL) or dyspnea in patients with COPD or CHF.

**Methods:** CENTRAL, PubMed and PEDro databases were searched for randomized controlled trials fulfilling inclusion criteria. Extraction of data, evaluation of study quality using the PEDro scale and the Cochrane risk of bias tool was performed by two review authors. Data and evidence for SLE were summarized in accordance with GRADE guidelines.

**Results:** Six RCTs, (two in COPD, and four in CHF) met the inclusion criteria. COPD: Low quality evidence indicates improved exercise capacity but no evidence on dyspnea after one-legged cycling compared to two-legged cycling. CHF: Low quality evidence indicate improved exercise capacity after single limb strength training compared to a control and two-legged cycling and improved QoL compared to a control. Meters walked and some QoL outcomes improved more after two-legged knee extension compared to one-legged knee extension. No differences between regimes on other exercise capacity and QoL outcomes was found.

**Conclusions:** The strength of the overall evidence to support the use of SLE regimes compared to other exercise regimes or control in patients with COPD or CHF is low and further research is requested.

P1164

**Changes in heart rate and blood pressure variability during and following a period of slow breathing**

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Hypertension is a complication of COPD and there is interest in developing non-pharmacological ways of managing the problem. Training with slow breathing is effective in reducing blood pressure but the physiological mechanism underlying this action is not known. Slow breathing is particularly effective in modulating heart rate variability (HRV) and also affects diastolic blood pressure variation (DBPV). We hypothesised that slow breathing would modify HRV and DBPV and the effects would persist for some time, being the basis of a training adaptation which might be of benefit to COPD patients. Eleven subjects (8 male, age 28-67 years) were recruited, 6 normotensive and 5 with well managed essential hypertension. Subjects breathed at 12 breaths per minute (brpm) then at 6 brpm and finally at 12 brpm, each or 10 min. There were no differences in mean heart rate, systolic or diastolic blood pressures with breathing rate but there were major changes HRV and DBPV during slow breathing, with an increase of power at low a and a decrease at high spectral frequencies. Heart rate was entrained to breathing in younger and normotensive subjects at 12 brpm while the older and hypertensive subjects showed little evidence of this until breathing at 6 brpm. In all subjects the spectral changes developed and resolved over several minutes following each change in breathing rate; DBPV changed more slowly than HRV.

Slow breathing modulates vagal and sympathetic activity which takes time to develop and resolve indicating neuronal plasticity which, with repetition, could be the basis of the anti-hypertensive action of slow breathing training.

P1165

**Effect of percutaneous transluminal coronary angioplasty on deep breathing heart rate variability**

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**Background:** Coronary angioplasty (PTCA) is a common treatment method in patients with coronary heart disease, but its effects on deep-breathing heart rate variability (HRV) has not been well established.

**Objective:** The aim of the study was to analyse deep breathing heart rate variability, which reflect the sympathovagal control of heart rate in patients before, after 1 and 30 days of elective PTCA.

**Methods:** The study consisted of 10 consecutive patients (7 men, 3 women) with age of 62±11.6 years, single-vessel coronary artery disease (CAD) who underwent elective coronary angioplasty with stent implant. Heart-rate variability (HRV) was obtained at rest (spontaneous breathing) and during respiratory sinus arrhythmia maneuver (RSA-M) by heartfrequency (Polar S810) before, after 1 and 30 days of PTCA. RSA-M consisted of deep-breathing in 6 respiratory cycles per minute. HRV analyses were obtained by the time, frequency-domain (high frequency- HF, and low frequency-LF) and non-linear methods (triangular R-R intervals-RRin and Approximate Entropy -ApEn).

**Results:** The PTCA did not induce changes during deep-breathing when compared to spontaneous breathing in the time domain indices (P>0.05). However, before
of PTCA higher values of BF/AF ratio were observed (P<0.05). Interestingly, deep-breathing increased RR-tri only before and after 1 day of PTCA (P<0.05) and ApnI decreased only after 1 month (P<0.05).

**Conclusion:** Patients with CAD presented sympathetic activation before PTCA, which produced altered responses during deep-breathing after the procedure.

**P1166**

Does music affect fatigue perception during exercise in COPD patients? 

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**Introduction:** Performing daily life activities is difficult for many COPD patients. Pulmonary rehabilitation (PR) is useful to improve exercise tolerance. If dyspnea remains the primary debilitating symptom associated with COPD, fatigue is also frequent in patients suffering from lung disease, especially during and after physical activity. The influence of music on dyspnea was previously reported. The aim of this preliminary study was to observe the influence of music on fatigue during pulmonary rehabilitation sessions.

**Material and method:** 12 COPD patients regularly attending our PR program were recruited (age:63.9 y.o. ± 13.0). Fatigue was measured during two sessions by a questionnaire comprising 8 items. Investigation was performed during two separate sessions with or without music. PR exercises were the same during both sessions.

**Results:** There was no difference in total fatigue score (16.7±4.7 vs 17.1±5.0; p = 0.58). The 8 items were not different between both sessions. Except for two items, anxiety and activity 63.7%, impact 35.6%.

**Conclusion:** In this preliminary study, we have shown that music does not influence fatigue perception during a PR session.

**P1167**

The results of a rehabilitation program including inspiratory muscle training in COPD patients

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**Background:** Respiratory muscle impairment could contribute to dyspnea, exercise intolerance and diminished quality of life in COPD patients.

**Aim:** To evaluate the results of a pulmonary rehabilitation (PR) program that includes inspiratory muscle training (IMT) in COPD patients.

**Methods:** Activity 63.7%, impact 35.6%. The ongoing review method of these patients needs further consideration.

**Results:** We included 20 COPD patients, stage II-IV GOLD, mean age 63 years, 16 males, mean FEV1 1.27 L (44.7% of predicted). Mean values for the measured parameters were: MIP 63.9 cm H20, 6MWT distance (6MWTD) 407.1 m, dyspnea MRC score 3.05 points and SGRQ score 46.5 (symptoms: 10.1; activity: 8.4; impact: 27.1). There was a significant improvement in the following mean values at the end of PR program: MIP increased by 9.6 cmH2O (p=0.005) and 6MWTD by 55 m (p=0.001); dyspnea score decreased by 0.75 (p=0.001). SGRQ score un-significantly decreased by 4.9 points (p=0.05). A greater improvement of MIP was seen in stage III-IV patients (12.5 cm H20) compared to stage II patients (8.6 cm H20).

**Conclusions:** Our rehabilitation program including general and inspiratory muscle training led to a significant improvement in inspiratory muscle strength, walking distance and symptoms. The greater improvement in respiratory muscle strength in severe and very severe COPD patients will be verified in a larger population study.

**P1168**

Chronic obstructive pulmonary disease (COPD) patient experiences of pulmonary rehabilitation (PR): A longitudinal qualitative UK study

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**Introduction and Background**

Attendance at PR in the UK is sub-optimal. Reasons for this have been explored. However, patient experiences have rarely been explored longitudinally through a PR programme regardless of patient participation. Furthermore, limited research has been performed in patient experiences of PR in primary care.

**Aims and objectives:** This research aimed to explore COPD patient experiences before and after PR, whether they completed, did not attend, or dropped out of PR.

**Method:** Fifteen participants were interviewed before and after PR regardless of patient completion. COPD patients were recruited from 2 Primary Care Trusts in the UK. Data were collected during semi-structured interviews using phenomenological research methodology.

**Results:** Of the 15 participants, 8 completed and 7 did not complete PR. Participants experienced uncertainty with regard to COPD, the care they received, PR, and their comparison with others. Prior to PR, uncertainty manifested itself in patients’ experience of panic and vulnerability. The experience of uncertainty reduced following PR programme completion. Non-completers seemed angry with their care, less able to cope with comorbidities or wished to remain naïve regarding COPD.

**Conclusion:** Patient experiences of PR in primary care have been explored. Uncertainty was experienced by participants prior to PR which reduced following PR completion. Completers appeared better able to cope with comorbidities than non-completers. The importance of social comparison in PR requires further research.

**P1169**

The effectiveness of carrying out 6 month and 1 year re-assessments for respiratory patients post pulmonary rehabilitation

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**Introduction:** Pulmonary Rehabilitation (PR) Re-assessment groups are offered at 6 months and 1 year post completion of PR. The purpose is to review patients current health status, monitor exercise tolerance, mood and quality of life and check compliance with self management skills taught in PR.

**Aim:** To determine the level of attendance at 6 months and 1 year re-assessments in order to establish whether this is an effective method of review, both for the patient and Community Respiratory Team.

**Methodology:** All patients who completed PR were invited to re-assessments at 6 months and 1 year post PR. The number of patients who attended were recorded.

**Results:** 262 patients completed PR between January 2009 and December 2012. 40 patients were excluded from assessments and analyses at the 6 months re-assessments due to staff shortages and severe weather. 13 patients (6 at 6 months and 7 at 1 year) had died and also excluded.

**Conclusion:** These data indicate a drop of 23% in attendance at the 1 year re-assessment (from 6 months) therefore suggesting this may not be the most effective method of review and furthermore provides reasonable evidence to support a re-evaluation of the 1 year re-assessment. There is cause to ensure review of those not attending reassessments as they are at high risk of poor self management and the ongoing review method of these patients needs further consideration.

**P1170**

One year follow-up after a program of physical activity promotion in smokers: Preliminary results

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**Background:** Programs to promote the increase of physical activity in daily life (PADL) have generated growing interest aiming to prevent the deleterious effects of physical inactivity. Recent literature has shown that a short-term protocol using pedometers (or step counters) was able to increase PADL in apparently healthy smokers. However, the long-term effects of such a protocol were not yet studied.

**Objectives:** To evaluate the results of a 1-year follow-up after a program aimed at increasing PADL in smokers.

**Methods:** 43 smokers without lung function impairment were studied (20 males; 52 [48-58] years; 20 [20-30] cigarettes-day). The 5-month program used infor- mative booklets and pedometers in order to achieve a goal of 10000 steps/day. Subjects were assessed at baseline, immediately after the end of the program, six months and one year later. Outcomes were PADL assessed for one week at each assessment point, besides five-minute walking distance (6MWMD), smoking habits and quality of life.

**Results:** Immediately after the program there was significant increase in steps/day (from 4379 [3476-5632] to 9563 [5632-11021] vs 10694 [8402-12482]; mean improvement of 2641 [452-4364] steps/day), together with improvements in the 6MWMD and general health status (p<0.05 for all). However, over the 1-year follow-up period (n=14) there was progressive reduction in steps/day when compared to the assessment at the end of the program (after six months: -599 [-3476-1707] and after one year: -1876 [-4297-440]).

**Conclusions:** Improvement in PADL obtained immediately after a program of physical activity promotion in smokers does not seem to be maintained over the long term. Strategies for maintaining these gains are needed.
P1171
Breathing exercises for cardiac surgery patients – A national survey of clinical practice

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There are differences in routines concerning recommendations of breathing exercises for cardiac surgery patients in EU countries. Physicians may be influenced by scientific literature, local routines, or current practice.

Aim: The aim of this national survey was to determine current practice of chest physiotherapy and breathing exercises for cardiac surgery patients in Sweden.

Method: A total population sample was identified and postal questionnaires were sent to the 33 physiotherapists working at the departments of thoracic surgery in Sweden. Structured and open-ended questions were asked about the routine care of patients undergoing cardiac surgery.

Results: In total, 29 replies were received. All physiotherapists instructed the patients to perform postoperative breathing exercises hourly, on a regular basis. Postoperative physiotherapy and breathing exercises was used as first choice treatment by 83% of the physiotherapists. Instruction how to perform the breathing exercises as well as the frequency and duration of exercises differed between physiotherapists. Recommendation to continue breathing exercises after discharge was given by 66% of the physiotherapists, but how long the patients were recommended to continue the breathing exercises varied from 1 to 3 months.

Conclusion: This survey provides an initial insight into chest physiotherapy management in Sweden. The routine use of breathing exercises is universal during the first postoperative days, but choice of breathing exercises and number of treatment sessions varied. Comparison with treatment regimens in other countries is warranted to improve the postoperative management of the cardiac surgery patient.

A total of 24 CF patients: age (12±3.7 years); BMI (18.3±3); FVC (97±20%pred); FEV1 (93±20%pred) answered a questionnaire specifically designed to evaluate the usability and management of the video game platforms for exercise training. Patients played three different video games Wii Fit Plus (Wii-Fit); Wii Family Training (Wii-Train) and Wii Active (Wii-Act). After this protocol they were asked about their feelings and impressions about them.

The questionnaire showed that video game platforms are usable in child environment (85.7%), they play about 1-4 days per week (50%), they spend playing about 1-2 hours per session (87%), and the main goal is to have fun (79%). During the protocol, the platform that the children liked the most was the Wii-Fit (42%) followed by the Wii-Act, and they considered both a good system to practice exercise at home (83.3%).

The video game platforms represent a common element in CF children and teenagers lifestyle. They use this type of platforms frequently and they show highly motivated to incorporate them as a training modality for respiratory rehabilitation programs at home.


P1174
Video game exercise effectiveness of a domiciliary respiratory rehabilitation program in cystic fibrosis (CF) patients

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CF is a multisystemic disease characterized by an abnormal ventilation response to exercise, the main limiting factor to exercise tolerance. Exercise training using video games platforms can be a key factor to guarantee the adherence to the respiratory rehabilitation programs. Our goal was to evaluate the efficacy of a domiciliary exercise program using the Wii™ video game platform as a training system in CF patients.

The study included 7 CF patients: age (11.4±3.9 years); BMI (18.4±3); FVC (78.9±18%); FEV1 (74.7±22%); All performed a domiciliary respiratory rehabilitation program using the Wii™ video game platform with the Active 2 game.

The program consisted of exercise about 30-min every day, 5 days/week during 6 weeks. The measurements evaluated from the beginning to the final were: exercise tolerance using the six minutes walk test (6MWT) and the shuttle test (Shut) and quality of life using the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

The exercise program improved the distance walked during the 6MWT (649 vs 703m) and during the Shut (622 vs 704m) (p<0.05, both), pre vs post respectively. However, the differences between the dyspnea and fatigue perception were not statistically significant. In relation with the CFQ-R, the data obtained from the respiratory symptoms (p=0.045) and physical tendency domains (p=0.047) were statistically significant (p<0.05, both).

The domiciliary respiratory rehabilitation program in CF patients, executed with the Wii™ video game platform, is feasible and can induce significant increases in exercise tolerance and quality of life.


P1175
Respiratory muscle training in impaired elderly: Threshold loading versus Pranayama breathing exercises

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Introduction: In the older elderly, the respiratory function may be seriously compromised when the decrease of respiratory muscle (RM) strength coexists with comorbidity and immobility syndrome. The aim of this study was to determine the effectiveness of RM training using the Threshold IMT device, or Pranayama breathing exercises vs. a control group in impaired elderly. Our general hypothesis was that RM training would improve RM function among this population.

Methods: Institutionalized elderly, who were unable to walk, were allocated randomly into three groups: a control group and two experimental groups (Threshold and Pranayama). Experimental groups performed a supervised interval-based training protocol, either through respiratory threshold loading or Pranayama breathing exercises, which lasted six weeks (5 days per week). Maximum respiratory pressures (MIP and MEP) and Maximum Voluntary Ventilation (MVV) were measured at four time points: pre-training, intermediate, post-training and follow-up (weeks 0, 4, 7 and 10, respectively).

Results: Seventy-one residents (90% female, mean age 85) completed the study: Control (n=24); Threshold (n=23); Pranayama (n=24). There was a significant treatment effect on the MIP (F(2,206)=4.75, p<0.001, n=20.166), MEP (F(6,204)=4.257, p<0.001, n=20.111) and MVV (F(6,204)=3.522, p<0.001, n=20.135).

P1173
Analysis of the usability and motivation of the use of video game platforms as a training system in patients with cystic fibrosis (CF)

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Objective: To determine the effectiveness of a domiciliary respiratory rehabilitation program, the Threshold IMT device, or Pranayama breathing exercises vs. a control group in impaired elderly. Our general hypothesis was that RM training would improve RM function among this population.

Methods: Institutionalized elderly, who were unable to walk, were allocated randomly into three groups: a control group and two experimental groups (Threshold and Pranayama). Experimental groups performed a supervised interval-based training protocol, either through respiratory threshold loading or Pranayama breathing exercises, which lasted six weeks (5 days per week). Maximum respiratory pressures (MIP and MEP) and Maximum Voluntary Ventilation (MVV) were measured at four time points: pre-training, intermediate, post-training and follow-up (weeks 0, 4, 7 and 10, respectively).

Results: Seventy-one residents (90% female, mean age 85) completed the study: Control (n=24); Threshold (n=23); Pranayama (n=24). There was a significant treatment effect on the MIP (F(2,206)=4.75, p<0.001, n=20.166), MEP (F(6,204)=4.257, p<0.001, n=20.111) and MVV (F(6,204)=3.522, p<0.001, n=20.135).

P1172
An effect of the home-based rehabilitation programme following the outpatient rehabilitation programme in patients with pulmonary sarcoidosis

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Background: Definition of the pulmonary rehabilitation (PR) precisely describes how such a programme should be established and what parts should be included. However, the programme should motivate patients to keep it at and thus to prolong the beneficial effect of it.

Aim: To evaluate an effect of a 6-week home-based PR following a 6-week outpatient PR on health-related quality of life (HRQL) in patients with pulmonary sarcoidosis (PS).

Methods: There were 18 patients with PS (mean age 50.3±11.3) recruited to the PR programme. The assessments included lung function tests, maximal inspiratory (MIP) and expiratory (MEP) mouth pressures, chest expansion, 6-minute walk test (6MWT) and HRQL using the Sarcoidosis Health Questionnaire. Patients underwent a 6-week outpatient PR followed by a 6-week home-based PR programme, which both consisted of respiratory physiotherapy and regular physical activity training.

Results: Baseline data showed decreased breathing muscle strength (MIP 89%, MEP 65%), limited chest expansion and relatively normal results in 6MWT (105% of predicted). Completing outpatient PR programme induced statistically significant changes in all measured parameters but lung function tests. Further significant improvement was observed in MIP during the following home-based PR programme.

Conclusion: Achieved improvements of the 6-week outpatient PR remained also after the 6-week home-based PR and therefore patients should be encouraged in continuing the PR programme at home.

Supported by grants of the Palacky University – FTK-2011010, FTK-2012023.
Conclusion: Pranayama training group works differently and significantly better than the other two groups, and may be therefore, a powerful alternative to general exercise conditioning in order to improve RM function (strength and endurance) in the elderly population with a significant loss of mobility and exercise capacity.

P1177
Impact of body position in premature newborn receiving nasal CPAP

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Introduction: The body position affects the cervical-thoracic-abdominal biomechanics and has impact on lung ventilation and perfusion. The impact of body position during CPAP is not well recognized.

Objective: To evaluate the clinical impact of the prone and supine positions in newborn preterm infants breathing without support or on nasal CPAP.

Methods: Thirty two preterm infants with GA from 26 to 35 weeks, BW < 2.75 kg and bronchopulmonary dysplasia were recruited. Infants were separated into two groups in use of nasal CPAP (n=16) or breathing without any support (n=16). Body position (pronation and supination) was changed following a random order. Preterm stand at each decubitus for one hour, and respiratory rate, oxygen saturation, heart rate and Silverman-Andersen bulletin (SA) were registered every ten minutes.

Results: The 16 infants of the nasal CPAP group presented GA of 30±2.0 weeks, BW of 1.53±2.81g, 56% were male and had 3±2.4 days of life at study. The 16 infants without breathing support presented respectively 33±1.5 weeks, 1.77±2.38 g, 37% were male and had 4±1.5 days of life at study. Clinical parameters of infants in nasal CPAP were not influenced by body position. Infants breathing without support presented at prone position better parameters, but with small clinical relevance, regarding oxygen saturation (95% ± 1.6 vs 94% ± 3.1, p=0.01) and SA (0.2±0.4 vs 0.7±0.6, p=0.01).

Conclusion: No difference in clinical parameters were found after changing the postural position in infants at nasal CPAP. When infants were breathing without support, prone position showed a small but statistically significant improvement in oxygen saturation and SA bulletin.

P1178
Comparative evaluation of vibrocompression and bag squeezing: A randomized study

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Introduction: Few scientific evidence has demonstrated the effects of respiratory physiotherapy in intubated children. The clearance maneuvers in mechanical ventilation without tracheal suction presented respectively 33±4.1±1.5 weeks, 1.77±2.38 g, 37% were male and had 4±1.5 days of life at study. Clinical parameters of infants in nasal CPAP were not influenced by body position. Infants breathing without support presented at prone position better parameters, but with small clinical relevance, regarding oxygen saturation (95% ± 1.6 vs 94% ± 3.1, p=0.01) and SA (0.2±0.4 vs 0.7±0.6, p=0.01).

Objective: Analyze and compare the hemodynamic effects, ventilation and respiratory mechanisms of two techniques in intubated children with respiratory failure.

Method: Eleven children with mean age of 28.42±15.42 month were randomized into two groups according to the technique used: (1) Bag Squeezing (BS; n=5) and (2) vibrocompression thoracic (VCT; n=6). All variables were studied before, immediately and 30, 60 and 120min after the maneuvers (p<.05).

Results: For both groups were found similar results, no significant differences. Heart rate and mean blood pressure presented higher in BS group in the post maneuver (p=0.04, p=0.43) compared with pre maneuver. The HR, ETCO2, platelet pressure and static compliance were also higher in the post-manuever in VCT group. There was no significant difference in the other respiratory variables or respiratory mechanics. Significant negative correlation between Rst e Cst was observed in the BS at all the times evaluated (R=0.97, p<0.00; R=89-p<0.04;R=75-p<.00). The same results were observed for VC and ETCO2 post maneuvers (R=.90-p.<.03). In the VCT was found positive correlation between the Rst and the Pp before maneuver (R=97-p<0.43;R=94-p<.00) and 120min post (R=.66-p.<.00) and between VC and ETCO2. There was also a positive correlation between VC and ETCO2 immediately after maneuver (R=.82-p<.04) and 30 min post (R=.87-p<.02).

Conclusion: Both techniques didn’t present changes in hemodynamic and ventilatory responses, even in the respiratory mechanic.

Discussion: To our knowledge this is the first report of patient satisfaction using the innovative LVR bag. 6/8 patients were able to clear sputum more easily after using the LVR bag. 7/8 patients agreed the verbal instructions easy to follow and strongly agreed/agreed that the bag was easy to use. In 7/8 patients, the technique required the assistance of a carer. Our study shows the LVR bag is easy to use and aids patient sputum clearance. Therefore, this technique warrants further investigation in a larger population with a wider range of conditions.

P1179
Experimental model of atelectasis in newborn pigs

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Background: There are few studies using animal models in chest physiotherapy, moreover, there are no models to assess these effects in newborns.

Aims: The objective of this study was to develop a model of atelectasis by bronchial obstruction in newborn pigs for the study of neonatal physiotherapy.

Methods: Newborn pigs resulting from a cross-breeding between Large White and Landrace, properly sedated, anesthetized, tracheostomized, paralyzed and mechanically ventilated were used. The animals received artificial mucus infusion through an infusion pump, underwent radiological assessment of the lungs and blood gas analysis was performed to confirm the production of atelectasis.

Results: The model showed consistent results between parameters of oxygenation and physiological analysis. The atelectasis model was successfully developed in over 70% of cases, surpassing 90% of attempts in the final phase of the study.

Conclusions: This model of atelectasis showed results consistent enough to be used in studies of chest physiotherapy techniques in newborn pigs.

P1180
Bag-squeezing maneuver in experimental model of meconium aspiration syndrome in newborn pigs

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Introduction: The use of broncho-alveolar lavage (BAL) and surfactant therapy has been tested in humans and in animal models getting promising results as well as Bag-squeezing maneuver has shown good results in adults.

Aims: To evaluate the effects of the combination of Bag Squeezing maneuver with broncho-alveolar surfactant in an experimental model of Meconium Aspiration Syndrome in newborn pigs.

Methodology: Were used in the study newborn pigs (n = 15), ventilated with fixed parameters. After instillation of human meconium 4mg/kg diluted to 20%, the pigs were randomized into three groups: CONTROL-SAM model subjected only to aspiration (n = 5), Grupo BAL-SAM model treated only with surfactant BAL (n = 5), and Grupo BAL + BAG-SAM model treated with BAL with surfactant associated with Bag Squeezing maneuver (n = 5). For the LBA used 15mg/kg of Carafate20 diluted in NaCl (5mg/ml). Blood gases, vital signs and behavior of mechanical ventilation were analyzed throughout the study.

Results: The group that received a BAL + BAG improved blood gas, reduced of airway resistance (p = 0,004) and compliance lung (p = 0.003) better than the other groups with a significant increase in the amount of meconium removed (p = 0.046) with the bag-squeezing maneuver.
Conclusion: The association of Bag-squeezing maneuver can bring benefits to gasometric parameters mechanical ventilation and increase the removal of mucus.

P1181

Comparison of two techniques of chest phisotherapy in experimental model of atelectasis in newborn pigs

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Objective: To compare the effectiveness of two techniques of respiratory therapy in an experimental model of atelectasis by bronchial obstruction in newborn pigs.

Methods: 24 pigs sedated, tracheostomized and mechanically ventilated. For the induction of atelectasis, artificial mucus was infused (Polyethylene oxide, Sigma-Aldrich®), USA) using an infusion pump through the tracheal tube. Confirmation of atelectasis was a chest X-ray and by a pressure drop of oxygen in arterial blood. The animals were divided into 3 groups: group 1 that received tracheal aspiration after 20 minutes of confirmation of atelectasis, group 2 underwent the technique of bag squeezing over tracheal aspiration and group 3 underwent vibration chest. To evaluate the effectiveness of techniques one second X-ray was done. To evaluate the changes during the procedures were performed arterial blood gases and pulmonary mechanics evaluation before and after the induction of atelectasis immediately and 30 minutes after the procedure.

Results: The mean percentage change in the PO2 was statistically detect significant between the groups (control: 97.8±37.33, bag squeezing: 166.75±68.63, and vibration: 104.41±45.45, p=0.0048), with improvement in oxygenation in the group undergoing the technique of bag squeezing. The remaining variables did not differ.

Conclusions: The results suggest that the technique of bag squeezing is more efficient than manual vibration chest in these animal model, but clinical improvement was not accompanied by detectable radiological improvement.

Incentive spirometry has been widely used in clinical practice for lung expansion; however, the effect of volumetric (VIS) and flow-oriented IS (FIS) on thoracoabdominal mechanics and respiratory muscular activity in morbidity obese are poorly known.

Objectives: To compare the distribution of pulmonary volumes and inspiratory muscular activity during use of VIS and FIS in obese morbidity.

Methods: Thoracoabdominal mechanics (optoelectronic plethysmography) were evaluated in 17 morbidity obese (54±11 yrs, BMI=21±3.5 kg/m2) simultaneously with respiratory muscular activity (electromyography) during quiet and deep breathing. Lung volume was evaluated using FIS and VIS (randomized sequences). Lung volume was evaluated using total chest wall (CW) and its compartments: abdominal (ABD) and upper (URC) and lower (LRC) ribcage. Muscular activity was evaluated in the sternocleidomastoid (SCM), upper (UIC) and lower intercostal (LIC) muscles. One way repeated measures ANOVA with post hoc Newman Keuls test were used and significance level was set at 5%.

Results: A greater chest wall volume was achieved using VIS compared with FIS (respectively, 1.98±0.7L vs 1.62±0.5L; p=0.02); however no difference was observed in all inspiratory evaluated muscles (SCM=21±4.9 vs 28±6.23±10^3 mV; UIC=9.6 vs 12±12±10^3 mV; LIC=6±2 vs 6±13±10^3 mV; p=0.05). Furthermore, thoracoabdominal asynchrony was observed during use of FIS (phase angle=37±3.8 vs 31±3.6; p=0.001) compared to VIS.

Conclusions: VIS induces greater chest wall volume with lower thoracoabdominal asynchrony in morbidity obese; however, without difference in the inspiratory muscular activity.

P1184

Chest wall motion and siting positions in patients with amyotrophic lateral sclerosis

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Respiratory muscle function is progressively altered in patients with Amyotrophic Lateral Sclerosis (ALS) leading to chronic respiratory failure. Moreover, diaphragmatic dysfunction starts to occur in supine position in neuromuscular diseases. Studies that analyze the chest wall motion, with special attention to the contribution of the diaphragm, may contribute significantly to earlier detection of ventilation failure.

Aims: Analyze chest wall motion in supine and sitting positions in patients with ALS and in a sex and age-matched healthy control group.

Method: Ten patients with ALS, aged 54±13 years and 10 healthy controls were included. Motion and volume changes of the chest wall and its compartments: rib cage (inspiratory and expiratory muscles) and abdominal compartment (abdominal muscles) were assessed by the optoelectronic plethysmography (OEP, BTS, Milan, Italy).

All participants were evaluated in supine and sitting positions during five minutes of quiet breathing in each position. Paired t-tests and independent Student t-tests were used, respectively, for intra-group and inter-group analyses. The significance level was set at p<0.05 for all comparisons.

Results: For both groups, the contribution of the rib cage compartment was significantly lower and the abdominal compartment contribution was greater in the supine compared with the sitting position; lower percentages of contribution of the abdominal compartment were observed in the supine position for the ALS group, when compared with controls.

Conclusion: The findings suggested that OEP proved to be a useful tool to identify significant decreases of the diaphragmatic movements in patients with ALS.

Partly supported by FAPEMIG and CNPq.

P1185

Laryngeal response patterns in amyotrophic lateral sclerosis during mechanical insufflation-exsufflation

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Introduction: Mechanical insufflation-exsufflation (MI-E) is the most effective approach to increase peak cough airflow in patients with neuromuscular diseases, thereby potentially augmenting airway clearance. Co-ordinated movements of the glottis may be crucial for effect in amyotrophic lateral sclerosis (ALS), but laryngeal response patterns to MI-E have not been studied.

Aims: To visualize laryngeal response patterns to MI-E in ALS patients.

Methods: Continuous videorecorded transnasal fiberoptic laryngoscopy (TFL) was obtained in eight ALS patients (two non-bulbar and six bulbar) during MI-E intervention (Cough Assist®, Respironics, USA), applying pressures of ±20 to ±50 cmH2O, and instruction to inhale during insufflation and to actively exhale

116. New insights in the physical assessment and therapy of respiratory patients
and cough during exsufflation. Laryngeal movements were assessed from the videorecordings.

**Results:** In one patient, severe hypopharyngeal obstruction was observed already ≥20 cmH2O. In the remaining patients, hypopharyngeal obstruction was observed during insufflation at 20-40 cmH2O and at 50 cmH2O in four patients, during pressure drop from + to - at 20-40 cmH2O in five, at 50 cmH2O in six, and during exsufflation in all patients, regardless of pressure. Aryepiglottic folds adducted during insufflation in four patients. The response of the vocal cords could not be observed in five patients due to hypopharyngeal obstruction or severe adduction of aryepiglottic folds.

**Conclusion:** Larynx can be studied with TFL during MI-E. Marked hypopharyngeal obstruction was observed during exsufflation and during high insufflation pressures. This may obstruct airflow, potentially disrupting positive effects of MI-E.

**P1186**

Comparison of the impact of laparoscopy and laparotomy on thoracoabdominal mechanics

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Abdominal surgery impairs respiratory system during the postoperative period. Laparoscopies (LPC) and laparotomies (LPT) are the most used surgical procedures; however, there is not enough evidence regarding the differences of both surgeries on the respiratory mechanics.

**Objective:** To compare the effect of laparoscopy and laparotomy on thoracoabdominal mechanics.

**Methods:** This prospective study enrolled 19 consecutive patients, 9 undergoing LPC and 10 LPT (56±9 yrs, BMI=24±4 kg/m²) that performed chest wall kinematics analysis (optoelectronic plethysmography) before and 2 days after surgery. Patients were evaluated during quiet and deep breathing. Two way repeated measures ANOVA and post hoc Student Newman Keuls test were performed and significance level was set at 5%.

**Results:** Surgical duration was similar between both groups (LPC=229±96 min; LPT=275±104 min; p=0.05). After LPC and LPT surgeries, patients presented similar decrease in chest wall volume at deep breath (respectively, 1.5±0.3 vs. 1.2±0.4L, and 1.6±0.5 vs. 1.1±0.3L; p=0.05). However, LPT induced a decrease in ABD volumes and a greater increase in URC and compared to LPC (respectively, URC 48% vs. 39% and ABD 23% vs. 28% p<0.001), after surgery.

**Conclusions:** Although LPC and LPT promote similar decrease on pulmonary volumes in the postoperative period, LPT induces a greater apical breathing pattern.

**P1187**

Comparison between maximal inspiratory pressures measured by unidirectional valve method and conventional method in healthy subjects without artificial airway

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The most used method to evaluate maximal inspiratory pressure (MIP) is by maintaining maximum negative pressure forced against an occluded airway (MIPsta). To eliminate the need for collaboration, a new technique was developed using a unidirectional expiratory valve (MIPuni) in patients undergoing invasive mechanical ventilation. The aim of this study was to compare these two methods of measurement in patients with spontaneous breathing without artificial airway. We also tested the intra- and inter-observer reproducibility of MIPuni. The study had a crossover design and twelve healthy volunteers performed the evaluation of MIP of each method in a randomized order. A digital manometer was attached to a mouthpiece (MIPsta) or facemask (MIPuni) and the maximal value in each method was considered. The MIPuni was evaluated by two independent observers (A and B), at two different times (1st and 2nd tests) with an interval of at least one week. MIPuni displayed significantly larger values than MIPsta (106.1±29.3 and 98.4±25.8, respectively; p=0.01). The MIPuni obtained by observer A was not different from that obtained by observer B for both the 1st test (105.9±30.4 and 104.3±26.1, respectively; p=0.32) and the 2nd test (105.5±30.1 and 102.6±31.7, respectively; p=0.24). The MIPuni obtained in the 1st and 2nd tests was not different for both observers A (105.9±30.4 and 105.5±30.1, respectively; p=0.13) and observer B (104.3±26.1 and 102.6±31.7, respectively; p=0.21). MIPuni is the better method for measuring MIP in individuals without artificial airway. The inter- and intra-observer measurements were similar.

**P1188**

Cardiovascular responses to maximal expiratory pressure and salvalsa maneuver in healthy men

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**Background/Aim:** The respiratory assessment, mainly the measure of maximal expiratory pressure (MEP), has some contraindications because of similarity with the Valsalva maneuver (VM). The objective of this study was evaluated the cardiovascular responses during MEP and identify if this measure reproduces the responses obtained in VM.

**Methods:** 19 healthy men participated in this study, 11 young (23±3 years) and 8 middle-age (45±3 years), divided in two groups – G1 and G2, respectively. They performed the VM (3x) with 40mmHg of oral pressure during 15s, at the sitting position using different mouthpieces (one with a leak of 2mm and another without). The MEP (3x) was performed from total lung capacity, according ATS/ERS in the same conditions of VM. We analyzed during VM and MEP the heart rate variation (ΔHR) and systolic and diastolic blood pressure variation (ΔSBP, ΔDBP). We compared the MEP and Valsalva index (MEPI, VI). ANOVA three-way with Holm-Sidak post-hoc test (p<0.05) was employed to analyse de effect of maneuvers, groups and mouthpiece.

**Results:** We observed that VM have values of ΔSBP (VM: 11±4 mmHg; MEP: 6±6 mmHg), ΔHR (VM: 30±11 bpm; MEP: 22±6 bpm) and indexes (IV: 2.0±0.4; IMEP: 1.5±0.2) were bigger than MEP (p<0.05), independent of the group or the mouthpiece. When we analyzed the groups influence we observed that G2 have higher values of ΔSBP and ΔDBP than G1 (p<0.05), but not to VI and MEPI (p=0.001). The mouthpiece effect was observed only in ΔDBP (p=0.006) and the piece without leak had the biggest values.

**Conclusion:** At the studied condition the MEP does not reproduce the cardiovascular responses observed in VM in healthy men.

**Financial support:** CNPq, FAPESP.

**P1190**

Cost effectiveness of an ambulatory oxygen (AO) clinic

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**Aim:** Inappropriate oxygen prescription proves costly to the NHS. There is great need to assess and review patients. We run an AO clinic to assess new patients and review oxygen usage. We assessed the cost effectiveness of this clinic.

**Method:** Data from a retrospective audit were analysed for all patients who attended clinic from April 2009 to November 2011. AO needs were assessed as per current guidance. Oxygen prescriptions for any mode (LTOT, SBOT, ambulatory) were reviewed to ensure the patient has the correct modality. HOOFs were amended to reflect correct oxygen usage or cancelled if no longer required. Costs of running the clinic were calculated along with actual oxygen savings to evaluate the effectiveness of this clinic (table 1).

**Results:** Data were available for 251 patients (199 new, 52 reviews). Of the new, 35% (n=70) had a current oxygen prescription. Of these 13% (n=25) did not meet the criteria for the modality prescribed. Of those for review, 71% (n=37) had received AO when they had undergone pulmonary rehabilitation, the remaining 39% (n=15) had been prescribed oxygen.
Muscle function in patients with COPD

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Background and objectives: The noninvasive ventilation (NIV) has been the technique chosen for the treatment of acute respiratory failure due to acute pulmonary edema (APE) and exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The objective was to evaluate predictors of success or failure of NIV in an emergency department from Brazil.

Methods: The NIV was in used patients with COPD exacerbation or APE. If no improvement in 2 hours or there is any contraindication to continue with NIV, endotracheal intubation (EI) is performed and considered the endpoint.

Results: A total of 152 patients. On average, the use of NIV was 10 hours for patients with COPD (n = 60) and 7.5 hours for patients with APE (n = 92). It was observed that 75.7% successfully evolved and 24.3% were intubated, and those who progressed unfavorably presented lower oxygen saturation 78.3% compared with those who achieved successfully after NIV, with mean oxygen saturation 84.2%. The findings showed there was a statistically significant difference when researching the APACHE II score and respiratory frequency above 25 in the patients who developed EI. Among patients diagnosed APE, a chance of evolution EI was 63% lower (adjusted OR = 0.37 95% CI: 0.14-0.96). Similarly, higher values of the Glasgow Coma Score (GCS) and oxygen saturation reduce the chance of adverse developments.

Conclusions: The NIV should be used in emergency services in this cases. Variables like oxygen saturation below 80%, respiratory frequency above 25, higher value of APACHE II and among those who received Bilevel may indicate progression to EI.

Muscle function in patients with COPD

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Objective: The aim of this study was to make a survey of muscle function in patients with COPD and to relate these findings to health related quality of life.

Methods: One hundred patients with COPD (FEV1% predicted, 43±17, stage II-IV) (59% women) with a mean age of 64±7 years for the women and 67±6 years for the men participated in the study. All patients carried out performance based tests including isometric muscle strength of the quadriceps muscle, hand grip strength, and 30 meter walking test (self chosen and maximal speed). Health related quality of life was assessed with SF-36 and SGRQ.

Results: Muscle strength in the quadriceps muscle reduced 45% in patients with COPD in comparison with a reference group of healthy persons. Comparable values for hand grip strength were 90% and walking speed 74-80%. Maximal walking speed correlated with SF-36 (r=0.38, p<0.001) and SGRQ (r=0.36, p=0.001). Conclusion: Muscle function is generally impaired in patients with COPD, and should be measured in addition to lung function.

Postural changes in children with non-cystic fibrosis bronchiectasis

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Bronchiectasis not caused by cystic fibrosis (CF) is often perceived to be rare in western societies, but seems to be an important cause of chronic suppurative lung disease in the developing world among children. Although, the clinical features, radiological, and histological findings in these children was investigated there is not enough knowledge about the musculoskeletal consequences of the disease.

The aim of this study is to document the musculoskeletal affects of the disease process. 24 patients with non-CF bronchiectasis (mean age 13.2(3.4) years) participated in the study. Anterior, posterior and lateral postural analyses was performed and thoracic kyphosis angle was measured from lateral chest X-ray (4.16.7%) patients had kyphosis (over 35 degrees) and mean angle of thoracic curve was 28.5(5.1) degrees. There was scoliosis in 3 (12.5%) of the children. Bilateral pes planus was present in 8 (33.3%) cases, broad chest deformity in 7 (29.2%), pectus carinatum deformity in 2 (8.3%) and pectus excavatum deformity in 4 (16.7%) patients. 17 (70%) patients had also protracted shoulders. Our results indicate a high rate of postural deformities or adaptations especially in the upper body of the patients with non-CF bronchiectasis. Since the upper body posture is carefully related to the pulmonary functions these changes should be closely monitored as soon as the patients are diagnosed and necessary preventive and corrective physiotherapy programs must be initiated.

Postural changes in children with non-cystic fibrosis bronchiectasis

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Background: Children with non-CF bronchiectasis (n-CF) present postural changes such as pes planus, thoracic kyphosis, and scoliosis which can be related to respiratory symptoms by decreasing chest mobility and increasing respiratory effort. The aim of this study was to evaluate the postural changes in children with n-CF bronchiectasis.

Methods: Twenty patients with n-CF bronchiectasis (mean age 12.8±2.9 years) were studied. We conducted the following procedures: controlled walk test (shuttle test) and heart rate variability. For recording the 360 seconds during the Shuttle Test. HRV was analyzed in the time domain (TD) (SDNN, RMSSD, NN50), and frequency domain (FD) (LF, HF). The SDNN index, the standard deviation of R-R intervals in the time domain; the LF/HF ratio in the frequency domain.

Results: The children with asthma (30-52 years) and fifteen healthy subjects (30-52 years) were studied. We conducted the following procedures: controlled walk test (shuttle test) and heart rate variability. For recording the 360 seconds during the Shuttle Test. HRV was analyzed in the time domain (TD) (RMSSD index, the root mean square of differences between successive R-R intervals), and the SDNN index, the standard deviation of R-R intervals in the frequency domain (FD) from the low frequency (LF) and high frequency (HF) in normalized units (NU) and LF/HF ratio.

Conclusion: It can be concluded that patients with difficult to control asthma showed a reduced HRV compared with healthy during the Shuttle Walk Test with an increase in vagal activity sympatric. Thus, it can be suggested that in future studies, HRV can become a useful tool for parameters in cardiovascular risk stratification in this population, and in the evaluation of different physical therapy interventions to treat these patients.
P1197

Chest expansion in preschool-age children with mild bronchial asthma
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Introduction: The presence of persistent bronchial asthma (BA) is usually connected with limited chest expansion (CE) [1], but there are no reference values to express if there is a serious limitation.

Aims: To evaluate an effect of a 4-week pulmonary rehabilitation programme (PRP) on CE in preschool-age children with mild BA.

Methods: One-hundred-and-fourteen children with BA (aged 12.0±2.6 years) were examined and recruited for the intervention group (I), which attended a 4-week PRP including respiratory physiotherapy, inhalation, physical activity training in group sessions. Two-hundred-and-eighty healthy children (aged 11.9±2.0 years) were examined and assigned to the control group (C). Both groups underwent a CE assessment, which was performed with a tape cloth measure at the level of 4th intercostal space (IC) and at the level of xiphoid process (XP).

Results: CE of the I group was significantly lower at baseline compared to the C group. After the 4-week PRP a significant improvement was achieved that resulted in a presence of not significant difference between the I and C group in almost all subgroups.

Boys IC 2.0±1.0 < 0.05 5.8±1.6 < 0.05 NS
Boys XP 2.7±1.3 < 0.05 5.9±1.7 < 0.05 NS

Conclusion: The PRP led to a significant improvement of chest expansion in BA children, who had CE previously decreased.

Study was supported by grants of the Palacky University – FTK_2011_010; FTK_2012_023.

Reference:

P1198

Chest expansion in preschool-age children with mild bronchial asthma
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Introduction: A chronic respiratory disease in adults is often connected with limited chest expansion (CE). We can not find the evidence about CE in preschool-age children at previous published studies and there are no reference values to express if there is a serious limitation.

Aims: To evaluate an effect of a 4-week pulmonary rehabilitation programme (PRP) on CE in preschool-age children with mild bronchial asthma (BA).

Methods: One-hundred-and-three children (aged 5.2±0.7 years) with BA were examined and recruited for the intervention group (I), which attended a 4-week PRP including respiratory physiotherapy, inhalation, physical activity training in group sessions. One-hundred-and-sixty-four healthy children (aged 5.2±0.9 years) were examined and recruited for the intervention group (I), which attended a 4-week PRP including respiratory physiotherapy, inhalation, physical activity training. The MIP and MEP assessment was performed at the baseline and after the PRP. The control group (C) consisted of 208 healthy children (aged 11.9±2.0 years) without any treatment.

Results: The MIP and MEP values of BA children were about the same or lower than those of C group at the beginning of the PRP, but there were no significant differences among the groups (Table 1). A significant improvement of MIP and MEP was observed in BA children after the PRP (Table 2) and furthermore the MIP and MEP values were higher than values in C group (Table 1).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
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<tbody>
<tr>
<td>MIP (cmH2O)</td>
<td></td>
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<tr>
<td>C baseline</td>
<td>76.5±2.9</td>
<td>58.3±2.3</td>
</tr>
<tr>
<td>C follow-up</td>
<td>74.6±2.3</td>
<td>58.2±2.3</td>
</tr>
<tr>
<td>E baseline</td>
<td>58.3±2.3</td>
<td>58.3±2.3</td>
</tr>
<tr>
<td>E follow-up</td>
<td>71.2±2.4</td>
<td>71.2±2.4</td>
</tr>
<tr>
<td>p (t-test)</td>
<td>NS</td>
<td>0.005</td>
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</table>

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
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<tbody>
<tr>
<td>Mouth pressure (cmH2O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E baseline</td>
<td>58.3±2.3</td>
<td>58.3±2.3</td>
</tr>
<tr>
<td>E follow-up</td>
<td>74.6±2.3</td>
<td>74.6±2.3</td>
</tr>
<tr>
<td>p (t-test)</td>
<td>0.005</td>
<td>0.005</td>
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</table>

Conclusion: The MIP and MEP values in children with mild BA are not significantly lower than values of healthy children.

Study was supported by grants of the Palacky University – FTK_2011_010; FTK_2012_023.

P1200

In vitro comparison of emitted dose with 2 types of nebulizers during non invasive ventilation
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Introduction: Non invasive ventilation (NIV) and inhaled therapy are important components of the medical management of COPD patients. Sometimes, both therapies need to be administered simultaneously. It has been shown that it is feasible and effective to deliver nebulized bronchodilators during NIV.

Objectives: Primary objective was to compare emitted dose (ED) of different types of nebulizers coupled with a single limb circuit bilevel ventilator. Secondary objective was to evaluate the impact of the position of nebulizers on the circuit. Material and methods: Amikacin (500mg in 4 mL) was nebulized by two vibrating mesh nebulizers (Aeroneb®Pro and Aeroneb®Solo, Aerogen, Ireland) and by a classical jet nebulizer (SideStream; Medic-Aid; UK). The nebulizers were connected to a single limb circuit ventilator (Trilogy® 100, Philips-Respirronics, USA), either before (Position 1) or after (Position 2) the passive exhalation port (Whisper Swivel II® Philips-Respirronics, USA). The bilevel ventilator was set in spontaneous mode and connected to a lung model to mimic a COPD patient breathing (RR of 16 breaths/minute, I:E ratio of 1:3 and VT of 400 mL). A filter was interposed between the lung model and the circuit. ED was measured by the residual gravimetric method.

Results:

Table: Emitted dose by nebulizer at each position

<table>
<thead>
<tr>
<th>Position</th>
<th>Aeroneb®Pro</th>
<th>Aeroneb®Solo</th>
<th>Jet nebulizer</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>98.7±4.8μg</td>
<td>113.1±14.8μg</td>
<td>76.8±6.8μg</td>
</tr>
<tr>
<td>2</td>
<td>309.9±8.5μg</td>
<td>343.3±10.9μg</td>
<td>96.8±5.9μg</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Conclusion: Associated with a single limb circuit bilevel ventilator, emitted dose of vibrating mesh nebulizers are greater than jet nebulizer. Moreover to place the nebulizer after the passive exhalation port is optimal for all the devices.
P1201
An initial investigation by electronic survey of current UK physiotherapy practice into the use and delivery of nebulised isotonic saline
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Introduction: Physiotherapy is used widely to assist with airway clearance. Nebu- lised isotonic saline (0.9%) as a method of enhancing airway clearance has become a clinically accepted adjunct to physiotherapy in the treatment of many chronic lung conditions. In current practice, there is little scientific evidence by which to base its use.
Aim: To explore the current UK physiotherapy practice regarding the use and delivery of nebulised isotonic saline.

Sample and Methods: This pilot study made use of a prospective mixed methods survey. A questionnaire was designed, validated and administered electronically to a convenience sample of UK respiratory physiotherapists who were members of the Association of Chartered Physiotherapists in Respiratory Care (ACPR).
Steps were taken to promote reliability and validity of findings and results were analysed using a combination of descriptive and inferential statistics.

Results: The majority of participants (90.3%) agreed that nebulised isotonic saline aids sputum clearance, however no participants thought that there was a strong evidence base. It was noted that there were deviations from the manufacturers guidelines for the use of nebulisers. In addition, findings illuminated that large variations of flow rates for the driving gas used to operate the nebuliser ranging from 50mL to 150mL.

Conclusions: Although a pilot, this study highlights the need for more training on the delivery and prescription of nebulised isotonic saline for respiratory physiother- apists. It also highlights the need for more research into the clinical applications of nebulised isotonic saline as an adjunct to physiotherapy treatment.

117. Nursing led education and follow-up strategies: impact on readmission, self care and patient experiences

P1202
Preventing readmission of patients with COPD
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Introduction: According to a recent report by the British Lung Foundation, 1 in 3 people with a COPD exacerbation in the UK are readmitted within 28 days of discharge.

Aim: To reduce readmissions of COPD patients within 30 day subsequent to hospital discharge.

Method: From June 2011, we introduced a telephonic follow up service (once a week phone call by outreach nurses for 30 days), thereby offering extended monitoring and advice beyond standard home visits, for patients sent home with early facilitated discharge. Further home visits were arranged and treatment advice was provided when appropriate. Patients were encouraged to contact the outreach team themselves if needed.

Results: Over the course of subsequent 6 months, 136 patients were sent home with early facilitated discharge. A total of 353 phone calls were made. 11% (n=10) of patients required antibiotics and/or steroids, prescribed by the outreach nurses. Interventions in this group led to 28 additional home visits and 8 telephone consultations. 11% of patients (n=16) were readmitted within 30 days of hospital discharge but only 5% (n=7) of readmissions were due to a respiratory cause. Of the 16 readmissions, 70% (n=11) were admitted out of service hours, of hospital discharge but only 5% (n=7) of readmissions were due to a respiratory hospital discharge.

Conclusion: The telephonic follow up service prevented 15 patients from read- mission with an exacerbation of their COPD. It may be that offering this simple intervention will lead to an improvement in readmission rates for COPD in South Tees. To assess this, we plan to review readmission rates of patients prior to June 2011 and compare them with our current figures.

P1203
Do telephone interventions of patients with COPD prevent readmission?
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Introduction: In 2009 at Hilleroed Hospital 22% of patients with COPD were readmitted within 30 days and 52% within 84 days. Literature showed that indicators for readmission were: MRC >3, comorbidities, physical inactivity, living alone, poor health-related quality of life and the patients’ need for social support.

Aims: To investigate whether telephone follow-up:
– Reduce number of readmissions
– Increase quality of discharge
– Improve patients’ knowledge

The hypothesis tested is that telephone interventions provide greater security for patients with COPD in order to support self-management and reduce number of readmission.

Methods: A randomized trial were performed with an intervention group (N=115), who was contacted by a nurse & 30 days after discharge. Additional telephone calls were offered if needed. Through appreciated inquiry the patients’ experience due to the admission was clarified. Dialog and providing knowledge were used to support self-management and coping with exacerbations. After 30 days the patients’ answered a question- naire containing generic questions about health status, managing COPD and an evaluation of the intervention. The control group (N=97) was also contacted on day 30 and answered the same questionnaire except questions about evaluation.

SPSS statistics were used to analyze data and SPSS software to create the questionnaire.

Results: The preliminary results indicate that there was no effect on the number of readmissions. The majority of the intervention group felt secure and content knowing that a nurse will provide the enhanced follow-up call. The ability to contact health professionals when needed was important.

Conclusion: Telephone follow-up did not reduce the number of readmissions for patients with COPD compared to a control group.

P1204
Self-care 3 months after COPD patient education: A qualitative descriptive analysis
Camilla Askov Mousing, Kirsten Lomborg. School of Health Sciences, Randers University of Southampton, United Kingdom

Introduction: The literature indicates a conflict between the documented effect of COPD patient education and the patients’ own experiences of the benefit in their everyday life.

Aim: To explore from the patients’ perspective how group patient education influences their self-care three months after completing the program.

Methods: In the period 2009-2010, eleven patients diagnosed with COPD com- pleted an 8-week group education program in a Danish community health center. The patients were interviewed 3 months after completion of the program.

Results: Patients reported that their knowledge of COPD had increased, that they had acquired tools to handle their symptoms; and that the social aspect of patient education had motivated them to utilize their new habits after finishing the course. The data indicate that patients need a “ripening period” to integrate new habits and competencies into everyday life. As a side effect of the study it appeared that the research interview focused the patients’ attention on their newly acquired skills and made them more aware of their enhanced self-care.

Conclusions: Patients’ self-care may be enhanced through group education, even though the patients are not always able to see the immediate outcome. Some patients may require professional help to implement their newly acquired knowl- edge and skills in everyday life. A planned dialogue concentrating on self-care in everyday life 3 months after finishing the course may enhance patients’ awareness and appraisal of their acquired competences.

P1205
Proper inhaler’s technique closely related to proper instruction
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Introduction: Evidence suggests that many patients don’t use their meter dose inhalers (MDI) correctly and mostly related to improper instruction.

Objectives: It is an observational pre & post-lecture assessment study aims to assess the knowledge and practical competency of the nurses.

Methodology: The assessment items including 4 categories, applicable to only MDI and Spacer inhaler device: 1. patient observation, 2. drug explanation to patients, 3 choice of assisting device, 4. instruction on how to use inhalers or spacer, 5. monitoring the effect & side effect and reporting. Four identical sessions of 1.5-hour lectures including hands-on workshops on inhalers have been held from September to October 2011. Returned demonstration and compulsory audit assessment were required pre and post lectures with 2 months intervals.

Results: 54 nurses completed the pre-lecture audit and 87% were registered nurses. 30% had at least 5 years’ medical experience but none show full competence in demonstrating all 14 steps for MDI and 12 steps for spacer correctly. The mean steps of MDI & spacer are only 5.6 and 6.6 respectively. A total of 32 nurses had attended the lectures and amongst which 26 nurses had performed the pre-and post-audit assessment. A significant improvement is found in mean steps for MDI (4.4 vs. 10.3) and spacer (5.7 vs. 10.25).The overall post-audit mean steps are 10.09 for MDI and 10.43 for spacer respectively (p<0.001) Both post audit assessment had been shown to achieve significantly improvement.

Conclusion: Proper inhaler technique depends on proper instructions. MDI and spacers checklists have been formulated and revised for providing step by step guidance. A regular training workshops and lectures will be held quarterly.
Objective: A multi-disciplinary integrated COPD programme has commenced since 2011 to reduce unplanned readmission and provide post-discharge care. Respiratory-nurse acts as a case-manager for disease management and provision of continuity in nurse-led COPD clinic.

Methodology: COPD Clinical Pathway is being adopted for in-patient recruitment including suspected patients with clinical features of COPD. We stressed on in-haler and spacer technique, appropriateness of the inhaler’s prescription, and early diagnosis detection before discharge. Proper referral will be coordinated for early rehabilitation, home-visit care and advanced specialty care. All recruited cases were scheduled for nurse-visit clinic and subsequent follow-up. The wide range of advanced specialized nursing care are including symptoms assessment, spirometry monitoring, self-care plan education, optimizing inhaler’s using skill and making referral.

Results: 355 in-patients, predominantly male (87.6%), had been recruited and 26.5% are referred to nurse clinic. 20.8% are chronic smokers and over 70% has successfully quit smoking. However 80% were knowledge deficit regarding COPD. 87.3% demonstrated failed inhalers and spacer technique but a significant improvement is found after continuous education. 53% vs. 28.8% (p=0.001). Overall, 92.3% express satisfaction and will continue follow-up in the clinic.

Conclusion: Respiratory nursing care plays a vital role in optimizing therapy and self-home plans management. The long term effectiveness and particularly unplanned readmission rates need to be evaluated in prospective controlled trials.

A national home oxygen service contract review is being undertaken in NHS Scotland and the implementation of a domiciliary oxygen service best practice/guidance Statement. The Respiratory nursing team in NHS Dumfries and Galloway have undertaken a regional review of all patients using any modality of home oxygen. Since March 2011 - 300 patient clinic reviews have been conducted regarding the oxygen prescription in the nurse led clinics.

Findings: Prescription of oxygen is often conducted without establishing that people meet the criteria for this. There is a perception that oxygen is a treatment for breathlessness without assessing for hypoxaemia. Inappropriate prescribing is arising both in primary and secondary care settings. The costs of inappropriate oxygen prescribing are significant.

Outcomes: 50 oxygen concentrators installed for those who met the criteria for LTOT resulting in a saving of £30,000 in previous oxygen cylinder prescribing costs. 30 patients identified who met the criteria for the more efficient Homefill Better technology/equipment that meets service user’s needs is being evaluated both in primary and secondary care settings. The costs of inappropriate oxygen prescribing are significant.

Conclusion: Respiratory-nurse acts as a case-manager for disease management and provision of continuity in nurse-led COPD clinic.

Identification of contributing factors to NIV treatment and NIV usage

Aim: To provide insight into how patients with COPD experience treatment with NIV. To develop new clinical strategies for treatment with NIV based on patients, their relatives and healthcare professionals perspectives.

Methods: A multi-disciplinary integrated COPD programme has commenced in 2011 and 3 of their relatives have been interviewed. Patient interviews revealed 11 patients wanted to be treated with NIV if necessary in the future even though 2 patients described fear during treatment and 10 experienced that all 11 patients expected and wanted to be treated with NIV if necessary in the future even though 2 patients described fear during treatment and 10 experienced difficulties.

Results: The findings suggest that personality traits exert an influence on patients’ self-management behavior and QoL. Due consideration should be given to the contributing factor when providing self-management support.

Chronic lung diseases such as asthma have a great impact on the everyday life of patients. The purpose of this descriptive study was to determine the difficulties experienced by the asthmatic patients in Turkey. Each patient was contacted by 105 asthmatic patients who had been receiving medical therapy in Akdeniz University Hospital. Data were collected through a demographic data form and the questionnaire about the asthma patients’ physical, psychological, social, economic and treatment-related difficulties. The asthma patients in the sample averaged 55.68 years of age (SD 12.29 years, range 18–85) and included most patients who were female (61.9%), married (77.1%), housewife (47.6%) and had completed primary education (40%). Difficulties experienced by the asthmatic patients physically were dyspnea (85.7%), wheezing (82.9%), tiredness (82.9%), cough (76.2%); psychologically were sadness (85.7%), anxiety (64.8%), anger (59.0%), panic (45.7%), social were do not enter to the closed/crowded places (65.7%), do not go to see their relatives/friends, economically were loss of income (36.2%), inability to pay for expensive drug charges (30.5%), inability to pay the hospital fees (14.2%), inability to pay for the treatment (12.4%), treatment-related difficulties were not having an adequate knowledge about the asthma attack (44.5%), not receiving an adequate information about the treatment (32.3%), not being aware of the consequences of the treatment (23.8%). The information gathered from this study led us to reevaluate the healthcare services for asthmatic patients to improve physical, psychological, and social aspects of the nursing care as a whole.
However, the EQ VAS attained significance (rho=0.883, p<0.01) when the analysis was limited to the telemonitoring intervention group.

**Discussion/Conclusions:** It is feasible to use condition-specific (FFSS-11) and generic (WHO-5/EQ VAS) questionnaires with lung CA patients; both generic measures correlated with a tested measure of functional status in telemonitored but not control group. Further study will identify best outcome predictors.

**P1212**

**Over-diagnosis of COPD in UK primary care**

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**Background:** Mis-diagnosis of COPD was reported to be common in Australia primary care practice. We conducted a study to evaluate the frequency of this problem in United Kingdom primary care.

**Objectives:** To determine the prevalence and correlates of mis-diagnosis of COPD and associated prescribing in UK primary care.

**Methods:** The records of COPD patients registered with 47 General Practices in London were searched electronically to identify patients with a ≥15 pack year of smoking history and age group of ≥40.

Spirometry was performed on those who were consented in the Trial of Vitamin D supplementation study, and the characteristics of those who met ATS/ERS spirometric criteria for COPD (FEV1/FVC ratio < 0.70%) were compared with those who did not. Normal spirometry was defined as predicted FEV1 ≥ 80%, predicted FVC ≥ 80% and FEV1/FVC ratio > 0.70%. The prescription among patients who did not meet these criteria was assessed.

**Results:** A total of 264 patients were screened, of whom 232 (87.9%) were confirmed to have COPD by spirometric criteria and 32(12.1%) were not. 10/32 had evidence of restrictive lung disease and 22/32 had normal spirometry. 63/32 patients wrongly diagnosed with COPD were prescribed respiratory medication; 11/32 were prescribed isotretinoin, 13/32 were prescribed a combination inhaler (LABA & ICS), 5/32 were prescribed inhaled corticosteroids, 2/32 were prescribed Xanthine, 21/32 were prescribed inhaled short acting bronchodilator.

Cost of misdiagnosis of COPD in UK primary care and it is associated with a significant degree of inappropriate prescribed respiratory medication. Tackling this problem has the potential to prevent needless adverse effects associated with a significant degree of inappropriate prescribed respiratory medication, and to save costs of inappropriate prescribing.

**Conclusion:** Low weight heat shock proteins play a major role in carcinogenesis of lung cancer, eventually has a prognostic value and may be used as targets for therapy.

**P1214**

**The effect of SDF-I/CXCR4 on expression of VEGF and MMP-9 in small cell lung cancer**

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**Objective:** To explore the effect of SDF-I, AMD3100, and LY294002 on expression of VEGF and MMP-9 in NCI-H446 cell, and to explore the mechanism of small cell lung cancer invasion by SDF-1.

**Methods:** There were 5 groups in the experiment: control group (SDF-I negative group); SDF-I 5ng/ml group; SDF-I 10ng/ml group; SDF-I (100ng/ml) + AMD3100 group; SDF-1 (100ng/ml) + LY294002 group. With serum-free medium for 24 hours, to observe the VEGF and MMP-9 expression with different treated conditions using RT-PCR to detect the expression of VEGF and MMP-9, and ELISA to measure the expression of VEGF and MMP-9 in cell culture supernatant.

**Results:** VEGF and MMP-9 expression in supernatants were increased in SDF-1 treated group and could be inhibited by AMD3100 and LY294002. Compared with the control group, 100ng/ml SDF-I treatment could significantly increase the expression of VEGF and MMP-9 was significantly increased. [(826±102) pg/ml VS (360±21) pg/ml, (P<0.05)]; VEGF concentration of SDF-I (50ng/ml)+AMD3100 treated group, SDF-1 (100ng/ml)+LY294002 treated group decreased, [(224±55) pg/ml VS (826±102) pg/ml, (P<0.05)]. In SCLC was significantly increased. [(9) pg/ml VS (6.1±2) pg/ml, (P<0.05)].

**Conclusion:** After treated with SDF-I, the expression of VEGF and MMP-9 was significantly increased, and could be inhibited by AMD3100 and LY294002, which suggested that SDF-I/CXCR4 participate in tumor invasiveness and metastasis in small cell lung cancer by promoting secretion of VEGF and MMP-9.

**P1215**

**Profile of WT1 methylation in human lung cancer**

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**Background:** CG island hypermethylation of the promoters of the genes is a well-known mechanism of genetic alteration involved in carcinogenesis. Wilms tumor gene (WT1) is involved in the regulation of human cell growth and differentiation and it is a modulator of oncogenic. K Ras signaling in lung cancer; methylation of WT1 was never studied in human lung cancer. The primary aim of this study is to compare the methylation profile of WT1 promoter in samples of neoplastic and non-neoplastic lung tissue taken from the same patient.

**Methods:** Lung tissue obtained from 16 patients with non small cell lung cancer (NSCLC) and 6 patients with small cell lung cancer (SCLC). The methylation status of 29 CpG islands in the 3' region of WT1 by means of pyrosequencing was investigated.

**Results:** The mean percentage of methylation, considering all CG islands of WT1 in the neoplastic tissues of all NSCLC patients, was 16.2±4.3, whereas in the control tissue from the same patients it was 5.6±1.7 (p<0.001). Adenocarcinomas present grater methylation vs squamous cell carcinomas (p<0.001). In SCLC was not statistically significant difference between neoplastic tissue and control tissue of same patients.

**Conclusions:** Although, WT1 methylation does not seem to play a role in the pathogenesis of SCLC, hypermethylation of WT1 seems to be involved in the carcinogenesis of NSCLC. CHT, histotype, exposure to cigarette smoke are all factors influencing the gene CG islands which become hypermethylated in NSCLC.
P1216

Global histone H3 lysine 4 (H3K4) dimethylation is an important prognostic factor in lung cancer
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Introduction: Epigenetic modifications may contribute to the development and progression of cancer. This study seeks to elucidate the role of global histone modifications as a clinicopathological factor in lung cancer.

Methods: A series of 92 surgical specimens from patients with lung cancer were utilized from the surgical files of Kanazawa Medical University Hospital between 2001 and 2008. The 92 tumor specimens were examined by immunohistochemistry. Dimethylated histone 3 lysine 4 (H3K4me2), Acetylated histone 3 lysine 9 (H3K9Ac), acetylated histone 3 lysine 18 (H3K18Ac), trimethylated histone 3 lysine 27 (H3K27me3), dimethylated histone 4 arginine 3 (H4R3me2) were assessed. The expression of the above markers was evaluated by Flow Cytometry, and its proliferation were examined by MTS.

Results: Lung cancers of various histologic subtypes showed that dimethylated histone 3 lysine 4 (H3K4me2), acetylated histone 3 lysine 9 (H3K9Ac), acetylated histone 3 lysine 18 (H3K18Ac), trimethylated histone 3 lysine 27 (H3K27me3), dimethylated histone 4 arginine 3 (H4R3me2) were high in tumor cells of 40, 10, 9, 9, 10%. Expression of dimethylated histone 3 lysine 4 (H3K4me2) correlated positively with recurrence (p=0.039) and stage (p=0.005) and cell differentiation (p=0.002). Univariate analysis showed that high expression of dimethylated histone 3 lysine 4 (H3K4me2) correlated with recurrence.

Conclusion: We hypothesize that expression of H3K4me2 may be considered as a significant factor for patients with lung cancer.

P1217

Expression of RASGRF2 in non-small cell lung cancer and its effect of transfection on biological behavior of human NSCLC lines H1299
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For RASGRF2 participating in H-ras signaling pathway, it has been identified as one of potential tumor suppressor genes. There are few reports on whether RASGRF2 plays a role in the pathogenesis of NSCLC. Our study was designed to explore the expression of RASGRF2 in NSCLC, and its effectiveness on clinical and biological features. Furthermore, the effectiveness of RASGRF2 on the biological characteristics of NSCLC lines H1299 was considered. The expression of RASGRF2 was detected by SP in cancerous tissues and adjacent non-neoplastic tissues of 48 patients with NSCLC. Of 18 cases, mRNA were detected by RT-PCR. H1299 were transfected with RASGRF2-GFP. The effectiveness of RASGRF2-GFP on mitotic cycle and apoptosis of stable expression ones were evaluated by Flow Cytometry, and its proliferation were examined by MTS. The loss expression of RASGRF2 in cancerous tissues was 54%, but it was 88% in normal tissues (P<0.05). The mRNA of RASGRF2 in normal tissues and cancerous tissues were 0.783±0.5349 and 0.229±0.6512137, respectively (P<0.018). There were no significant differences between the expression of RASGRF2 and gender, age, smoking status, histological types, classifications, lymph node metastasis and stages(P>0.05). The mitotic cycle of transfected H1299, which had stable expression of RASGRF2-GFP, were found blocked at S stage, but the apoptosis and proliferation had no significant changes.

Conclusion: We detected a small portion of CD4+IL17+Foxp3+T cells in the peripheral blood. The frequency of blood Th17 cells and IL-17A levels in plasma were increased in all patients with non-small cell lung cancer. The ratio of Th17 and Treg cells in patients with stage IV were much higher than that in early stage. Particularly, we detected a small portion of CD4+IL17+Foxp3+T cells in the peripheral blood. Patients with Stage IV have much this kind of double positive helper T cells than other groups.

Conclusions: Reciprocal imbalance of Th17/Treg were found in patients with early disease. The elevated Th17 cell and Treg cell responses were associated with advanced disease, which indicated coexistence of Th17 cell and Treg cell instead of reciprocal imbalance was the major part in the antitumor immunity with the progression of non-small cell lung cancer.

P1218

Regulator and effector T lymphocytes in late stages of non small cell lung cancer and chronic obstructive pulmonary disease
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The outcome of lung cancer may be determined by anticancer immune response. There are only few data available on how DCs (dendritic cell), effector T, NK cells and various regulatory subsets like Treg-s (foxp3+), or NK T-s respond to lung cancer cell lines which demonstrate the highest glycolytic phenotype; we choose to study representative of adenocarcinoma (e.g. H2030, A549, H1563, H1650), squamous carcinoma (e.g. H249) and SCLC cell line (e.g. SHP-77) to determine the development of carcinoma by interfiting mitotic cycle.

P1219

Reciprocal imbalance or coexistence? The distribution of Th17 and Treg cells in peripheral blood lymphocytes in patients with non-small-cell lung cancer and its significance
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Objective: To investigate the distribution of Th17 in relation to Treg in PBMC in patients with non-small cell lung cancer and its significance.

Methods: We analyzed T cells in the peripheral blood of 22 patients with Stage IV, 18 patients with Stage III, 8 patients with Stage I-II and 20 healthy volunteers. The proportions of Th17 and Treg cells in peripheral blood were determined by flow cytometry.

Results: The plasma level of IL-17 and TGF-β were measured by ELISA and the mRNA expressions of RORγt and FOXP3 were detected by realtime PCR.

Conclusions: Reciprocal imbalance of Th17/Treg were found in patients with early disease. The elevated Th17 cell and Treg cell responses were associated with advanced disease, which indicated coexistence of Th17 cell and Treg cell instead of reciprocal imbalance was the major part in the antitumor immunity with the progression of non-small cell lung cancer.

P1220

Glycolytic phenotype mapping in lung cancer cell lines
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Background: It is well established that cancer cell can activate their glycolysis pathway in order to survive in hypoxia micro-environment. Tumors cells show a stinking rate of glycolysis and lactate production, even in the presence of oxygen. Importantly, some cancer cells demonstrate impaired mitochondria respiration and high glycolysis, namely Warburg effect. It is known that most types of cancers fit the “Warburg hypothesis” because a decreased expression of mitochondrial ATP synthase, which is a bottleneck of mitochondrial oxidative phosphorylation. Our overall goal is to profile the lactic acid production in lung cancer cell lines (NSCLC vs SCLC) in order to prototype the glycolytic phenotype that might be used as a diagnostic tool for the early detection of lung cancer.

Study design and preliminary data: Our main steps are: (1) quantify lactic acid production of representatives of NSCLC and SCLC cell lines in order to select lung cancer cell lines which demonstrate the highest glycolytic phenotype; we choose to study representative of adenocarcinoma (e.g. H2230, A549, H1563, H1650), squamous carcinoma (e.g. H249) and SCLC cell line (e.g. SHP-77) (2) measure the glycolysis (e.g.GAPDH and pyruvate kinase) and oxidative phosphorylation...
enzymes (e.g. ATP synthase) level in order to study the glycolytic phenotype of lung cancer cell lines. Our preliminary results indicate that the adenosquamous cell lines, namely A549 and H2300 secreted lactic acid to the medium in concentration of 9.5 and 11.6 mmol/l, respectively.

Impact: Our study could serve as a basis for understanding the glycolytic phenotype mechanism in vitro and therefore for developing diagnosis test for early detection of lung cancer.

P1221
Induced expression of B7-H3 on the lung cancer cells and macrophages suppresses tumor-specific T cell immunity
Jian An Huang 1, Tae Chen 1, Chuan Yong Ma 1, Yuan Zeng Gui 2

Objective: To investigate the effect on tumor invasion and the role of PI3K signaling pathway after the binding of SDF-1 and CXCR4 receptor.

Methods: Flow cytometry (FCM) and RT-PCR were utilized to detect the expression of vascular endothelial-cadherin (VE-cadherin) in different groups to observe the changes of adhesion and invasion ability.

Results: NCI-H446 and H460 cell lines were pretreated with SDF-1 and CXCR4 antagonist AMD3100 and the PI3K inhibitor LY294002. The VE-cadherin expression level correlated with lymph node metastasis. These results indicate that both of them may take part in the growth and invasion of NSCLC.

P1222
The ability of SDF-1/CXCR4 axis to proliferation adhesion and invasion of small lung cancer cell
Jian An Huang 1, Tae Chen 1, Chuan Yong Ma 1, Yuan Zeng Gui 2

Objective: To investigate the effect on tumor invasion and the role of PI3K signaling pathway involved in the proliferation works in the adhesion and invasion of NCI-H446 by CXCR4 activation.

Methods: The clinicopathologic characteristics of 144 patients (73 adenocarcinoma, 71 MPM) were reviewed retrospectively. The tissue samples were evaluated by immunohistochemical staining. The patients who were given adjuvant chemotherapy and/or radiotherapy, with an evidence of residual tumor and who died due to postoperative mortality and due to reasons not related to lung cancer were excluded for survival analysis. Data from remaining 77 patients (37 adenocarcinoma, 40 MPM) were used for survival analysis.

Results: AMACR expression was more frequent in adenocarcinoma group than MPM group (p=0.046). The specificity and sensitivity of AMACR immunostaining in detecting adenocarcinoma were 95.89 and 95.77 respectively. AMACR-positive and negative groups were similar for age, sex, smoking history, tumor diameter, lymph node involvement, tumoral differentiation, T,N factor, and stage. Overall survival was not significantly different between the groups, either.

Conclusion: The specificity and sensitivity of AMACR immunostaining was not high enough to use it as a diagnostic tool in differential diagnosis of MPM and lung adenocarcinoma. AMACR expression did not have a prognostic value in MPM or in adenocarcinoma.

P1224
Ablation of HEDGEHOG pathway enhances apoptosis in lung cancer
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Introduction: Systemic methylation changes may be a diagnostic marker for tumor development or prognosis. We investigated the relationship between gene methylation in lung tumors relative to normal lung tissue, and whether DNA methylation changes can be detected in stored blood samples.

Material and methods: 65 patients were enrolled in a surgical case series of non-small cell lung cancer (NSCLC) at a single institution. Using bisulfite pyrosequencing, CpG methylation was quantified at five genes (RASSF1A, CDH13, MGMT, ESR1 and DAPK) in lung tumor, pathologically normal lung tissue, and circulating blood from enrolled cases.

Results: The analyses of methylation in tumors compared to normal lung identified higher methylation of CDH13, RASSF1A and DAPK in lung tumors compared to normal lung tissue. The lack of reflection of these methylation changes in blood samples from patients with NSCLC indicate their poorly suitability for a screening test.

P1225
Expression of vascular endothelial-cadherin and epithelial cadherin in non-small cell lung cancer and their clinical significances
Jian Tao 1, Hong Chen 2

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 their expression with the clinicopathological characteristics of NSCLC. The expression of them were examined by immunohistochemistry in NSCLC tissues from 97 patients and their adjacent non-neoplastic tissues. The mRNA of them were detected by RT-PCR in 18 specimens. The positive rates of them were 51.5% and 42.3%, respectively. The positive rate of VE-cadherin was higher than that in adjacent non-neoplastic tissues (P < 0.05). The positive rate of E-cadherin was lower than that in adjacent non-neoplastic tissues 67.0% (P < 0.05). The VE-cadherin expression level correlated with lymph node metastasis (P < 0.05), while the E-cadherin expression level inversely correlated with lymph node metastasis (P < 0.05). There were no significant differences between the expression of VE-cadherin, E-cadherin and sex, age, smoking, histological type, differentiation of tumor and TNM stage. The expression of VE-cadherin mRNA in NSCLC tissues and adjacent non-neoplastic tissues were 0.626 ± 0.192 and 0.209 ± 0.602 (P < 0.05). The relative expression intensity of E-cadherin mRNA were 0.700 ± 0.123 and 1.050 ± 0.254 (P > 0.05).
P1226 Expression of vascular endothelial-cadherin and vascular endothelial growth factor in non-small cell lung cancer and their clinical significances  
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To investigate the expression of Vascular Endothelial-cadherin(VE-cadherin) and Vascular Endothelial Growth Factor(VEGF) with the association of clinicopathological characteristics and their correlation in non-small cell lung cancer (NSCLC). Expression of them were examined by immunohistochemical staining in 72 cases of NSCLC patients and their adjacent non-neoplastic tissues, 45 of them were measured by RT-PCR. The positive rates of them in cancer cells were 69.4% and 84.7% respectively, which were higher than the normal tissues(0% and 16.7%) (P<0.01); they were 52.8% and 62.5% in the vascular endothelial cells, which were higher than the normal tissues(20.8% and 29.2%) (P<0.01). In cases without lymph node metastasis, the expression of them in cancer cells and vascular endotheial cells were respectively higher than those in cases without lymph node metastasis. The positive rates of them in III-IV stage were higher than that in I-II stage (P<0.05). There were no significant differences between the expression of them and sex, age, smoking, histological type, differentiation of tumor(P>0.05). The relative expression intensity of VE-cadherin mRNA in NSCLC tissues and adjacent non-neoplastic tissues were 0.62±0.10.182 and 0.44±0.05(P<0.05). The relative expression intensity of VEGF mRNA in NSCLC tissues and adjacent non-neoplastic tissues were 0.27±0.103 and 0.05±0.134(P<0.05). The expression of them in lymph node metastasis were higher compared to that in cases without lymph node metastasis(P<0.05). Our results suggest that VE-cadherin may play an important role in angiogenesis and act in a synergistic manner in NSCLC.

P1227 Increased incidence of Merkel cell polyoma virus in non-small-cell lung cancer  
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Objective: To determine the incidence of Merkel Cell Polyomavirus (MCPyV) in lung tissues of non-small cell lung cancer patients.

Methods: MCPyV DNA was amplified by nested PCR in 150 lung cancer tissues from patients attending University Hospital, Münster, Germany. The positive rate (PR) and mean PR (±SD) in different stages of lung cancer were calculated. The PR was compared using the χ² test.

Results: The MCPyV prevalence in NSCLC was 7.3% (11/150). No significant difference in the PR was observed between stages I-II (3.3% ± 3.2%) and III-IV (10.0% ± 5.9%). The PR was higher in squamous cell carcinomas (9.7% ± 4.2%) than in adenocarcinomas (4.0% ± 2.0%).

Conclusions: MCPyV is present in 7.3% of NSCLC cases and the PR does not vary significantly by stage.

P1229 The effect of siRNA on invasion capability of small cell lung cancer  
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Objective: To determine the effect of siRNA on invasion capability of small cell lung cancer (SCLC).

Methods: Small cell lung cancer cell line NCI-H446 was transfected with four different siRNAs targeting CXCR4. The effect of siRNA on invasion capability of NCI-H446 in vitro was evaluated by transwell chamber model.

Results: Transfection with CXCR4 siRNA led to a significant reduction in cell invasion compared to the control group.

Conclusions: CXCR4 siRNA effectively down-regulated the expression of CXCR4 gene and decreased invasion capability of NCI-H446 cells in vitro.

P1230 microRNA-155 negatively regulates Apaf-1 and enhances sensitivity of A549 to cisplatin  
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MicroRNA-155(miR-155) overexpression is often found in malignancies including lung cancer. The objective of this study is to verify the hypothesis that miR-155 is involved in development and progression of lung cancer by modulating cell apoptosis and DNA damage through regulation on Apaf-1, which is postulated according to the bioinformatics analysis. Firstly, the expression of miR-155 and Apaf-1 protein in the lung cancer tissues were measured. The results showed that expression of miR-155 is significantly higher in lung cancer tissues compared with the paracarcinous tissues. The Apaf-1 protein expression level decreased in lung cancer tissues. Then the miR-155 silenced and Apaf-1 overexpressed A549 cell models were established through transfection with pMAGic2.0-BIC-siRNA and pMAGic2.0-BIC-siRNA-Apaf-1, respectively. The cell apoptosis and DNA damage of different cell models under treatment with cisplatin were assessed, and the untransfected A549 cells were used as negative control. The results showed that silenced miR-155 resulted in elevated apoptosis of A549 cells, but the Apaf-1 mRNA level had no significant difference compared with the control group. Both miR-155 silencing and Apaf-1 overexpression in A549 cells seemed greatly increase the cellular sensitivity to cisplatin treatment as evidenced by elevated apoptosis rate and DNA damage. Further, dual-transfection with both miR-155 siRNA and Apaf-1 siRNA in A549 cells resulted in attenuation and alleviation of cell apoptosis and DNA damage. In conclusion, inhibition of miR-155 can enhance the sensitivity of A549 cells to cisplatin treatment by regulation on cell apoptosis and DNA damage through Apaf-1 mediated pathway.

P1231 The effect of methylene blue in the photodynamic therapy on A549 lung cancer cell lines  
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Background: Methylene blue (MB) is a safe and cheap chemical widely used in the medical fields for a long time. MB was recently known to act as a photosensitizer and some clinical trials of using it in the photodynamic therapy on the tumor cell lines were reported. In this study, we investigated the effects of MB as a photosensitizer on the lung cancer cell lines.

Methods: After pretreatment of A549 cells with MB in the concentrations of 1 μM and 2 μM respectively, the cell apoptosis and DNA damage were evaluated.

Results: Out of 290,000 genes, 250 genes were significantly (at least twofold) up-regulation or down-regulation. Differentially expressed genes were categorized into "Top BIO Functions" groups. The three most important groups were "cellular growth and proliferation" (n=80), "cell movement" (n=75), and "inflammation response" (n=65). The observation of a positive association of MALAT-1 gene expression with cellular growth, migration and proliferation was confirmed in vitro with migration assays, colony assays, and scratch assays (p<0.01, all comparisons).

Conclusions: These data demonstrate that enhanced MALAT-1 expression levels stimulate cellular migration, colony formation and wound healing and contribute to the idea of multidimensional effects of MALAT-1 on important cellular functions in malignant lung cells.

P1232 Vascular endothelial-cadherin and vascular endothelial growth factor in non-small cell lung cancer and their clinical significances  
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Objective: To study the inhibitory effect of CXCR4-targeted small interference RNA on invasion capability of NCI-H446 in vitro.

Methods: To design chemical synthesis of CXCR4-specific siRNA based on the target sequence for CXCR4 cDNA with NCI-H446 cells transfected with siRNA. To detect the expression of CXCR4 by RT-PCR and Western Blot. Invasion capability of NCI-H446 cells in vitro was evaluated by transwell chamber model. The proliferation capability was determined by CCK-8 assay.

Results: After transfected with the expression of CXCR4 mRNA and protein was down-regulated significantly. The invasion capability of cells in vitro decreased compared with the empty liposome group. The penetrating number iniferior to CXCR4-siRNA transfected group was 12.5±8.62 vs 32.8±9.45 (p<0.05). There was no effect on cell proliferation after transfection of CXCR4 siRNA on NCI-H446 cells.

Conclusion: CXCR4 siRNA effectively down-regulated the expression of CXCR4 gene and decreased invasion capability of NCI-H446 cells in vitro.
with MTI, and the formation of ROS was checked with DCFH. To evaluate the mechanism of apoptosis, the activation of Caspase family was checked, and the fragmentation of PARP-1 was studied by the western blotting method.

Results: By the increases of the concentration of MB and the energy of Diode LASER, the level of apoptosis of cell lines and ROS synthesis were significantly increased. Pretreatment with antioxidant suppressed these findings. In the induction of apoptosis, the activation of Caspase 3, 8, and consequent fragmentation of PARP-1 was observed.

Conclusion: MB induced apoptosis in the A549 lung cancer cell lines as a photo-sensitizer, and its effect was increased by the concentration of MB and the energy of Diode LASER.

P1232
Tumor size and inflammatory cytokines in exhaled breath condensate in patients with non small cell lung cancer (NSCLC). Luisa Brunnen1, Marta Morando2, Marta Malandra2, Caterina Buca4, Giovanni Roli1, Robert Giobbe3, Irene Parisi2, Monica Boita2.

Background: Local and systemic inflammation play a key role in the genesis and progression of lung cancer; vascular endothelial growth factor (VEGF) has been related to progression and local extension of many tumors. Involvement of Th17 lymphocytes (Th17) and their cytokines (IL-17, IL-6) in cancer has been recently postulated. Lung inflammation may be non-invasively assessed by cytokine assay in exhaled breath condensate (EBC).

Aim and objectives: To assess the possible correlations between systemic and local Th17 related cytokines, VEGF and tumor size evaluated by CT-scan in patients with NSCLC.

Methods: Fifteen consecutive patients (12 males; mean age 64 years) with NSCLC classified in stage IA-IIIA, were enrolled. Lung CT-scan, EBC and serum samples were obtained in each patient. IL-6, IL-17 and VEGF were measured by ELISA.

Results: Tumor mean diameter was 3.28 cm (SD 2.33). Mean cytokines values in serum and EBC are shown in table 1.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Serum</th>
<th>EBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17</td>
<td>0.17</td>
<td>2.85</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.05</td>
<td>0.29</td>
</tr>
<tr>
<td>VEGF</td>
<td>19.27</td>
<td>78.45</td>
</tr>
</tbody>
</table>

Mean (±SD) serum and EBC cytokines levels (ng/ml).

EBC level of VEGF was significantly correlated with EBC-IL-6 (p=0.314, p=0.030) and IL-17 (p=0.697, p=0.011). A significant correlation between tumor diameter and IL-6, IL-17 and VEGF in EBC was observed (r=0.440 p=0.013, r=0.444 p=0.013, r=0.332 p=0.039 respectively). No correlation was found between serum cytokine and tumor size.

Conclusion: This is the first observation reporting Th17 cytokines in EBC in NSCLC. The correlation between Th17 cytokines and tumor size suggests the involvement of Th17 cells in the progression of neoplasia.

1.19. Instructive clinical aspects of thoracic oncology

P1233
Octogenarians with non small cell lung carcinoma – Advanced disease

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Approximately 50% of new non-small cell lung cancers – advanced disease (NSCLC-AD) cases are diagnosed in the elderly and nearly 20% are detected in patients aged 80 years and older. Limited information is available about the correct approach in octogenarians.

Objective: Retrospective observational analysis of elderly patients with NSCLC-AD in order to assess epidemiological characteristics, performance status (PS), co-morbidities, concomitant medications, therapy and survival.

Results: In seven years (2004-2010), 108 octogenarians were diagnosed with NSCLC-DA. The median age was 82 years and 68.5% were men. We found 54.6% former smokers, 34.2% non-smokers and 11.2% active smokers. Adenocarcinoma was found in 51%, squamous carcinoma in 41.7% and NSCLC – NOS in the remaining patients. At diagnosis, 48.1% had PS 0, 31.8% had PS 2 and 13.9% had PS 3. Evaluation of co-morbidities showed that 58% of patients had ≤ 3, while the remainder had > 3 co-morbidities (4-9). These co-morbidities warranted that 62% of the patients received more than 4 drugs as concomitant medication. Chemotherapy was the option in 45 octogenarians. In 11 patients we decided to do a doublet with a platinum plus gemcitabine. In the remaining 34, our option was monochemothepmy with oral vinorelbine in 26 and pemetrexed in 8 patients. Toxicity with serious side effects explains why only 14 of the 43 patients completed 4 cycles. Overall median survival was 3.1 and 8.6 months for those who started chemotherapy, regardless of whether single or doublet.

Conclusion: The increase in life expectancy, along with the research of new and less toxic therapies justifies a revisit of this population group, where prospective clinical trials are needed.

P1234
The primitive bronchogenic carcinoma in the elderly

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The increased incidence of lung cancer in the elderly is associated to the increase of the intrinsic risk to develop a cancer with age, to the ageing of the population and especially to the smoking and the exposure to occupational and environmental carcinogens. We realized a retrospective study of 108 patients aged of 65 year old and older, hospitalized in the department of Respiratory Diseases, UHC Ibn Rochd between January 2008 and January 2010. It is about 96 men and 12 women. The average age is 69 years old. Smoking is found in 90 cases, the symptomatology is dominated by coughing, chest pain, dyspnea in 80 cases, and hemoptysis in 46 cases. The thoracic imaging showed, more the tumoral processus of mediastinal adenopathies in 50 cases, a bone lysis in 12 cases, a balloon release in 10 cases, the peripheral ganglia biopsy in 26 cases, pleural needle biopsy in 4 cases. The bronchoscopy revealed a budding tumor in 56 cases, a tumor infiltration in 24 cases. The diagnosis is based on bronchial biopsies in 68 cases, the transnasal needle biopsy in 26 cases, the peripheral ganglia biopsy in 4 cases, pleural needle biopsy in 4 cases and the thoracotomy in 5 cases. The epithemoid carcinoma is the most common histotypical type in 45 cases, followed by adenocarcinoma in 40 cases, small cells carcinoma in 10 cases and undifferentified carcinoma in 13 cases. At the end of the complete physical examination, 55% of the patients were classified stage IV. The bronchogenic carcinoma of the elderly is often revealed in the late stages. Its therapeutic management depends on the patient's general condition and related defects.

P1235
Impact of radon residential concentration in the development of lung cancer in Transilvania, Romania

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Lung cancer represents the most frequent cause of mortality caused by malignancies in the world. The World Health Organization (WHO) has classified radon (Rn) as a [Class A] known human carcinogen, because of the wealth of biological and epidemiological evidence and data showing the connection between exposure to radon and lung cancer in humans.

The aim of this study was to investigate the correlation between the exposure to radon and lung cancer in patients from the centre counties of Transilvania, Romania.

Material and method: We conducted a case-control study, by location of 250 Rn detectors between 2009-2011. 104 Rn detectors in patients with lung cancer and 146 Rn detectors in controls from the centre counties of Transilvania.

Results: We observed that the risk of developing lung cancer has increased with the magnitude of Rn exposure. At a Rn concentration between 0-49.8 Bq/m³ OR was 1; at 50-79.9 Bq/m³ OR was 2.14 (CI 1,04-5,11); 80-139.9 Bq/m³ OR was 2.44 (CI 1,9-5,10); > 140 Bq/m³ OR 2.60 (CI 1,9-5,45).

Conclusion: The strenght of association between residential Rn exposure and lung cancer is increasing with higher concentration of Rn. This findings support the implication of Rn in developing lung cancer.

P1236
Seroprevalence of human herpesvirus type 8 infection in patients with lung carcinoma

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Background: Human herpesvirus type 8 (HHV-8) DNA is found consistently in all types of Kaposi’s sarcoma (KS), which is sometimes seen in human immunodeficiency virus (HIV) infected patients with immunologic abnormalities. Lung carcinoma is one of the most common malignancies developing in immunocompromised patients. However, the prevalence of HHV-8 infection in lung carcinoma patients is unclear.

226s
Methods: Blood samples were collected from 109 lung carcinoma patients with malignant pleural effusion and 109 age-matched healthy controls and analyzed for lymphocyte and monocyte counts, and presence of HHV-8 antibody and DNA. All study subjects were negative for anti-HIV antibodies.

Results: Lung carcinoma patients had significantly lower mean lymphocyte counts and significantly higher monocyte counts than the healthy controls (P < 0.001). Three patients with lymphopenia and stage IV tumor were positive for HHV-8 DNA, one of them was negative for HHV-8 antibody. HHV-8 positivity was significantly higher in patients (42.2%), particularly in male patients (50.8%), than in healthy controls (24.8%) (P = 0.006 and < 0.001, respectively). HHV-8 positivity was significantly greater in male patients (50.8%) than in female patients (29.5%) (P = 0.028), and in patients with stage IV tumors somewhat greater than with stage III B tumors (P = 0.416). HHV-8 antibody titers in patients also significantly exceeded those in healthy controls (P = 0.004). All subjects positive for HHV-8 were not associated with clinical manifestations of HHV-8 infection.

Conclusions: HHV-8 seroprevalence was significantly greater in lung carcinoma patients than in healthy controls, and associated with gender.

P1237
Pulmonary function testing in patients with lung cancer
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Introduction: Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) have the same predisposing factor. We studied lung function on patients diagnosed with LC in our hospital.

Methods: Patients diagnosed with LC from April 1st 2009 to September 30th 2010 were prospectively studied. Clinical data included histology, stage, spirometry, weight lost, body mass index (BMI) and albumin. For statistical analysis, Student’s t-test was used.

Results: Of 221 patients who fulfilled in our inclusion criteria, 78% were male, and the mean age was 62.4 years. Histology types were adenocarcinoma (39), squamous cell carcinoma (22) and Small-cell lung cancer (14). 53 patients (58%) were classified as stage IIIB or IV. Mean Spirometric values were: FEV1 71%, FVC 86%, FEV1/FVC 65%. The three Spirometric parameters were smaller in men (no statistical differences with women). 54.8% of patients were diagnosed as COPD, with FEV1/FVC < 0.70. Among the stages IA to IIIA, 52% of patients had COPD, among stages IIIB and IV, 58% FEV1 and FVC values were smaller in patients with a weight loss over 5% (P < 0.05 and P = 0.035, respectively). BMI had a positive effect in the three Spirometric parameters. A positive effect of the albumin level was found in FEV1 and FVC, but not in the relation FEV1/FVC.

Conclusions: More than half of patients diagnosed with LC in our hospital have also COPD, with similar frequency for all stages.

P1238
Rate of chest x-rays (CXR) 12 months prior to diagnosis of lung cancer
Thomas Chin1, Rehan Mustafa, Anthony Roberts.

Aim: To analyse the number of CXRs performed in the 12 months prior to a diagnosis of lung cancer according to stage at presentation.

Methods: We reviewed 315 patients with a thoracic malignancy between Jan 2010 and Feb 2011. Number of CXRs in the year prior to diagnosis and stage of disease at presentation were recorded. We examined the proportion of patients that had fewer than 2 CXRs in that year for each stage of disease. These results were then compared using a Chi square test.

Results: After exclusions, 259 cases of non-small cell lung cancer were analysed. The results are compiled in Table 1 below. A significant proportion of patients presenting with later stage disease had fewer than 2 CXRs in the year prior to diagnosis than those with early disease (p = 0.019).

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;2 CXRs</th>
<th>%</th>
<th>2 or more CXRs</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>25</td>
<td>40</td>
<td>37</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>Stage II</td>
<td>24</td>
<td>49</td>
<td>25</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Stage I</td>
<td>90</td>
<td>61</td>
<td>58</td>
<td>39</td>
<td>148</td>
</tr>
</tbody>
</table>

Conclusions: It appears that patients with later stage disease are having fewer CXRs in the year prior to diagnosis than those with earlier disease. The results probably calls for increased awareness of lung cancer symptoms by both primary care physicians and general public, to facilitate early referral to secondary care.

P1239
Importance of further follow up in patients with negative histology from CT guided biopsy
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Background: Ongoing conclusive histology to diagnose lung cancer is an important part of the management of potential lung cancer patients. Due to recent advancement in the techniques CT guided biopsy is becoming increasingly important in obtaining histology samples. We describe our experience of usefulness of CT guided biopsy samples over 4 years and follow-up of negative histology samples in suspected lung cancer patients.

Results: We collected samples (2008-2011) of CT guided biopsy booked in our hospital. 314 procedures were planned in 313 patients. 292 procedures were carried out. The main reason for not carrying out the procedure was shrinkage of the mass seen on the day of the procedure. 23/292 (80.1%) confirmed the diagnosis of lung cancer. 10/292 (3.4%) lead to diagnosis of other cancers (myeloma, metastatic cancer, lymphoma). 42/292 (14.8%) showed non-cancers (mainly inflammation). The biopsy was inconclusive in 292 (2%) samples.

The 81 patients who did not have a biopsy or were labelled as non-lung cancers, underwent further investigation or had clinical diagnosis due to ill health. 26/81 (32%) had lung cancer, 14/75 (19%) had other cancers, 41/81 (50.6%) did not have a cancer diagnosis after follow up.

Conclusions: We have shown that CT guided biopsy provides us with good histology samples and if correct patients are identified the histological diagnosis rate is greater than 90%. At the same time the patients with a high suspicion and negative biopsy have approximately 1 in 3 chance of having a lung cancer. It is therefore recommended that patients with negative histology should have further diagnostic tests.

P1240
Diagnostic value and prognostic significance of pleural C-reactive protein in lung cancer with malignant pleural effusions
Hak-Ryul Kim, Ki-Eun Hwang, Hwa-Jung Kim, Eun-Taik Jeong. Pulmonology, Wonkwang University Hospital, Iksan, Korea

C-reactive protein (CRP) has been implicated in various inflammatory and advanced malignant states. Increased serum CRP levels have been shown in association with independent prognostic factor for survival in patients with advanced lung cancer. However, only few studies have focused on the role of CRP in pleural effusions. This study aimed to evaluate the diagnostic value of pleural CRP to discriminate lung cancer with MPE from benign effusion and its prognostic role in lung cancer patients with MPE. Pleural effusion samples were collected from patients with MPE (68 lung cancers, 12 extrathoracic tumors), and from 68 with various benign conditions. Concentrations of pleural (p) and serum (s) CRP were measured by ELISA. The expression profile of CRP in pleural fluid, and its association with survival were investigated. P-CRP levels correlated with s-CRP levels (P = 0.0088). The area under the ROC curve (AUC) of p-CRP (0.86) in their diagnostic accuracy to differentiate lung cancer with MPE from benign pleural effusion was greater than those of s-CRP (0.77). High p-CRP expression was significantly correlated with shorter overall survival (P = 0.0001). A multivariate Cox regression analysis, p-CRP was independent prognostic factor significantly associated with overall survival (P = 0.0001). The relative risk of overall survival for lung cancer patients with high p-CRP was 3.909 (95% CI, 2.500-7.639). In conclusion, P-CRP is superior to s-CRP in determining the pleural fluid etiology. Quantitative assay of CRP in pleural effusion might be useful complementary test both in diagnosis and prognosis for lung cancer patients with MPE.

P1241
The elevation serum napsin A in primary lung adenocarcinoma, compared with CEA
Takuya Sunumukai, Tsutomu Hamada, Keiko Mizuno, Ikkiy Higashimoto, Hiromasa Inoue. Pulmonary Medicine, Graduate School of Medical and Dental Science, Kagoshima University, Kagoshima, Japan

Napsin A is an aspartic proteinase with a molecular weight of approximately 38 kDa, which is expressed in normal lung parenchyma in type II pneumocytes. It has been reported that napsin A immunohistochemical reactivity is associated with primary lung adenocarcinoma. However, napsin A has never been tested as a serum marker for primary lung adenocarcinoma.

The aim of this study was to investigate the potential of serum napsin A as a tumor marker in patients with primary lung adenocarcinoma, compared with CEA. Subjects consisted of 46 patients with primary lung adenocarcinoma, 16 patients with non-pnodiagnosis, and 43 healthy subjects. Serum CEA and napsin A were measured by ELISA. Statistical analysis was performed using SPSS ver19.0.
Baykal Tulek 1, Habibe Kaylir 2, Fikret Kanan 1, Ugur Arslan 3, Furak Ozer 4.

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The basic uses of C reactive protein (CRP) and procalcitonin (PCT) in the clinical practise is in the diagnosis and follow-up of infectious disease. The fact that CRP already achieves high levels in cases with lung cancer, however, limits its diagnostic specificity. PCT may be an important marker in the differential diagnosis of febrile lung cancer patients with high CRP levels. Our objective in this study was to determine the levels of CRP and PCT in patients with newly diagnosed non-infectious non-small cell lung cancer (NSCLC) and to relate these results to patient and disease characteristics.

Serum CRP and PCT levels were measured in 79 histopathologically proved NSCLC patients and 20 healthy controls. Results were compared with demographic and clinical variables in patients with NSCLC. Serum CRP concentrations were significantly higher in NSCLC patients compared to control group (CR 7.79 ± 1.185 mg/dl; p < 0.001). There were no significant difference between two groups in PCT levels (p > 0.05). A mild, positive correlation was found between CRP level and tumor diameter. When comparing CRP levels in the lung cancer patients grouped according to age, sex, smoking status, clinical TNM staging and performance status (PS), the only significant difference found was that according to PS score. High serum CRP levels in noninfectious NSCLC patients are mainly related to PS status and tumour size. Adding serum PCT measurement in these patients may contribute to exclude infections in patients with NSCLC.

P1243

An unusual diagnostic tool in metastatic bronchogenic carcinoma: Peripheric embolectomy

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Heart may rarely be affected by primary or secondary tumors. Rarely, arterial tumor embolization may be first and/or most important issue during the course of the tumor. Most common sites of arterial tumor occlusions are common femoral and popliteal arteries. A 77-year-old man admitted with chest pain and cough. Thoracic computed tomography revealed a heterogeneous ill-defined mass originated from left upper lobe bronchus extending and invading hilar structures. Fiberoptic bronchoscopy revealed an endobronchial lesion on the orifice of lingular bronchus. In PET/CT, increased FDG uptake of satellite lesion on upper lobe destructing the fourth rib posteriorly, and probably metastatic mass invading left ventricle of the heart were conspicuous.

Echocardiography confirmed an intracardiac mobile mass, implanted to the left ventricle. On the 10th day, cyanosis of the right arm developed. It was due to right brachial artery occlusion confirmed by angiography. Urgent embolectomy was performed and clot specimens were sampled. Histopathological examination of embolectomy material showed atypic squamous cells, thus final report was metastatic lung cancer.

Arterial embolization highlights the advanced disease, poor prognosis with significant costs and morbidity. Embolectomy is often enough for symptomatic relief. This unique case illustrates the quite rare occurrence of peripheric tumor embolization originated from metastatic heart disease.
effects, so the usage of cisplatin has a limitation. Recently, autophagy has become an important mechanism of cell death. The purpose of this study was to determine whether low dose cisplatin treated lung cancer cell induce autophagy and the autophagy inhibition resulted in the apoptosis or necrosis. H460 cells were treated using autophagy specific inhibitors(3-MA). To confirm the result of autophagy inhibition, we had done Annexin-V/PI and cell cycle assay. To find out the cisplatin mediated autophagic mechanisms, we examined the apoptotic regulator, p53. We used p53−/− nude cancer cell line, H1299, to prove the role of p53 during cisplatin treatment. Low dose of cisplatin(5 μM) induced the apoptosis after 24 h treatment in H460. Also low dose of cisplatin showed autophagic vacuoles and cytoplasmatic LC3 formation in H460. The induction of autophagy by low dose cisplatin was inhibited by 3-MA, which was proven by reduced acidic vesicles. When the autophagy inhibited, Annexin-V+/PI− and subG1 was an increased. The inhibition in inhibition resulted in the decrease of LC3-II band. Also cleaved caspase-3 and PARP were increased. Taken together, low dose cisplatin induced autophagy and autophagy inhibited, Annexin-V+/PI− and subG1 was an increased. The inhibition of autophagy resulted in the decrease of LC3-II band. Also cleaved caspase-3 and PARP were increased. Taken together, low dose cisplatin induced autophagy and the inhibition of autophagy resulted in the apoptosis.

P1247
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. 7-year follow-up of a rare clinicopathologic syndrome
Roger Fei Falkenstein-Ge, Martin Kimmich, Godehard Friedel, Andrea Tannapfel, Volker Neumann, Martin Kohlhann, Pathomology, Clinic Schillerhoehe, Center for Pulmonology and Thoracic Surgery, Gerlingen, Baden-Württemberg, Germany Thoracic Surgery, Klinik Schillerhoehe, Center for Pulmonology and Thoracic Surgery, Gerlingen, Baden-Württemberg, Germany Pathology, Ruhr University of Bochum BG, Bochum, Nordrhein-Westfalen, Germany

Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare clinical pathological syndrome. There have been only 49 cases of DIPNECH reported in the literature so far.

Aims and objectives: DIPNECH is confined to the airway mucosa without penetration through the basement membrane and appears in a diffuse pattern, little is known about the clinical course and treatment of DIPNECH.

Methods: DIPNECH is primary proliferations and can combine with obliterator bronchitis and bilateral reticulonodular infiltrates. The diagnosis requires the presence of hyperplasia of the airway neuroendocrine cells without invasion beyond the basement membrane. If DIPNECH breaks through the basement membrane and invades locally, this is called tumors, whereas nodules caused by DIPNECH > 5 mm in diameter are classified as carcinoid tumors.

Results: During the 7 years follow up, the patient was repetitively treated with oral steroids because of coughing and dyspnea. The oral steroid therapy was finally replaced by inhaled steroids. All CT-scans over a 7−year period showed stable disease without progression of the bilateral pulmonary lesion.

Conclusions: We present a 7-year-follow-up of DIPNECH with stable disease by a non-smoking male patient. The long-term follow up is necessary because there is an association between DIPNECH and peripheral carcinoid tumours. The majority of patients presenting with DIPNECH are middle-aged females with symptoms of cough and dyspnea. In general the clinical course remains stable, however progression to respiratory failure does occur.

P1248
Disappearance of hypoglycemic attacks after resection of solitary fibrous tumors with high expression of insulin-like growth factor II
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Hypoglycemia rarely accompanies solitary fibrous tumors (SFT) of the pleura, occurring in only about 4% of patients. We describe our experience with 2 patients whose hypoglycemic attacks disappeared after the resection of SFT.

Patient 1: The patient was an 81-year-old woman. Computed tomography of the chest showed a mass compressing the entire right lower lobe. SFT was diagnosed on histopathological examination of a percutaneous needle biopsy specimen. Subsequently, tumor resection was performed, and the hypoglycemia disappeared. Histopathologically, the tumor was associated with abundant proliferations of markedly hyalinated collagen fibers. The tumor contained small bundles of round cells or spindle cells with mild atypia, proliferating in an irregular, intermingled fashion. On immunohistochemical staining, the tumor cells were positive for CD34.

Patient 2: The patient was a 77-year-old man with dyspnea on exertion. Preoper- ative computed tomography showed a well-demarcated, giant mass compressing the right middle lobe. Therefore, the mass was resected, and the hypoglycemia disappeared. Histopathological examination revealed proliferations of collagen fibers containing spindle cells with low-grade atypia, proliferating in an irregular storiform fashion with positive for CD34. In both case, serum insulin level valued remarkably lower than 0.2μU/ml and the immunohistochemical staining of Insulin-like growth factor II (IGF-II) were positive.

Tumor resection was suggested to be an effective treatment for hypoglycemic attacks in patients with SFT. IGF-II may provide negative feedback with respect to insulin secretion.

P1249
A temporal effect of EGFR tyrosine kinase inhibitor in lymphoepithelioma-like carcinoma of lung
Koichiro Chiu1, Koichiro Chiu1, Tzu-Sheng Chen1, Division of Chest Medicine, Buddhist Tzu-Chi General Hospital; Tzu-Chi, Tainan, Taiwan; 2Chest Medicine, Saint Mary’s Hospital, Hualong, Yilan, Taiwan

Introduction: Primary lymphoepithelioma-like carcinoma (LELC) is a rare in lung. Recent studies suggested a prevalent mutation on epidermal growth factor receptor (EGFR) in LELC of lung. However, the therapeutic effect of EGFR tyrosine kinase inhibitor (TKI) has not been tested. We hereby report an effect of EGFR TKI on LELC of lung.

Case report: A 70-year-old woman presented to have a lung tumor, 6.1x5.1x5.0 cm, over left upper lobe. CT-guided core-needle biopsy of lung tumor confirmed the diagnosis of LELC, and a clinical stage of TNM0, stage IIIB, was met. The patient had a partial response after completing 6 cycles of 1st-line chemotherapy (CIT) with gemcitabine plus cisplatin, and 4 cycles of 2nd-line CIT with docetaxel.

After having a progression, she went on a TKI therapy. The tumor kept shrinking through 6 months, until progressing after 9-month TKI treatment.

Discussions: This is the first report demonstrating a therapeutic effect of EGFR TKI on LELC of lung, as a 3rd-line therapy in this case. The case report suggests EGFR TKI, at least erlotinib, may be beneficial for patients with LELC of lung, at least for a significant period of time.

P1250
Late lung metastasis of endometrial cancer. Two rare cases of patients with late lung metastasis of primary endometrial cancer 14 and 17 years after initial treatment
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Introduction: The longest interval of lung metastasis from endometrial cancer was initially reported 17 years after standard surgical treatment. Aims and objectives: Nearly 80% of all recurrences of endometrial cancer occur within 3 years after the initial treatment. We report two cases of lung metastasis 14 and 17 years after the initial surgical treatment of endometrial cancer.
Methods: A 71-year-old female was referred to our center for histological diagno-
sis of lung lesions. Histological biopsy showed lung metastasis of an endometrial
cancer which was resected 17 years ago. A 77-year-old female was also referred for histological diagnosis of multiple lung lesions and a clavicle metastasis. Both clavicle and lung biopsy revealed metastasis of an endometrial cancer treated 14 years ago surgically.

Results: Our first patient was treated with organ-preserving metastatic wedge resection. The latency period in the first case between initial treatment of endometrial cancer and pulmonary metastases was 17 years. Our second patient with widespread metastasis was treated with palliative radiotherapy and systemic chemotherapy. The latency period between initial diagnosis and treatment of endometrial cancer and pulmonary metastases in the second case was 14 years.

Conclusion: Lung metastases originating from tumors of the female genital tract endometrial cancer and pulmonary metastases in the second case was 14 years.

P1254
Malignant mesothelioma. A survival analysis of 123 consecutive cases at an occupational clinic
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Aim: To describe the asbestos exposure, to identify factors associated to the prognosis, and to calculate the median survival time in 123 consecutive patients (1984-2010) with pathological verified diagnosis of malignant mesothelioma (MM).

Method: From medical records we identified age, sex, asbestos fibres exposure, localisation and subtypes of MM, performance status, and treatment.

Results: Median age was 65 years (min. 41 - max. 90) and 111 (90.2%) were men and 12 (9.8%) were women. We identified asbestos exposure in 112 (91%) patients. Shipbuilding- and other industries were the most common occupational exposures. Among the patients, there were significant variables for mortality rate ratio (MRR) (95% CI) were male sex: 2.26 (1.90-2.70) and asbestos exposure: 2.03 (1.65-2.49) where the patients were exposed to asbestos fibres by nature and type.

Conclusion: The survival of patients with malignant mesothelioma is highly dependent on asbestos exposure. Further, asbestos exposure was identified in 91% of the patients, shipbuilding- and other industries were the most common occupational exposures. Among the patients, there were significant variables for mortality rate ratio (MRR) (95% CI) were male sex: 2.26 (1.90-2.70) and asbestos exposure: 2.03 (1.65-2.49) where the patients were exposed to asbestos fibres by nature and type.
P1255
Prognostic factors and survival in malignant pleural mesothelioma at a large tertiary referral center in Turkey
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Malignant pleural mesothelioma is a rare tumor but increasing incidence and poor prognosis despite new therapy modalities. In this study we aimed to investigate the effects of various pretreatment clinical and laboratory characteristics on survival of patients with malignant pleural mesothelioma (MPM).

During last five years, 125 histologically proven MPM cases were evaluated at large tertiary referral center in eastern part of Turkey. Patients age, gender, performance score, histology, asbestos exposure, smoking history, symptoms, plasma platelet count, haemoglobin, white blood cell (WBC), plasma LDH levels, stages were evaluated in both univariate and univariate analysis. Univariate analysis showed that patients with extensive stage, N2 nodal invasion and M1 metastasis have a worse prognosis. Multivariate Cox regression analysis showed that survival was independent on indicators of worse prognosis (HR 1, 95 CI 1.015-2.19, p=0.017).

As a result: The patients with extensive stage, N2 nodal invasion and M1 metastasis were found to related with shorter survival. Sarcomatous histology were found as an independent worse prognostic factor in MPM.

P1256
Malignant pleural mesothelioma stage III and IV: retrospective analysis of ten years in a central hospital
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Introduction: Pleural mesothelioma (PM) is the most frequent malignant primary tumor of pleura. The incidence in Western Europe is still rising due to the prolonged latency of the disease.

Aims: Determine demographic, epidemiological, histological and therapeutical aspects of malignant PM in stage III and IV. Evaluate survival rates.

Methods: The study was conducted in an European central hospital covering approximately 475.000 inhabitants. We performed retrospective analysis of cases diagnosed in our department over a period of 10 years. Survival analysis was performed using Kaplan Meier method and Cox regression.

Results: We diagnosed 32 cases in stages III/IV (91.5% of total), 84.4% men, median age 61.0 ± 10.2 years, 50% of cases with current smoking, and 20% of cases exposure to tobacco. Exposure to asbestos was reported in 56.5% and had occurred, on average, 41.4±10.8 years before. Approximately 50% of exposures were associated with building construction and 24% with car mechanic. In 87.5% the diagnosis was obtained with video-assisted thoracic surgery. Histology was epithelioid in 84%. All patients received chemotherapy: 53.1% carboplatin+gemcitabine, 37.5% pemetrexed+cisplatin and 9.4% cisplatin+gemcitabine. Hematological toxicity occurred in 18.8% and non haematological toxicity in 12.5% (grade 3/4). Prophylactic local radiotherapy was performed in 75%. Median survival was 51.6±9.4 weeks. There was no statistically significant difference according to chemotherapy regimen.

Conclusion: Malignant PM must be considered, particularly in men involved in mechanics, even with unrecognized or remote exposure to asbestos. In our series no difference was seen combining platinum analogs with gemcitabine or pemetrexed.

P1257
Pleural atypical mesothelial hyperplasia: An early stage of pleural malignant mesothelioma?
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Mesothelioma is a neoplastic process most often secondary to asbestos exposure. Atypical mesothelial hyperplasia (AMH) is thought to be a benign process in reaction to various processes, including infectious pleurisy and recurring transudative pleural effusion. However, it is unknown if there might be a link between AMH and malignant pleural mesothelioma (MPM).

Herein, we present the case of a 69 year-old patient with documented asbestos exposure in whom MPM was diagnosed four months after a first diagnosis of AMH. Thoracoscopy showed inflammation of the posterior parietal pleura and white lymphangitis of the anterior pleura, without nodules or other suspicious lesion. Biopsies taken from the anterior pleura showed AMH.

Two months later, the patient returned with a recurring right sided effusion. CT-scan revealed a subcarinal lymph node measuring 15x8mm and a pleural effusion with partial atelectasis of the right lower and middle lobes.

The thoracoscopy was performed, four months after the initial one. The pleura was dramatically changed, with numerous nodules and neoplastic lymphangitis. Multiple biopsies were performed on the diaphragmatic and posterior pleural surface to investigate the causal relation with asbestos. Whether mesothelioma evolves from atypical hyperplasia, as epithelioid-derived cancer of other origins, remains to be elucidated.

Conclusion: Diagnosis of MPM relies on pleural biopsy specimens. Thoracoscopy is particularly useful in guiding pleural biopsies and in symptomatic improvement if pleurodesis is performed.

P1258
Role of medical thoracoscopy in diagnosis of recurrent undiagnosed pleural effusion
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Background: The urge for the resurgence of thoracoscopic techniques came essentially from the depressive situation of chronic exudates not diagnosed in 20-40% of cases after using the ordinary diagnostic methods.

Methods: This study comprised 20 cases with exudative pleural effusion, all of them were subjected to full history taking, clinical examination, laboratory investigations, radiological examination (chest x-ray and CT), abdominal US, chest US if needed, tuberculin test, sputum for AFB, ABG and ECG. For all patients, pleural tapping and biochemical, cytological, bacteriological and immunological examinations for the pleural aspirates, as well as blind Abrams needle pleural biopsy and histopathological examination were done. The etiologic diagnosis of pleural effusion was not settled after all these investigations, and thus, medical thoracoscopy, under local anesthesia, was carried out for each patient.

Results: The mean age of patients was 57.6 years. The diagnosis was achieved in 85% of cases, while 15% of cases diagnosed as non specific pleuritis. The range of biopsies were 65% malignant (mesothelioma, 35% metastatic adenocarcinoma, 5% of either lymphoma or thymoma), and 35% of cases were non malignant, 15% undiagnosed, 10% TB, 5% of either erythema or RA). 20% of cases had complication in the form of 10% malposition of the intercostal tube and 5% of either hemotoma or infection at the site of tube entry.

Conclusion: Medical thoracoscopy, under local anesthesia and conscious sedation, is an effective procedure for diagnosing the underlying etiology of recurrent pleural effusion of unknown etiology, with minimal complications.

P1259
Study of thoracoscopic pleural biopsies for nondiagnostic pleural effusion
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Background: We performed thoracentesis and pleural biopsy by cope needle to find cause of exudative pleural effusion. Usually about 20% of them can’t find cause. We study thoracoscopic biopsy for nondiagnostic pleural effusions.

Method: We enrolled patients from April 2004 to May 2010. We included patients with nondiagnostic pleural effusion through stumput study, thoracentesis, washing microbiologic study and cytology by bronchoscopy. Twenty-six patients were performed thoracoscopic pleural biopsy.

Result: Twenty-four patients were identified. Their mean age was 60.5±15.3years, and 16(66.7%) of the patients were men. Four patients weren’t performed thoracentesis. Characteristics of pleural effusion were lymphomatous (9/75%), poly-dominent(2;10%), eosinophil dominant (1/5%) and unknown(2/10%). Final diagnosis of patients with undiagnostic pleural effusion were malignant effusion (n=14, 58.3%), Tb pleurisy(n=3, 12.5%), chronic inflammation and fibrosis(n=5, 20.8%) and hemorrhagic effusion and cosinophilic effusion (n=2, 8.3%). The most common cause of malignant effusion was secondary not primary lung cancer. Metastatic effusion were 5 patients (35.7%). Malignant mesothelioma were 3patients (21.4%). adenocarcinoma of unknown origin were 2patients (14.3%). Primary lung cancer were 4patients (25.8%).

Conclusion: Fifteen patients(58.3%) of nondiagnostic effusion were diagnosed malignant effusion. In These 15 patients, secondary malignant effusion were 10 patients(74.3%). In Conclusion, we consider thoracoscopic biopsy and systemic examination to identified nodiagnostic pleural effusion.

P1260
Medical thoracoscopy experience: 3 years on
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Aim: To describe the qualitative and quantitative experience and outcomes at 3 years of medical thoracoscopy (MT) in a DGH.

Methods: Retrospective case series review of all consecutive adult patients under- going MT.

Results: To date, 39 MT’s have been done between Sept ’09 and Sept’11. Median age 71 years (range:28.6-87 years); 28 (72%) male. Median age of patients with malignancy 70(range:48.3-87 years), 15 male (65%). MT was non-diagnostic in 3 cases (7.7%) with one confirmed as metastatic carcinoma on CTGBx. 9/10 MPM were pleurodesed; 8(89%) successful All 13 non-MPM were pleurodesed; 9(70%)
successful. Overall pleurodesis success rate was 77.3%. Excluding the two patients who died within 30 days, pleurodesis success rate is 85% (17/20) for all malignant pleural effusion.

Conclusions: Success rates are reported in literature 82.1% - 95% in patients having a single procedure and one pleurodesis only, similar to ours but for the 2 patients aged 72 and 76 years who died; having significant co-morbidities and confirmed metastatic carcinomas with poor pre-op performance status of 3.

MT was well tolerated in our cohort of patients who had median age of 70, and success rates varied dependent on pathology; better in MPM than carcinoma. Qualitatively, the most significant result was the duration of pleural fluid recurrence free days that patients achieved, thus mitigating symptoms and avoiding further or repeated invasive pleural interventions.

P1261

Results of treatment of the metastatic pleural effusion

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Metastatic pleural effusion is big health, social and personal problem. Diagnosis of patients is 1 to 60 months which is according underlying disease, stage of the disease, treatment response, characteristics of the patients and their reserve.

We analyze 60 patients with confirmed malignant pleural effusion: 28 patients with breast cancer, 14 with lung cancer, 8 with mesothelioma, 5 with gastric carcinoma, and 5 with other malignant lesions. Mean age were 56 years.

At this 60 patients we have done 194 procedures. We analyze effects of thoracocentesis only (60), placing pleurocurt (37), placing of thoracic drain (54), VATS with talk pudrage (13) and thoracoscopic drain and thoracic drainage with slurry talk pleurodesis (14). Recurrence of pleural effusion, febrile condition, appearing of the empyema problems with heart, dispnea, life treating conditions were followed at all patients.

Results: Recurrence of pleural effusion were detected at 71.2%, where the best results were with use of VATS with talk pudrage (53.8%), than is thoracic drainage with slurry talk pleurodesis with success rate of 50%. With only placing of drain success rate was 29.6% or with pleurocurt placing 27%. With thoracocentesis only, no one has had success.

Unwanted conditions were detected the most frequently at thoracic drainage with slurry talk pleurodesis where were detected 14.3% heart problems, 35.7% dispnea and respiratory symptoms, 35.7% febrile conditions with septic conditions. Conclusion: VATS with talk pudrage give the best results with control of the malignant pleural effusion, but need hospitalization and general anesthesia procedure, procedure which was not recommended for many patients which is in bad general conditions.
Iodopovidone is an effective, safe, cheap, easily available alternative to other agents used via thoracoscopy. The combination of low-dose doxycycline with low-dose talc appears to be a safe and rational approach to pleurodesis with reasonable side-effects.

Methods: In a prospective study, 20 consecutive patients with recurrent and biopsy-proven malignant effusions and 4 patients with recurrent pneumothorax were included. All pleurodesis was performed with talc plus doxycycline as the sclerosing agent. Doses of doxycycline (250 mg) and talc (2.5 grame) were half the "usual" doses. The sclerosing agents were administered via tube thoracostomy. Post-pleurodesis postero-anterior (PA) radiographs were obtained after tube removal and 30 days following the procedure. Successful therapy was defined as a complete absence or minor re-accumulation of pleural effusion one month after pleurodesis.

Results: Twenty-four cases were identified (8 women, 16 men, Mean age was 65.2 years). No immediate perioperative complications were noted. Chest tube drainage averaged 4.3±2.5 days. Length of stay after the procedure 4.8±3.2 days. Eight patients (33%) reported persistence or worsening dyspnea in the immediate postoperative period. Only one developed respiratory distress; no any parenchymal changes on chest radiography and no required ventilatory support. Other immediate postoperative period events included chest pain in 10 patients (42%) and fever in 28% patients. Twenty patients (83%) had successful pleurodesis and 4 (17%) failed.

Conclusions: The combination of low-dose doxycycline with low-dose talc appears to be a safe and rational approach to pleurodesis with reasonable side-effects.

P1265
Combination therapy with intrapleural doxycycline and talc in reduced doses for pleurodesis
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Background: We hypothesized that combining doxycycline and talc in half the usual doses would be synergistic in inducing pleurodesis.

Objective: The aim of the study was to evaluate safety and efficacy of low-dose doxycycline combined with low-dose talc for pleurodesis.

Methods: In a prospective study, 20 consecutive patients with recurrent and biopsy-proven malignant effusions and 4 patients with recurrent pneumothorax were included. All pleurodesis was performed with talc plus doxycycline as the sclerosing agent. Doses of doxycycline (250 mg) and talc (2.5 grame) were half the "usual" doses. The sclerosing agents were administered via tube thoracostomy. Post-pleurodesis postero-anterior (PA) radiographs were obtained after tube removal and 30 days following the procedure. Successful therapy was defined as a complete absence or minor re-accumulation of pleural effusion one month after pleurodesis.

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Conclusions: The combination of low-dose doxycycline with low-dose talc appears to be a safe and rational approach to pleurodesis with reasonable side-effects.

P1266
Iodopovidone: An effective agent pleurodesis used through chest tube
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Background: Most variety of pleural irritants have been used for pleurodesis, the ideal agent should produce pleurodesis effectively, safely, and in shortest possible time.

Objective: Compare efficacy and safety of iodopovidone used through chest tube to other agents used via thoracoscopy.

Patients and methods: Fifty six patients (35 men and 21 women) with malignant pleural effusion (n=40) or pneumothorax (n=10) aged from 5 to 76 years, were distributed into 2 groups:

– G1: 40 patients treated with injecting iodopovidone 3 successively days (20 ml iodopovidone + 30 ml saline solution) via chest tube.
– G2: 16 patients had pleurodesis through thoracoscopic using talc.

Results: Time to pleurodesis was similar in 2 groups (8±3 vs 6±2 days). As the mean length of hospitalization (31.3±12 vs 27±4.15 days) and mean length of drainage (6±1 days vs 10.6±8.1 days), there is no statistically difference in the 2 groups. A complete response with no recurrence was similar in 2 groups obtained in 44 (78.5%) of cases. After instillation of the sclerosing agent, intense cough and dyspnea were noted only during G1 (n= 3), and 2 patients had systemic hypotension and intense pleuritic pain. Local complications were observed in 10 cases (18%) with no statistically difference in 2 groups: pneumothorax (n=7) and empyema (n=3). Chest pain evaluated with visual scale measurement after a removed tube was similar in 2 groups. As the mean length of follow-up, there is no statistically difference (5±2.9 and 6.3±1.8 months).

Conclusion: Iodopovidone is an effective, safe, cheap, easily available alternative to achieve chemical pleurodesis in cases of recurrent, incapacitating effusions regardless of etiology.

P1267
Pleural effusions in lung cancer
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The most common cause of malignant effusions in males is lung cancer. Malignant effusions are the result of spread of lung cancer to pleura or dissemination of metastatic tumour to one of the pleural surfaces. Paramalignant effusions are the result of lung cancer, but not a result of spread of malignant diseases to pleura.

Methods: The study group comprised of patients in territory of Montenegro, in time period from 01.01.2008 to 31.07.2011. All patients with pleural effusions had their pleural liquid cytologically tested, and histological processing of samples of pleural tissue obtained by blind needle biopsy (66 patients) or VATS (8 patients) was done. Descriptive statistical method and retrospective study were used.

Results: Total number of newly diagnosed cases of lung cancer was 585 (squamous cell ca - 361 (62%), SCLC- 139 (23.5%) adenoca 85– (14.5%). Paramalignant effusion was diagnosed in 33 patients (5.64%). Paramalignant effusion was found in 17 patients with squamous cell ca (4.7%), in 9 patients with SCLC (6.5%) and in 3 patients with adenoca (3.6%). No statistical significance was found when correlating frequency of paramalignant effusion to histological type of lung cancer (p<0.05). Malignant effusion was diagnosed in 55 patients. Malignant effusion was the most common in pts suffering from adenoca (found in 26 patients – 30.6%, p<0.01), while malignant effusions were found in 13 pts with squamous cell ca (3.6%), and in SCLC in 9 patients (6.5%).

Discussion: No statistical significance was found when trying to correlate frequency of paramalignant effusion in different histological types of lung cancer. In the group of patients with malignant effusion adenoca is the most common causal factor of spread of malignant disease to pleura.

Bronchoscopic revealed an almost complete obstruction of the left main stem bronchus with extensive infiltration of the mucosa by tumorous tissue. The EBUS-TBNA biopsies demonstrated the suspect of a neoplasm of hematologic origin. The patient was transferred to a referral center for hemat-o-ncology and underwent a bone marrow biopsy. It could be diagnosed an acute myeloid leukemia. The mediastinal mass and bronchial infiltration corresponded to a chloroma (myeloid sarcoma) as a rare and severe initial manifestation of the disease.

Chloroma is an extramedullary, solid tumor which occurs in association with myelodysplastic or leukemic disorders. It affects 3-8% of patients with acute myeloid leukemia and can present as the initial manifestation of hematologic malignancy. The anatomic distribution includes bone, nerve, lymph node, and skin, but may involve a variety of soft tissues. Pulmonary and mediastinal involvement is rare. Just one case has yet been reported in literature with an identical pattern of airway infiltration.

P1269
Ectopic heterotopic mediastinal thyroid tissue mimicking lung cancer
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Objective: Ectopic intrathoracic thyroid tissue is a very rare presentation of a mediastinal mass, comprising 1% of mediastinal tumors and can be distinguished from restenormal goiter or secondary intrathoracic goiter from the fact that the former receives its blood supply from mediastinal vessels rather than the neck and is not connected to the cervical thyroid. We present a series of 9 patients with heterotopic mediastinal thyroid mimicking lung cancer.

Material: Nine patients, 5 male and 4 female ranging in age between 56 and 79 years were admitted at our hospital. All patients but two were asymptomatic. Chest radiography revealed a mass in the superior middle or posterior mediastinum, in 2 cases with tracheal deviation. CT scan revealed a mass and further investigation took place with MRI. Preoperative staging was negative for metastatic disease in all cases and ultrasonography, scintgram and I131 uptake precluded the possible existence of thyroid tissue. Thyroid function tests were also normal.

Results: All patients were led to surgery and were submitted either to lateral mini-thoracotomy (n=5), or cervical incision (n=3) or thoracoscopry (n=1). In all cases there was an encapsulated mass with blood supply from intrathoracic vessels.
and histopathology revealed thyroid. The postoperative course was uneventful and no recurrence was observed in a follow up of 2 months to 4 years.

**Conclusion:** Although malignant transformation in heterotopic thyroid tissue is extremely rare, these masses should be resected in order to put the diagnosis and to avoid later complications such as progressive enlargement, hemorrhage within the mass causing respiratory failure, and compression of vital mediastinal organs.

**P1270**
Endobronchial ultrasound transbronchial needle aspiration at Aberdeen Royal Infirmary: How are we doing?

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**Background:** Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a more convenient alternative to mediastinoscopy for sampling mediastinal lymph nodes. We describe the demographics, results, and diagnostic sensitivity of EBUS-TBNA in the 1st 100 procedures performed.

**Methods:** Since the service began in 2010, patient age, gender, length of procedure, sedative doses, numbers of passes for each node and results were recorded and retrospectively analysed.

**Results:** Of 100 patients, 66 were male with mean age 62 years (range 22-88). Mean procedure duration was 16 minutes, and median doses of midazolam and fentanyl were 4mg and 100mcg respectively. 142 lymph nodes were sampled with median number of passes of 4 per node. Lymphoid material was obtained from 126 (86%) of all nodes sampled. A pathological abnormality was found in 73 patients: NSCLC (n=34), SCLC (n=20), granulomatous inflammation (n=14), possible lymphoma (n=1) and metastatic neck (n=1), urological (n=2) and breast cancer (n=1). In the remaining 27 patients, no lymph node was sampled in 10 and lymph node was sampled in 17 cases with no abnormality noted; of the latter, 9 were true negatives. The diagnostic yield that trainees should achieve before becoming independent bronchoscopists.

**Conclusion:** Locally our experienced bronchoscopists are exceeding the 80% diagnostic yield in cases of a definite tumour. Using the lower limit for success, we suggest that 95% of trainee bronchoscopists should be achieving a minimum diagnostic yield of 75%. More data is needed in order to obtain more robust statistical data which can be developed into realistic benchmarks and assessment tools to measure trainee competency.

**P1271**
Ideal volume sampling in the diagnosis of malignant pleural effusions

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**Introduction:** Management of pleural effusion is based on established guidelines deriving from scientific committees and experts on pleural diseases all over the world. Nevertheless true consensus on volume sampling in malignant pleural effusions has not yet been achieved. Only few publications have been published over the past 10 years. Further studies should take place in order to clarify this essential point in the management of malignant pleural effusions.

**Hypothesis:** 20 to 40 ml of pleural fluid could improve cytology yield in high risk malignancy patients.

**Methods and materials:** Patients with at least medium sized pleural effusion and high risk for malignancy are enrolled. Pleural fluid is extracted as follows:

1. 10cc of pleural fluid sent for cell typing and ALB, PFT, LDH, CHOL, TG analysis
2. 20cc of pleural fluid extracted and placed as sample A
3. 30cc of pleural fluid extracted and placed as sample B
4. 150cc of pleural fluid should be extracted and placed as sample C

Samples A, B and C are sent for cytology.

Cytology results include the following:

1. Positivity or negativity for malignancy
2. Malignant cells numerosity (rare, infrequent, frequent, dense)
3. First data in our research strongly support our hypothesis and we feel that with our sample growing we will be able to show that a larger quantity of pleural fluid will not improve results (whilst will affect costs and laboratory man hours), but 20 to 40 ml could play a role in diagnosis and should be the target quantity. We hope our study will help to decrease time to diagnosis, reduce cost (less paracentesis, less adverse effects, less hospitalization time) and provide material for evidence based guideline development in the future.

**Conclusion:** Practising doctors tend to develop their own rational examination routine which can be improved by adding items of high precision (e.g. crico-sternal...
The impact of hands-on respiratory management for physicians in clinical practice and its future perspective
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Introduction: To respond to the demands of systemic mechanical ventilation management education, the Respiratory Management Hands-on Workshop for Physicians in-training (RMWP) began in November of 2010 as an extracurricular program, followed by the Brush-up workshop for supervisory doctors in July of 2011.

Objectives: To evaluate the impacts and the value of RMWP on clinical practice and to establish a future direction, we conducted a pre/post-test, a questionnaire on the contents, and a post-survey of the workshop attendees via the Web.

Methods: The pre/post-test and the anonymous questionnaire were conducted during the workshops. As for the post-survey, the e-mail with questions regarding workshop was sent in September 2011 to the attendees of the workshop and the first day brush-up workshop for advisory doctors.

Results: The attendees’ knowledge base requiring for respiratory management was not correlated with experiences of mechanical ventilation. In regard to the post-survey, a total of the 55% (61 out of 111) answered. There are two remarkable findings. Firstly, the number of physicians using Assist-Control mode increased, whereas SIMV mode decreased. Secondly, the lecture of Graphic monitoring & Lung mechanics, although the lecture had been marked as less useful than others in the questionnaire taken right after the workshop, was marked as the most useful lecture in their practice.

Conclusions: The results of post-survey indicated the potential to change physicians’ behavior in respiratory management. RMWP should provide both lectures and practice sessions with expert eyes to overcome the physicians’ misunderstandings and lack of the whole picture.
Patients’ knowledge and prejudices about chronic obstructive pulmonary disease

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Background: Proper patients’ (Pts) knowledge on a chronic disease is an important issue in successful disease management.

Aim: To estimate Pts’ knowledge and prejudices about chronic obstructive pulmonary disease (COPD).

Methods: Observational, questionnaire based study included 68 pts (mean age 63 yr, M/F=41/27) treated for COPD at University hospital in Belgrade, Serbia, from June to December 2011. Pts completed the 9-item questionnaire voluntarily and anonymously.

Results: A total of 50 (73.5%) pts underestimated recommended respiratory rehabilitation and have not used it; 28 (41.2%) pts prefer teophyllin compared to the other therapy; 41 (60.2%) pts have not get vaccinated against influenza to reduce exacerbation of the disease; 33 (48.5%) pts used more frequently short-acting β2 agonists instead advised therapy scheme; 29 (42.6%) pts had correct technique of using inhalation therapy; 22 (32.4%) pts overreact in using antibiotics during exacerbation; 53 (77.9%) Pts do not seek help for symptoms of depression in COPD; 20 (29.1%) pts cut down therapy themselves; 36 (52.9%) Pts are active smokers and one third of them do not recognize tobacco smoking as risk factor for pulmonary disease.

Conclusion: COPD Pts’ knowledge about the disease should be improved to achieve their better adherence to treatment, quality of life and more successful disease management.

Pleural procedures – Are junior doctors struggling to gain experience?

Manish Gautam, Diana Lees, Josheel Naveed, Chris Warburton, Lisa Davies.

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Introduction: BTS guidelines and UK training curricula highlight the importance of gaining experience in pleural procedures. By the end of core medical training (CMT), trainees are required to demonstrate competency in pleural aspiration and Seldinger chest drain insertion.

Aim: To investigate the self-reported competency of junior doctors in performing pleural procedures

Method: On the spot’ questionnaires were randomly distributed to 64 doctors training in a large university teaching hospital. Participants graded their level of confidence in performing a variety of pleural procedures and possible reasons for lack of experience.

Results: Response rate was 91%; 7 Speciality trainees (ST3-7), 17CMTs, 12 Foundation Year 2 (FY2) and 1 FY1 trainees. 36% reported independent ability to perform pleural tap, 31% aspiration, 21% chest drain insertion, 22% pleurodesis, 45% removal and 34% flushing of chest drains. All STs reported competence, but, 76% of trainees felt they were struggling to gain sufficient practical experience. Those with respiratory experience were more likely to report competence (p=0.001) although only 1/3 could insert a chest drain independently. Top reasons for ‘struggling’ were increasing use of ultrasound (US) (33%), followed by perceived lack of senior encouragement (17%).

Conclusion: Our data suggest that the majority of trainee physicians do not feel competent to undertake pleural procedures independently. With increasing use of US for pleural procedures, trainees are having difficulty gaining experience. For CMTs, UK curricula now state mandatory competency in chest drain insertion for pneumothorax only, but training programmes must ensure adequate exposure to important pleural procedures.

Beyond PROs – Using narrative techniques to understand the real life of patients with COPD

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Background: The experience of living with COPD is complex and emotional [1,2]. Knowledge of illness experience is different from biological disease [3]. Traditional COPD questionnaires were based around patient-reported outcomes, but did not have enough focus on patient-reported information about the illness [4]. Narrative capture technique [5] could offer new insights. It has been applied outside of health care in anthropology, defence and development contexts. Unlike structured PROs it accepts the patient giving information as a story, a narrative. And in narrative capture technique, the person telling the story is also the person explaining its meaning.

Method: Asking patients daily to enter stories, and to indicate the meaning of each of these stories through labeling.

Conclusion: This narrative technique may be a feasible one for understanding how COPD fits into the patient’s overall life.

References:
[5] Snowden D. Naturalizing Sensemaking’ in Mosier and Fischer (eds) Informed Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Impact of a structured educational program for nursing staff on chest drain care

Raman Ahmed, Rehan Naseer, Allison Scott, Matthew Callister. Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Background: At the 2011 ERS congress we presented findings from a survey of nursing staff regarding chest drain knowledge, care and management in our tertiary care centre. Worryingly we found only 17% felt they had adequate training in chest drain care. We present our intervention and subsequent feedback.

Intervention: Unlike doctors in the UK, nursing staff usually do not have a structured training program. We developed an interactive self- directed workshop on chest drain knowledge and management, based on the adult learning principles of Andragogy. The instructional design theories used to help learning included constructivism and the use of cognitivism and behaviouralist design which allowed efficient construction and transfer of knowledge. Nursing staff based on respiratory wards were asked to complete the workbook and a self assessment at the end. They also attended a workshop which included 30mins of lectures followed by 30mins of group discussion. Structured forms were used to collect feedback.

Feedback: 24 feedback forms were analysed. 96% ‘agreed’ or ‘strongly agreed’.
1. The workbook was relevant to their current role.
2. The activities and tasks helped to improve their understanding of the topic
3. The training provided them with new knowledge on chest drain management.
4. Completion of the training improved their confidence in dealing with chest drains.

Subjectively we felt patient care and safety improved on the wards.

Conclusion: Formal training sessions of nursing staff on chest drain care has proved very popular and productive for nursing staff and we recommend other hospitals should consider developing similar sessions to improve the standard of care.

A pleural information programme: For patients and training

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Background: Pleural effusions usually signify advanced disease, increased symptom load and limited life expectancy when malignant. They need prompt effective management, safely and with least possible inconvenience and discomfort. Patient choice is key and informed consent is crucial because of possible risks related to the invasive pleural intervention.

Aim: To develop an interactive tool for healthcare professionals to illustrate and explain the various pleural modalities to patients and trainees.
PI283
Survey of bronchoscope disinfection practices by chest physicians attending IP CME in Navi Mumbai, Maharashtra
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Aim: To study various methods used for disinfecting bronchoscope by delegates attending a CME on Interventional Pulmonology.

Methods: A 23 question survey was divided into sub groups like location of bronchoscopy suite, disinfecting techniques, bronchoscope care and sedation practices. The survey was distributed to participants from Western India in a CME on Interventional Pulmonology.

Results: 31 out of 40 participants completed the questionnaire. One was excluded as it was incomplete. 8 questionnaires were completed by medical director of bronchoscopy suite, 18 by chest physicians and 5 by the fellows.

Conclusion: Increased awareness and education is required for bronchoscope disinfection techniques and adherence to guidelines.

PI284
Online self-management in patients with COPD or asthma: With or without the healthcare provider?
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Introduction: Self-management plays a key role in integrated care strategies for chronic diseases. Curavista Health is an online patient self-management platform for severe chronic diseases, including asthma and COPD. MyCOPDOnline & Myasthmaonline which consists of 3 basic-elements: 1. Health status; 2. Self-management; 3. eConsult. We incorporated the program into our daily hospital routine for outpatients. Patients however also can participate without health care provider, as open access program.

Aim: The aim of the study was to retrospectively analyze the adherence to the program of patients with or without health care provider.

Results: The content of the program was identical in both groups. Age and gender were comparable. In the group without coaching (n=831), 68% used the program once, 18% twice and 14% three times or more. In the group with coaching (n=95), 33% used the program once, 17% twice and 50% three times or more (p<0.001).

Discussion: Self-management suggests that patients manage themselves and the role of the professional is limited. In contrast, these data suggest that participants make better use of eHealth programmes when supported by healthcare professionals. Therefore eHealth should be embedded into regular care. It might imply not only a role change for patients to achieve self management, but also for the health care professional in transition from ‘medication manager’ to coach.

PI285
The general practitioners knowledge and educational programs efficiency in antibiotic use
Roman Bontsevitch1, Ruslan Bontsevitch2. 1Internal Medicine, St. Iouasof Belgorod Regional Clinical Hospital, Belgorod, Russian Federation; 2IT and Optimization Department, AXOR ltd, Dnipropetrovsk, Ukraine

Aim: To study and compare the level of general practitioners (GPs) knowledge in questions covered problems of rational antibiotic (AB) use in pulmonology in different regions. To estimate the importance of rational AB use educational and control programs (ECP).

Methods: During 2006-2012 ECP were developed and carried out among 58 GPs in Dnipropetrovsk’s region (DN), 35 – in Lрабатунгardi (LA) and 31 – in Belgorod (BE). Special questionnaire included 10 complex tasks with a set of questions has been created to estimate an initial and final levels of medical staff awareness (LMSA). The knowledge of AB groups, dosage, frequency and indications of usage, combinations, timing of therapy, cancellation and replace of AB was assessed.

Results: After GPs completed questionnaire at the first time, the level of correct answers (LCA) has totalled 48.6%, in DN – 51.6%, LA – 39.8% (p<0.05, BE – 53.1%. Taking into account the results of received data there have been developed and carried out special ECP Comparative exercise was repeated year later. Summary LCA was statistically (p<0.05) increased to 62.5% (in DN – 62.7%, LA – 60.1%, BE – 64.9%) without statistically differences between regions. The validity of AB prescribing, quality of treatment was statistically increasing, and on the opposite, quantity of GPs mistakes was statistically decreasing (p<0.05).

The most difficult questions were the following: rationale combinations, empirical therapy, pneumonia therapy and MO sensitivity.

Conclusions: There is a necessity to carry out the rationale AB use ECP among GPs to increase LSMA and quality of treatment, and to decrease mistakes. Therefore, the most difficult questions are to be studied more deeply.

PI286
Tele-education in asthma management. What are the benefits?
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The aim was to research two approaches of asthma education and to find the most effective one.

98 mild asthmatic patients have been involved randomly so far (age 41.0±15.2 yrs). We study 3 groups according to the type of chosen education: 1st group have passed the ordinary asthma education (were educated by physician) (n=22), 2nd-have passed tele-education asthma program (n=36), 3rd-didn’t have any advantage (n=30).

Criteria to objectify the effectiveness were: asthma control assessed by ACT and ACQ, life quality level, lung function, Cooperation Index (CI), the cost of intervention, self-management, knowledge control test results.

The majority of patients initially had partly controlled asthma (43.9%) and current working social status (60.6%). Finally we have detected that patients of the 1st and 2nd groups have obtained significantly higher control level, higher life quality values, decrease in taking reliever medications in comparison with the 3rd group (p<0.05). The higher Cooperation Index was observed in the 1st group (Mean=67.0%, p<0.05). Cost of ordinary asthma education, performed by physician (the 1st group) was 20.1 € and tele-education (the 2nd group) –10.7 €. There were significant correlations in the 2nd group between results of asthma control (ACT™ and ACQ scores) and knowledge control test results (rACQ=0.77, p<0.05 and rACQ=0.68, p<0.05). ACT and ACQ results were significantly lower in the 3rd group (MeanACQ=16.3 pts, MeanACT= 1.8, p<0.05).

Abstract PI283 – Table 1

<table>
<thead>
<tr>
<th>Questions</th>
<th>Response, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of bronchoscope disinfection?</td>
<td>Suite 18 (60%), Operating room 8 (28.6%), Don’t know 3 (13.4%)</td>
</tr>
<tr>
<td>Preclean with an enzymatic cleaner?</td>
<td>Yes 15 (50%), No 11 (37%), Don’t know 4 (13%)</td>
</tr>
<tr>
<td>Manual/automated disinfection system?</td>
<td>Manual 19 (64%), Automated 1 (3%), Don’t know 10 (33%)</td>
</tr>
<tr>
<td>Sterile tap/filtered water rinse (final)?</td>
<td>Yes 25 (83%), No 2 (7%), Don’t know 3 (10%)</td>
</tr>
<tr>
<td>Final alcohol rinse?</td>
<td>Yes 13 (43%), No 14 (47%), Don’t know 3 (10%)</td>
</tr>
<tr>
<td>Blow air at the end of the process?</td>
<td>Yes 24 (80%), No 3 (10%), Don’t know 3 (10%)</td>
</tr>
<tr>
<td>Familiar with any guidelines for disinfecting bronchoscope?</td>
<td>Yes 14 (47%), No 12 (40%), Don’t know 4 (13%)</td>
</tr>
<tr>
<td>Frequency of culture?</td>
<td>Monthly 10 (31.5%), Yearly 1 (3%), Don’t know 3 (22.5%)</td>
</tr>
<tr>
<td>Reagent used for disinfection?</td>
<td>Glutaraldehyde 26 (87%), Ethylene oxide gas sterilization 1 (3%), Don’t know 3 (10%)</td>
</tr>
</tbody>
</table>

*For those who answered yes to the above question.
Conclusion: So, each of the approaches to asthma education leads to higher asthma control. Besides this, tele-education has shown more cost-effectiveness. This instrument is required to be available to each patient.

P1288
Semantic pattern analysis of patient perceptions using automated co-occurrence information mapping
Mark Rolfe1, Jo Powell-Bright1, Daniel Dodd2, Research Evaluation Unit, Oxford, United Kingdom; 2The Thoughtware Group, Byron Bay, NSW, Australia

Background: The majority of patients with chronic diseases seek additional information from the internet following medical consultations. Text analytics is a widely recognized, validated system for modelling the structure and information content of text. Here we describe a unique method for identifying and analysing linguistic information from the internet to provide quantitative, unprompted insights into patients’ sentiments about their conditions.

Methods: Boolean- and thesaurus-based, machine-learning software is used to conduct an iterative nonlinear search of the web for all relevant texts containing broad keywords related to a given chronic disease. Texts are then analysed by Leximancer (v4.0), a text-mining tool that identifies themes and concepts from large bodies of text using a statistics-based algorithm.

Results: This innovative approach ensures that a comprehensive disease-specific dataset is captured from the web. Leximancer automatically identifies commonly occurring concepts (weighted combinations of words that co-occur within the text). They were presented visually as maps, showing the strength of the relationship between different concepts (relative frequency and inter-connectedness) to facilitate semantic classification. Positive and negative sentiments about specific aspects of the disease and its management can be identified and selected for statistical analysis, demonstrating the validity of this technique.

Conclusion: The internet is a data-rich source of patient-to-patient and patient-to-healthcare professional communications. The sentiment analysis method described can facilitate broader understanding of patient perceptions of their disease and its management.

P1289
Home telemonitoring of CPAP: A feasibility study
Jean Louis Fraysse1, Nathalie Delavillemarque2, Bernad Gasparutto2, Ludvine Leseux1, Paul Leophonte1, Alain Didier1, 1Prestataire de Santé à Domicile, 2SADIR, Larrey, France; 3Prestataire de Santé à Domicile, Aliseo, Orvault, France; 4Prestataire de Santé à Domicile, ADR Assistance, Isneauville, France

Background: The most commonly used treatment for sleep apnea syndrome (SAS) is the application of constant positive airway pressure (CPAP) during sleep. Compliance is an essential element of CPAP efficiency. Compliance is dependent on the quality of the coverage care and on the information of the patients. With the telemedicine emergence, telemonitoring of the CPAP makes its appearance in France.

Methods: This study is observational and multi centers. The main aim of this study was to evaluate the feasibility of CPAP telemonitoring in SAS patients (n=90). During the installation of equipment, patients receive the instruction to connect the CPAP SD card to a connecting box named twitoo, every week during 2 months. The data transmission is made towards the study coordinator, the home care provider named SADIR, by the way of a telemedicine platform, located in Toulouse, France. Actual numbers and frequency of remote-monitoring box connexions are quantified.

Results: 92% of patients (n=62) connected SD card to twitoo at least once. We expected a maximum of 8 connections with a frequency of one connection every 7.6 days. We observed a mean of 6.2 connections during the 2 months, with a frequency of one connection every 7.6 days.

Conclusion: This study demonstrated good adhesion of the patients to this new tool of data transmission, by telemonitoring, of their CPAP treatment. Its efficacy on treatment compliance has to be evaluated in a larger group using a randomized procedure.

P1290
Parental educational intervention for asthma in children: A randomized controlled trial
Anita Dodos1, Joanne Hardman1, Caroline Hardman2, Claire Jambor1, 1University of Sydney, School of Nursing and Midwifery, Sydney, Australia; 2Macquarie University, Sydney, Australia

Introduction: Byron Bay, NSW, Australia

Objective: To investigate how important parent’s level of general education was for the success of organized Asthma Educational Intervention (AEI) program. We assessed parents’ knowledge of asthma by questionnaire before, during and after the AEI. Success of the AEI was determined using the control group and the intervention group. The AEI group was divided into low level of education (parents with low education) and high level of education (parents with high education) groups. Parents: with low (≤ 12 years) and high (> 12 years) levels of education. This study is observational and multi centers. The main aim of this study was to evaluate the feasibility of CPAP telemonitoring in SAS patients (n=90). During the installation of equipment, patients receive the instruction to connect the CPAP SD card to a connecting box named twitoo, every week during 2 months. The data transmission is made towards the study coordinator, the home care provider named SADIR, by the way of a telemedicine platform, located in Toulouse, France. Actual numbers and frequency of remote-monitoring box connexions are quantified.

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P1291
Cost-utility analysis of indacaterol – A once-daily maintenance bronchodilator for patients with COPD
Yumi Asukai1, Jiatiti Ananthapavlan1, Bill Malcolm1, Ann Radwan1, Ian Keyzer2, 1Health Economics and Outcomes Research, IMS Health, London, United Kingdom; 2Scientific Operations, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom; 3Clinical Development & Medical Affairs, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom; 4Health Economics and Outcomes Research, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom

Introduction: COPD is a chronic incurable disease; however, there are effective treatments available. In the UK, long-acting bronchodilators are first-line treatments for COPD patients requiring maintenance therapy, and there are several options available. Aims: To establish from the UK NHS perspective, the cost-effectiveness (CE) profile of indacaterol, the first once-daily LABA, compared to tiotropium and salmeterol, in patients with moderate to severe COPD.

Methods: A Markov model was developed with four health states describing the GOLD severity stages. From each of the states, patients could experience a severe or non severe exacerbation, move to a different COPD state, remain in the current state or die. Transition probabilities were based on data from the indaceterol clinical trials. Cost and resource use data was taken from UK based sources, published literature and expert opinion. Sensitivity analyses (SA) were also conducted.

122. Looking at the cost effectiveness of asthma and COPD treatment by novel drugs and improved management

P1292
A UK based cost-utility analysis of indacaterol – A once-daily maintenance bronchodilator for patients with COPD
Yumi Asukai1, Jiatiti Ananthapavlan1, Bill Malcolm1, Ann Radwan1, Ian Keyzer2, 1Health Economics and Outcomes Research, IMS Health, London, United Kingdom; 2Scientific Operations, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom; 3Clinical Development & Medical Affairs, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom; 4Health Economics and Outcomes Research, Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom

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Methods: A Markov model was developed with four health states describing the GOLD severity stages. From each of the states, patients could experience a severe or non severe exacerbation, move to a different COPD state, remain in the current state or die. Transition probabilities were based on data from the indaceterol clinical trials. Cost and resource use data was taken from UK based sources, published literature and expert opinion. Sensitivity analyses (SA) were also conducted.
Results: Indacaterol dominates both tiotropium and salmeterol over a 3-year time horizon with a cost saving of €137 and €289 respectively. The one-way SA indicated that the time horizon and the mortality rate associated with very severe COPD had the largest impact on the results. The probabilistic SA showed that over 75% and 90% of the iterations when compared to salmeterol and tiotropium respectively produced dominant results for indacaterol.

Conclusion: The CE analyses demonstrate that indacaterol dominates both tiotropium and salmeterol and is likely to remain cost-effective under a range of assumptions.

P1293
The drug costs associated with COPD prescription medicine in Denmark
Peter Lønberg1, Marie Jakobsen2, Niels Aaker3, Jens Dollerup4, Peter Bo Poulsen5
1Department of Public Health, Section of Social Medicine, University of Copenhagen, Denmark; 2Department of Labour and Health, COW AS, Lyngby, Denmark; 3Medical & Access, Pfizer Denmark, Ballerup, Denmark

Background: Spirometric studies of the general population estimate that 430,000 Danes have chronic obstructive lung disease (COPD). COPD is mainly caused by smoking with smoking cessation being considered the most important intervention to prevent disease progression. Cost-of-illness of COPD in Denmark is significant. However, the use of prescription medicine for COPD has not been analysed for the Danish population.

Aim and objective: Analyse the societal costs associated with prescription medicine for the treatment of COPD in Denmark.

Methods: The study was designed as a nation-wide retrospective register study of the drug costs (ATC group R03) associated from COPD from 2001-2010. Data were retrieved from the Prescription Database and the National Patient Register. The population included individuals (40+ years) having had at least one prescription of medications (R03) with an indication code indicating COPD. Patients dying were included up to time of death. A societal perspective included both public reimbursement costs and co-payment. Costs were calculated in fixed 2010-prices using a Laypeyres price index (average treatment cost per DDD and DDD amount sold).

Results: In the period 2001-2010, 292,646 individuals (40+ years) have had at least one prescription of R03 medication. Among these, 124,020 with a COPD diagnosis had been hospitalized, whereas 46,218 have not. The annual average drug cost (R03) was DKK 8,017 per patient (Euro 1,069) with a total average cost per year of 680 million DKK (91 million Euros).

Conclusions: The annual costs of prescription medicine for COPD in Denmark are significant. For comparison smoking cessation treatment costs, i.e. the primary intervention towards COPD, are much lower.

P1294
Varenicline is a cost-effective pharmacotherapy in smoking cessation of nicotine dependent patients with mild to moderate COPD
Heikki Ekroos1, Jarmo Hahl2, Kaisa Tippurainen3, Kari Linden4, Miika Linna5, Maarit Saarinen6, Aino Pikkarainen7, Heikki Soininen8, Maria Saarinen9, Kari Manninen10, Pasi Savela11
1 of 239s

Background: Smoking causes significant burden to health care systems and societies and is the most common cause of COPD, one of the leading causes of death globally. Smoking accelerates progression of the disease, yet many people continue to smoke after COPD diagnosis.

Objective: To study the cost-effectiveness (CE) of varenicline combined with physician advice as a smoking cessation compared to physician advice alone in smokers with mild to moderate COPD from a Finnish health care payer perspective.

Methods: A Markov cohort health state transition structure was used to model the lifetime transitions of a smoker cohort through COPD stages I-IV, lung cancer and death. Data from pivotal safety and efficacy study of varenicline for smoking cessation were used with Finnish morbidity, mortality, smoking and health care resource consumption registry data and results from local quality of life studies.

Results: In the base case analysis incremental CE ratio (ICER) of varenicline is €1,1000/Quality Adjusted Life Year (QALY) gained or €1,000/Year Life gained in lifetime analysis. A frequently referred ICER threshold of € 4000/QALY gained is achieved before 11 years. Both univariate and probabilistic sensitivity analysis (PSA) confirm the robustness of these results; in PSA the probability of varenicline being cost-effective is 100% at a willingness to pay (WTP) level of €4000/QALY gained in lifetime horizon, and exceeds 50% at WTP level of €3000/QALY gained after 10 years.

Conclusions: The study suggests that varenicline combined with physician advice is cost-effective compared to physician advice alone in smoking cessation of Finnish patients with mild to moderate COPD.

P1295
The potential cost-effectiveness of glycopyrronium bromide, a novel LAMA muscle antagonist (LAMA). It will provide a potential alternative therapy option for the maintenance treatment of moderate-to-severe COPD.

Objective: To estimate resource utilization and economic impact of switching uncontrolled asthma and exacerbating COPD patients on monotherapy to fixed dose combination treatment in Germany
Sadik Ardic1, Maria Jakobsen2, Niels Anker2, Jens Dollerup3, Peter Bo Poulsen4
1Ankara University, Ankara, Turkey; 2Clinic of Chest Diseases, Yedikule Chest Research Hospital, Ankara, Turkey; 3Medical Department, Pfizer Oy, Helsinki, Finland; 4HEMA institute/Department of Industrial Engineering and Management, Aalto University and National Institute for Health and Welfare, Helsinki, Finland

Aim and objective: The potential cost-effectiveness of glycopyrronium bromide, a novel LAMA therapy, was evaluated in the Swedish market, given different pricing scenarios.

Methods: An economic evaluation was conducted based on the use of a Markov model to evaluate the cost-effectiveness of glycopyrronium with varying thresholds of cost-effectiveness. The main clinical inputs were the improvement in lung function and the rate ratio of exacerbation. These were obtained from the phase III clinical trial data comparing glycopyrronium with tiotropium and placebo. Drug acquisition costs in Sweden for the comparators were estimated from the Swedish Formulary (PSS). Costs of maintenance therapy and exacerbation treatment were obtained from published Swedish studies.

Results: When evaluated over a three year time horizon, glycopyrronium is cost-effective (at 500,000 SEK (USD 75,188) per QALY) compared to tiotropium, up to a public price of SEK18.15 (USD 2.73) using a payer perspective and SEK18.49 (USD 2.78) using a societal perspective.

Conclusion: Results of the economic analyses show that once-daily glycopyr- nonium is a cost-effective treatment alternative to tiotropium under a number of different pricing assumptions.
TL (3595 Euro) for asthma and 10798 TL (4629 Euro) for COPD. LABA+ICS combination (1132 TL, 485 Euro) was the highest drug-related cost. Poor control and increased severity of both asthma and COPD caused higher hospital cost and higher total direct cost (for p < 0.001).

Conclusions: The study revealed that based on the significant relation to direct costs, strategies to enable better disease control and to reduce severity of the disease in asthma and COPD must be considered in healthcare policies to limit economic burden.

Reference:

P1298
Cost-effectiveness of early assisted discharge for COPD exacerbations in the Netherlands
Lucas Goossens1, Cecile Utens1, Frank Smeenk3, Onno van Schayck2, Maureen Rutgers-van Molken1 1 Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands; 2CAPHRI, Maastricht University, Maastricht, Netherlands; 3 Pulmonary Disease, Catharina Hospital, Eindhoven, Netherlands.

Background: Hospital admissions for exacerbations of chronic obstructive pulmonary disease (COPD) are the main cost drivers of the disease. An alternative is treating suitable patients at home. This study reports on the cost-effectiveness of the GO AHEAD trial in the Netherlands.

Methods: Patients (n=139) were randomized to seven days of inpatient hospital treatment (HOSP), or to three inpatient hospital days and home treatment by community nurses for four days (EAD). Nursing and physician activities were analysed in detail in order to estimate costs for inpatient days. Healthcare resource use, absenteeism, and informal care were recorded in cost diaries. Calculations were performed from a healthcare perspective and a societal perspective, including costs outside healthcare.

Results: Seven days after admission, mean change from baseline Clinical COPD Questionnaire (CCQ) score was better for HOSP, but not statistically significantly: -0.5% (95% CI: -0.04; 0.61). EAD saved costs. The difference was significant from a healthcare perspective: -244 (95% CI: -315; -168). Societal: -65 (95% CI: -152; 25) After three months follow-up, differences in effectiveness had disappeared. The difference in quality-adjusted life years (QALYs) was 0.0054 (CI: -0.021; 0.0095). EAD saved costs from a healthcare perspective, but not significantly: -168 (95% CI: -1253; 922). From a societal perspective, total costs increased, due to higher informal costs: €908 (CI: -553; 2296).

Conclusions: No clear evidence was found to conclude that either treatment was more effective or less costly.

P1299
Inpatient hospital care or hospital-at-home for COPD exacerbations: A discrete choice experiment
Lucas Goossens1, Cecile Utens1, Frank Smeenk3, Bas Donkers4, Onno van Schayck2, Maureen Rutgers-van Molken1 1 Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands; 2 Pulmonary Disease, Catharina Hospital, Eindhoven, Netherlands; 3 Erasmus School of Economics, Erasmus University, Rotterdam, Netherlands.

Objective: Quantifying patient preferences for different aspects of hospital-at-home care in the Netherlands for patients with COPD.

Methods: In a discrete-choice experiment, respondents were asked to make multiple choices between hospital treatment as usual (7 days) and two combinations of hospital admission (3 days) followed by treatment at home. The latter was described by attributes: training of homecare nurses (general/pulmonary), number of different nurses involved, number of daily visits, co-payments, readmission risk, contact in case of worsening disease (GP/hospital), and informal caregiver burden.

Hospital treatment was constant. Respondents were COPD patients in an RCT where focused effort can improve care and outcomes: finding out, living with the condition, when things go wrong and towards the end of life.

Results: 202 questionnaires were returned. 25% of patients and caregivers opted for hospital treatment regardless of the description of the hospital-at-home program, 46% never chose the hospital. The best models contained four latent classes, defined by different preferences for the hospital and for the caregiver burden. Preferences for other attributes were shared by all classes. Except for the number of visits, all attributes had a significant effect on choices in the expected direction.

Conclusion: Considerable proportions of patients and caregivers have a preference for either admission or hospital-at-home, irrespective of the characteristics of the hospital-at-home program. Financial burden and informal caregiver burden weighed most on the choice between hospital-at-home options. The number of daily visits did not play a role.

P1300
Health care claims analysis to quantify the burden of moderate-to-severe asthma
James Zazzali1, Eunice Chang2, Michael Broder1, 1Medical Affairs, Genentech, Inc, South San Francisco, CA, United States; 2Health Economics and Outcomes Research, Partnership for Health Analytic Research, LLC, Beverly Hills, CA, United States

Objectives: To describe the economic burden and health services use among moderate to severe asthma patients.

Methods: Retrospective cross-sectional cohort analysis using health insurance claims. Study period was 01/07/2006 through 30/06/2007. It included patients aged ≥12 who had an asthma diagnosis and used medium to high dose ICS/LABA with or without oral steroids and/or omalizumab (US National Heart Lung and Blood Institute [NHLBI] Steps 4-6) and who did not have chronic obstructive pulmonary disease (COPD).

Results: Conclusions: The economic burden of health care on patients with moderate-to-severe asthma is quite high and increases with disease severity. Although health care utilization by asthma patients has decreased in recent years, patients with severe asthma still spend significantly more time and money on health care than those with more manageable symptoms. Medications that better target both asthma symptoms and the underlying disease process should reduce these costs.

P1301
Managing COPD as a long term condition: Reducing variation and improving quality of care
Catherine Blackaby1, Phil Duncan, Alex Porter, Lung Programme, NHS Improvement, Leicester, United Kingdom

Introduction: COPD costs the UK healthcare system an estimated £1112m pa with national data indicating significant unwarranted variation in quality of care, recorded prevalence and hospital admission. Experience across a national improvement programme has identified four stages of any long-term condition where focused effort can improve care and outcomes: finding out, living with the condition, when things go wrong and towards the end of life.

Aim: To identify what information and approaches can help primary care teams in England use capacity differently to improve care and outcomes for patients living with COPD.

Method: Two practices, two clinical commissioning groups and one specialist respiratory team tested approaches to improve delivery of long term care for COPD patients. Evaluation of the patient pathway and current use of primary and secondary care resources identified priority areas. Clinical teams then tested how information, consultations and organisation of work could be adapted to improve healthcare resource use and patient-reported outcomes.

Results: Understanding current resource use and comparative performance demonstrated potential for more proactive use of capacity in areas such as education, self care and medicines management. The first two sites who spent increased time proactively with patients reported improvement in self management of exacerbations and medicines management.

Conclusion: Focusing effort on a small number of sites, regularly using comparative data and providing practical support can facilitate change and demonstrate how capacity may be used differently to improve quality of care for people living with COPD.

Abstract P1300 - Table 1

<table>
<thead>
<tr>
<th></th>
<th>Medium Dose ICS/LABA N=25,614, 78%</th>
<th>High Dose ICS/LABA N=6,998</th>
<th>ICS/LABA + Oral Steroids N=241</th>
<th>Total N=32,853</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual Healthcare Charges (USD), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total charges</td>
<td>15,403 (31,509)</td>
<td>19,499 (32,597)</td>
<td>42,855 (68,793)</td>
<td>16,477 (32,294)</td>
</tr>
<tr>
<td>Rx charges</td>
<td>3,747 (4,478)</td>
<td>5,670 (6,407)</td>
<td>10,900 (9,500)</td>
<td>4,209 (5,119)</td>
</tr>
<tr>
<td>Non-Rx charges</td>
<td>11,657 (30,119)</td>
<td>13,829 (30,685)</td>
<td>31,955 (65,174)</td>
<td>12,268 (30,700)</td>
</tr>
<tr>
<td><strong>Annual Asthma-related Utilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office visits, mean (SD)</td>
<td>1.4 (2.6)</td>
<td>2.3 (4.3)</td>
<td>4.4 (6.4)</td>
<td>1.6 (3.1)</td>
</tr>
<tr>
<td>≥1 hospitalization, no. (%)</td>
<td>427 (1.7)</td>
<td>222 (3.2)</td>
<td>40 (16.6)</td>
<td>689 (2.1)</td>
</tr>
</tbody>
</table>

*P*-test to compare across three groups; *Chi-square to compare across three groups.

240s
Pl302
Improving adult asthma care in England: Emerging learning from a programme of national improvement projects
Hannah Wall, Phil Duncan, Alex Porter. Lung, NHS Improvement, Leicester, Leicestershire, United Kingdom

Introduction: Asthma is a long-term respiratory condition affecting up to 5.9% of the England population. There have been between 1000 and 1200 deaths a year since 2000 with almost 40% of these under 75 years old. Asthma is responsible for large numbers of emergency attendances to Emergency Departments and emergency admissions.

Aims: To use service improvement approaches to define the patient pathway in order to improve the patients experience and outcomes of care – and reduce overall variation.

Method: Seven improvement projects from primary and secondary care used improvement methodologies to analyse the existing patient pathway, implement service redesign and assess the impact for patients with asthma in relation to: diagnosis and medicines optimisation, chronic disease management and acute care. Primary care data was used to identify cohorts of patients eligible for diagnosis and review and secondary data was used to demonstrate areas of duplication and gaps in service provision.

Results: Implementation of principles such as: primary care register reviews, self-management support, medicines optimisation, standardised care in acute settings and primary care follow up on discharge have demonstrated cost savings and increased productivity in a number of improvement projects. Project data on reduction in admissions and Emergency Department attendances demonstrates improved outcomes. Patient feedback highlights a positive experience of redesigned services.

Conclusion: There is variation in the delivery and quality of asthma services in England. Systematic improvement approaches reduces variation and increases productivity as well as delivering a positive experience of care.

Pl303
Efficacy and safety of applying the British Thoracic Society (BTS) criteria to determine appropriateness of follow up in general respiratory clinics
Satinder Dalay, Vikan Panammyo, Shiva Bikmall, Alces M. Turner, Rahul Mulherker. Department of Respiratory Medicine & Physiology, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

Introduction: Respiratory physicians are under increasing pressure in England to discharge patients with chronic illnesses to primary care. The BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease (Thorax 2008; 63(Suppl I):i1–i16.) remains the only available basis for this dialogue.

Aim: To assess the impact of implementing BTS criteria for discharge on follow-up to new ratio (“new-to-follow up” ratio) in a general respiratory clinic (efficacy) and to assess readmission rates of those discharged as a measure of appropriateness of discharge.

Methods: Retrospective analysis of “new-to-follow up” ratios of one pilot general respiratory clinic in a large teaching hospital covered over a 2 week period in July 2010; repeat analysis undertaken (Oct-Dec 2010) after a BTS statement-guided clinical reform was implemented (Jul-Dec 2010) with a management plan in the clinic letter. Unscheduled hospital admission in 6 months following the date of the clinic discharge were compared with preceding 6 months.

Results: Number of Follow-up-to-new ratio pre-reform was 5.0 (144/29); post-reform improved to 0.86 (111/129); clinic waiting time fell from 13 to 5 weeks. There was a significant drop in all-cause and respiratory-related admission rates for those who were reviewed and discharged.

Re-admission data

<table>
<thead>
<tr>
<th>Admissions</th>
<th>Pre-Reform</th>
<th>Post-reform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83</td>
<td>55</td>
</tr>
<tr>
<td>Respiratory</td>
<td>57</td>
<td>25</td>
</tr>
<tr>
<td>% of total</td>
<td>67</td>
<td>45</td>
</tr>
</tbody>
</table>

Conclusion: Patient-focussed, multidisciplinary approach to long-term respiratory conditions allows accurate diagnosis and appropriate discharge planning to take place using the BTS criteria.

Pl304
Economic analysis of costs associated with a respiratory intensive care unit (RICU) in a tertiary care teaching hospital in northern India
Kumari Shweta1, Sachin Kumar2, Anil Kumar Gupta2, Surinder Kumar Jindal2, Ashok Kumar2,1.1Hospital Administration, All India Institute of Medical Sciences, New Delhi, Delhi, India; 2Pulmonary Medicine, Institute of Liver & Biliary Sciences, New Delhi, Delhi, India; 3Hospital Administration, Post Graduate Institute of Medical Education & Research, Chandigarh, India; 4Pulmonary Medicine, Post Graduate Institute of Medical Education & Research, Chandigarh, India

Background: There is paucity of cost analytical studies from resource constrained developing countries defining the costs of intensive care.

Objective: Economic analysis of costs associated with RICU.

Methods: Prospective cost analysis study conducted in 74 patients admitted in the RICU from Dec 2008 to Feb 2009. Costs segregated into fixed and variable cost. Correlation of the costs to the length of stay, mechanical ventilation and therapeutic intervention scoring system-28 (TISS-28) also done.

Results: The total cost per day was U.S. $ 222.

Cost of RICU care (per patient per day)

<table>
<thead>
<tr>
<th>Total cost</th>
<th>INR 10,364 (U.S. $222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fixed cost</td>
<td>INR 4,478 (U.S. $104.43)</td>
</tr>
<tr>
<td>Total variable cost</td>
<td>INR 5,886 (U.S. $137.74)</td>
</tr>
<tr>
<td>Total drug cost</td>
<td>INR 5,824 (U.S. $131.87)</td>
</tr>
<tr>
<td>Total cost for ventilated patient</td>
<td>INR 6,585 (U.S. $140.98)</td>
</tr>
<tr>
<td>Total cost for ventilated patient</td>
<td>INR 12,429 (U.S. $286.09)</td>
</tr>
</tbody>
</table>

53.6% of the total cost was borne by the patients. The mean daily drug cost represented 69.8% of the variable and personnel salary constituted 86% of fixed cost. The TISS-28 score per nurse was significantly higher in non-survivors (69.2) than in survivors (30.6) and strongly correlated with the total cost (r = 0.91).

Conclusions: Great disparity exists in economic terms in the intensive care in the western and developing world. Although, considerably less expensive, intensive care is expensive relative to the cost of living in India. The cost block methodology provides a framework for estimation of costs; is useful in future planning of resource allocation within the financial constraints and allows comparisons between ICUs internationally in an economical model of evidence based care.

P1305
Verbal abuse and other violence types against doctors in chest diseases polyclinic
Sumeet Beri, Fatih Alasan, Peri Arback, Chest Diseases, Duzce University Faculty of Medicine, Duzce, Turkey

Aim: There are a few studies focused on unexpected patient-doctor relationship such as verbal abuse and the other types of violence.

Materials and methods: Two hundred thirty one patients (134 male, 97 female) who accepted filling out the forms and admitted to Chest Diseases Polyclinic between September and December 2011, were included in the study.

Results: The mean age of the patients was 53.6±16.7 (15-85) years. The mean duration for anamnesis was 10.1±4.2 minutes. Forty five patients used verbal abuse or other types of violence (6.1%). Mostly, patients used violence by themselves (78.6%). Seven patients ridiculed (50%), two patients abused (14.3%), two patients threatened (14.3%) and three patients tried to enter free of turn (21.4%). Negative interaction mostly occurred in examination room (63.4%) and before the beginning of anamnesis (64.3%). The mean duration from the anamnesis to the final diagnosis was 41.7±75.2 minutes (min:0-max:180). The mean duration rates of verbal abusers to university hospital (27.9±24.6, Median=25) were significantly higher than the others (8.7±12.7, p=0.007, Median=5). The mean number of households of verbal abusers (2.8±2.0, Median=2) was significantly lower than the others (3.8±1.7, p=0.041, Median=4).

Conclusion: Verbal abuse is the most seen form of the negative relationships between patient and doctor. Making realistic changes in referral system can satisfy the expectations of patients. The positive relationship rights are necessary not only for patients but also for doctors.

146. Prognosis and outcome of respiratory infections

1360
Dynamic changes of serum sTREM-1 and its gene polymorphisms associated with sepsis prognosis
Longoxiang Su1,2, Lixin Xie1,2, Zhaoyou Jiang1,2, Xin Zhang1,2, Dan Feng1,2,
1Department of Respiratory Medicine, Hainan Branch of Chinese PLA General Hospital, Sanya, Hainan, China; 2Department of Respiratory Medicine, Chinese PLA General Hospital, Beijing, China

Introduction: More and more studies have confirmed that sepsis is an acquired generic disease.

Objectives: To explore how sepsis prognosis is associated with the dynamic changes of serum sTREM-1, as well as with gene polymorphisms.

Methods: 80 subjects were selected from inpatients in the RICU, SICU and EICU. 80 healthy volunteers acted as control. To detect the dynamic changes of serum sTREM-1 over a 14-day observation, ELISA was performed. Four exons of TREM-1 gene were sequenced on ABI3730.

Results: The nonsurvivors’sTREM-1 levels remain significantly higher than the survivors’ over period of 14 days(<0.01). The curves show that the nonsurvivors
register higher sTREM-1 levels at the initial stage, which steadily go up with the passage of time. In contrast, the survivors’ sTREM-1 levels are on the decline all the time. Three TREM-1 SNPs (rs14472509, rs2234237 and rs2234246) are detected from four exons. In three inherited models, rs2234237 is clearly related to sepsis prognosis ($P<0.05$). The log-rank test shows that patients with the rs2234237 genetic variant stand a greater probability of a 28-day death ($P<0.05$). However, no relationship is spotted between TREM-1 gene polymorphism and the dynamic concentrations of serum sTREM-1. Logistic regression analysis shows that sTREM-1-APECH II score, and TREM-1 rs2234237 genetic variation are risk factors affecting the prognosis.

Conclusions: Dynamic changes in serum sTREM-1 may be more accurate and valuable for sepsis monitoring and for dynamic assessments of prognosis. It is proved that TREM-1 rs2234237 polymorphism is associated with high 28-day mortality among sepsis patients, constituting a risk factor affecting prognosis.

1361 Vitamin D level predicts clinical outcome in community-acquired pneumonia
Hilde Remmelts1,2,3, Ewout van de Garde4,5, Sabine Meurant4, Evelyn Peck5,6, Jean Danoiseaux5, Jan Grutters7, Douwe Biesma1,11, Willem Jan Bos1, Ger Rijkers1,10,11, 1Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, Netherlands; 2Department of Internal Medicine and Infectious Diseases, University Medical Centre, Utrecht, Netherlands; 3Department of Internal Medicine, Gelderse Valles Hospital, Ede, Netherlands; 4Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, Netherlands; 5Division of Pharmacoeconomics and Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; 6School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, Netherlands; 7Department of Internal Medicine, Division of Clinical and Experimental Immunology, Maastricht University Medical Centre, Maastricht, Netherlands; 8Academic MS Centre Limburg, Orbis Medical Centre, Sittard, Netherlands; 9Laboratory for Clinical Immunology, Maastricht University Medical Centre, Maastricht, Netherlands; 10Department of Pulmonology, St. Antonius Hospital, Nieuwegein, Netherlands; 11Department of Internal Medicine, University Medical Centre, Utrecht, Netherlands; 12Department of Sciences, Roosevelt Academy, Middelburg, Netherlands; 13Department of Medical Microbiology and Immunology, St. Antonius Hospital, Nieuwegein, Netherlands

Rationale: Vitamin D plays a role in host defense against infection. Vitamin D deficiency is common. The prognostic value of vitamin D in pneumonia is unknown.

Objective: To examine the impact of vitamin D status on outcome in community-acquired pneumonia (CAP).

Methods: Subanalysis of a prospective study in 272 adults presenting to the emergency department with CAP. 25-hydroxyvitamin D, leukocytes, C-reactive protein, total cortisol, the Pneumonia Severity Index (PSI) score and the CURB-65 score were measured. Intensive care unit (ICU) admission during hospitalization and 30-day mortality were assessed.

Results: 143/272 patients (52%) were vitamin D deficient ($\leq 50$ nmol/L), of which 65 patients were severe deficient ($\leq 30$ nmol/L). Severe vitamin D deficiency was associated with an increased risk of ICU admission and 30-day mortality. Vitamin D was an independent predictor of 30-day mortality (area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.63-0.87). When combined with the PSI score, the prognostic accuracy was superior to that of the PSI score alone (AUC 0.85, 95% CI 0.75-0.96 vs. AUC 0.78, 95% CI 0.64-0.91). The association between severe vitamin D deficiency and the combined endpoint mortality/ICU admission persisted after thorough adjustment for confounding, adding to a possible causal relationship.

Conclusion: The vitamin D level is an independent predictor of 30-day mortality, and adds prognostic value to the PSI score.

1362 Obesity is associated with improved outcome in community-acquired pneumonia
Anika Singanayagam1, Aran Singanayagam2, Adam Hill3, James D. Chalmers3, 1Department of Infection and Immunity, The Royal London Hospital, London, United Kingdom; 2Department of Respiratory Medicine, Imperial College, London, United Kingdom; 3MRC Centre for Inflammation Research, University of Edinburgh, United Kingdom

Background: Obesity was shown to be an independent risk factor for adverse outcome from 2009 pandemic H1N1 influenza. There is a relative paucity of information regarding whether this link applies to other pulmonary infections. We aimed to investigate whether body mass index (BMI) correlates with outcome in community-acquired pneumonia (CAP).

Methods: We performed a prospective observational study of consecutive patients presenting to hospital with a primary diagnosis of CAP between January 2005 and December 2009. BMI measured on admission was used to classify patients into 2 groups: obese (BMI $\geq$30) and non-obese (BMI <30). Outcomes of interest were 30-day mortality and need for mechanical ventilation or vasopressor support (MV/VS). Multivariable logistic regression was used to compare outcomes in these patients to non-obese patients, adjusting for admission severity of illness (CURB65 criteria), diabetes mellitus, COPD and prior statin use.

Results: 1079 patients were included in the study with 21% classified as obese. Mean age was 62.5 years. There was no difference in admission severity (mean CURB65 score 1.44 vs 1.39) or immediate requirement for MV/VS between obese and non-obese groups. Despite this, obese patients had lower 30-day mortality compared with non-obese patients (6.7% vs 10.5%, p=0.3). After multivariable adjustment for confounders, obesity remained significantly associated with reduced 30-day mortality (OR=0.54, 95% CI 0.30-0.97, p=0.04).

Conclusions: In our prospective study, obesity was shown to exert a protective effect on mortality from CAP. The mechanism of this effect is unclear. Further correlation from clinical and scientific studies is warranted.
Cigarette smoke extract (CSE) alters the secretion profile of the Pseudomonas aeruginosa strain PA14

Nasreen S, Richard Waite, Joe Aduse-Opoku, Jonathan Gregg. Academic Unit of Paediatrics, QMUL, London, United Kingdom Centre of Infectious Disease, QMUL, London, United Kingdom Centre of Infectious Disease, QMUL, London, United Kingdom

Background: In North America, a major cause of morbidity and mortality is due to chronic obstructive pulmonary disease (COPD), an emerging epidemic that requires a better understanding of the pathobiology of the disease. The single most important factor in the development of COPD is cigarette smoke, where the mechanisms and pathogenesis of the disease remain unclear. The airways of COPD patients are colonized with potential pathogens, including Pseudomonas aeruginosa (Ps). However, the effect of cigarette smoke on the cellular physiology of Ps is not known. Since Ps utilizes a variety of secreted virulence factors during infection, we sought to assess whether CSE affects protein secretion in the Ps strain PA14.

Methods: An overnight growth of Ps strain PA14 (Ps) was inoculated into cell culture media 1) only 2) Ps +0.1% CSE 3) Ps+0.5% CSE and 4) Ps+1% CSE and harvested (OD 0.8). The cultures were then filter sterilised and the proteins precipitated by acetone; culture secreted proteins were then determined by SDS-PAGE.

Results: CSE increased the production of low molecular weight proteins in a dose dependent manner by the virulent Ps strain PA14 when stimulated with 0.1, 0.5 and 1% CSE as observed on an acrylamide gel.

Conclusion: We have shown that CSE causes a significant physiological response in PA14 by up-regulating the production of its secreted proteins. Enhanced production of these proteins can potentially cause severe damage to the upper and lower airways of smokers which can therefore influence the development of progressive COPD.

References:

1365 Obesity and outcomes in patients hospitalized for pneumonia

Sharif Khabah, T. D. Eirich, R. S. Padwal, A. M. Malhotra, J. K. Minhas-Sandhu, T. F. Marrie, S. R. Majumdar. Department of Medicine, University of Alberta, Edmonton, AB, Canada

Background: Obesity is a risk factor for acquiring pneumonia, but studies also suggest it is associated with better pneumonia-related outcomes. We examined the impact of obesity on short-term mortality in patients hospitalized with pneumonia.

Methods: For 2-years clinical data were prospectively collected on all consecutive adults admitted with pneumonia to 6 hospitals in Edmonton, Alberta, Canada. We identified 907 patients who also had body mass index (BMI, kg/m²) collected. Patients were categorized as underweight (BMI<18.5), overweight (18.5 to 25), overweight (25 to 30), and obese (>30).

Results: Overall, 65% were <65 years, 52% were female and 15% reported recent weight loss. 84 (9%) were underweight, 358 (39%) normal, 228 (25%) overweight, and 108 (12%) obese. Two-thirds had severe pneumonia (63% PSI class IV/V) and 79 (9%) patients died. In-hospital mortality was greatest among the underweight (12 [14%] vs normal 36 [10%]) vs overweight (21 [9%] vs obese (10 [4%], p<0.001 for trend). Compared with normal weight, obese patients had lower rates of in-hospital mortality (4% vs 10%, unadjusted odds ratio (OR) 0.39, 95%CI 0.19-0.81) that remained significant in multivariable analyses adjusted for age, sex, comorbidities, and clinical-radiographic severity of pneumonia (adjusted OR 0.44, 95%CI 0.21-0.94, p=0.035). However, these effects were not observed with normal weight, neither underweight (adjusted p=0.47) nor overweight (adjusted p=0.64) were associated with mortality.

Conclusion: In patients hospitalized with pneumonia, obesity was independently associated with lower short-term mortality, while neither underweight nor overweight were. This suggests a protective influence for BMIs in the range of 18.5 to 25.

Bacterial prevalence and load during COPD exacerbation and recovery

Davinder Garcha1, Anant Patel1, Alex Mackay1, Tim McHugh2, Gavin Donaldson1, Jadwiga Wedzicha1.

Background: Acute respiratory infections (ARI) share features with common, non-infectious complications after lung transplantation (LTx) making accurate and rapid diagnosis crucial for the management of LTx recipients.

Objectives: To evaluate the performance of a novel multiplex-PCR assay in addition to routine evaluation.

Methods: In this ongoing prospective cohort study, LTx-outpatients with any new symptom of ARI were screened for 24 respiratory viruses (RV) and atypical bacteria by a multiplex-PCR assay performed on throat swabs. Routine evaluation included PCR for 14 RV on throat washes and lower respiratory tract (LRT) sampling (BAL for quantitative microbiology, direct immunofluorescence, viral culture, PCR, and tranbronchial biopsy), if indicated.

Results: Between Sept. 2011 and Feb. 2012, among 104 episodes from 95 LTx recipients, 30 RV were detected in 29 patients (31%): 9 rhino-, 7 parainfluenza, 6 metapneumovirus-, 4 corona-, 3 adenovirus, 2 RSV, 2 CMV, and 3 viral coinfections. The most common bacterial pathogen wasPs strain PA14 (12/104 episodes) compared to 26% (23/90) with routine evaluation (p=0.20, p=0.03), including additional 4 RV. RV were more frequently detected in LRT than in URT samples (24% vs 14%; p=0.10, p=0.40). Agreement between both PCR assays in URT specimens was moderate (RV detected in 7 of 21 throat washes; k=0.45, p=0.011). Definite clinical diagnoses were suspected (28 subjects) and proven viral infection (26%), BOS (23%), AR (11%), bacterial infection (9), obstructive airway complication (4), pneumonia (3), and CMV infection (1).

Conclusions: In LTx recipients, virological methodology and sampling are complementary, with LRT specimens resulting in higher diagnostic yield.

147. Asthma: from childhood environment to adult phenotypes

1368 Feasibility of measurements of fraction of exhaled nitric oxide (FENO) in a large population based study (ADONIX)

Kristina Waa1, Lars Modig1, Kjell Toren1, Anna-Carin Olin1. 1Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; 2Occupational and Environmental Medicine, Umeå University, Umeå, Sweden

FENO is used in epidemiological studies as a non-invasive marker of airway inflammation in COPD and asthma. However, no studies has systematically evaluated the feasibility of this method in a large population-based study. We studied the possibility of implementing FENO measurements in the ADONIX study. FENO measurements were performed at baseline and annually thereafter in all ADONIX participants. The feasibility of the measurements was assessed by measuring the number of participants responding to the invitation, the distribution of the FENO values was evaluated, and the area under the curve was calculated for each participant.
inflammation. Some patients do not manage to fulfill the measurement criteria. The objective was to examine if there are any differences between subjects that do and do not manage to perform a correct FENO measurement, mainly relating to respiratory disease and differences in lung function. The Adonix-cohort comprises a general population sample of 6,296 subjects (52% women), aged 25 to 75 years. They have all been examined with FENO (NIOX, Aerocrine, Sweden), lung function questionnaires and blood samples. To fulfill the measurement criteria for FENO the subjects had to exhale to a 50 mL±10% (mean level 45-55 mL/s and allowed instant flow 40-50 mL/s) during the last 3 seconds of the expiration. In total 14,625 children (50% female) aged 8 years from 5 European birth cohorts (MAS, BAMSE, PIAMA, LISA, and GINI) were included in the statistical analyses. A total of 217 subjects (3.4%, 67% women) were unable to perform a correct test. These subjects were characterized by significantly lower lung function; FVC 3.6 vs 4.2 L (p=0.001) and FEV1 2.8 vs 3.3 L (p=0.001), but also lower predicted lung function: FVCpred 105 vs 109% and FEV1pred 98.3 vs 103.4%. In addition, we found a statistically significant over representation of subjects with asthma (13.1 vs 8.8%) in the group that did not manage to perform the test.

Conclusions: Although adolescence levels in classrooms are relatively low, long-term exposure seems to be a risk factor for respiratory health of schoolchildren.


Manuela C. Wehrens1, Ana Maria B. Menezes1, Ludovica A. Silva1, 

Maternal obesity and inhaled corticosteroid use in childhood

Methods: To assess whether indoor toluene may affect respiratory health in schoolchildren of five European countries (HESE study)

Results: in 628 children (mean age 10yrs) of five European countries: Sweden, Norway, Denmark, France, and blood samples. To fulfill the measurement criteria for FENO the subjects had to exhale to a 50 mL±10% (mean level 45-55 mL/s and allowed instant flow 40-50 mL/s) during the last 3 seconds of the expiration (OR 4.37, 95%CI 2.19-9.75 per 1 μg/m³ increment) and wheeze (OR 3.24, 1.25-8.45). These associations were significant after further accounting for the fixed effect of the classroom.

Conclusion: Although toluene levels in classrooms are relatively low, long-term exposure seems to be a risk factor for respiratory health of schoolchildren.

L372 IgE-associated phenotypes in 8-year old children. Cluster analysis of European birth cohorts

Marta Benet1, Jean Bousquet2, Josep M. Amo1, Joachim Heimrich1, Tomasz Król1, Heenette A. Silva3, Fernando C. Wehrmeister, 

Judith García-Aymerich1, on behalf of the McDALL Consortium. 

Objective: to examine if there are any differences between subjects that do and do not manage to perform a correct FENO measurement, mainly relating to respiratory disease and differences in lung function. The Adonix-cohort comprises a general population sample of 6,296 subjects (52% women), aged 25 to 75 years. They have all been examined with FENO (NIOX, Aerocrine, Sweden), lung function questionnaires and blood samples. To fulfill the measurement criteria for FENO the subjects had to exhale to a 50 mL±10% (mean level 45-55 mL/s and allowed instant flow 40-50 mL/s) during the last 3 seconds of the expiration. In total 14,625 children (50% female) aged 8 years from 5 European birth cohorts (MAS, BAMSE, PIAMA, LISA, and GINI) were included in the statistical analyses. A total of 217 subjects (3.4%, 67% women) were unable to perform a correct test. These subjects were characterized by significantly lower lung function; FVC 3.6 vs 4.2 L (p=0.001) and FEV1 2.8 vs 3.3 L (p=0.001), but also lower predicted lung function: FVCpred 105 vs 109% and FEV1pred 98.3 vs 103.4%. In addition, we found a statistically significant over representation of subjects with asthma (13.1 vs 8.8%) in the group that did not manage to perform the test.

Conclusions: Although adolescence levels in classrooms are relatively low, long-term exposure seems to be a risk factor for respiratory health of schoolchildren.
was different between groups (see Table): 5% vs 54% for ever asthma, 6% vs 54% for ever allergic rhinitis, and 26% vs 69% for ever eczema, in Groups 1 and 2, respectively. Specific IgE positivity was observed in 28% and 64% of children, respectively. Thus, Group 1 could correspond to healthy children from the general population, while Group 2 puts together children with different allergic diseases. These data suggest that allergic diseases could be better described as one single entity rather than as independent, solely organ-related diseases.

1373 Temporal stability of asthma phenotypes identified by a clustering approach: An ECRHS-SAPALDIA-EGEA study

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Background: The temporal stability over time of asthma phenotypes identified using clustering methods has never been addressed.

Aims: To assess whether repeated Latent Class Analysis (LCA) applied in asthma a decade apart leads to the identification of comparable phenotypes, and to characterize the transition between them.

Methods: The LCA was applied twice, 10 years apart, on data from 2399 asthmatic children in 3 epidemiological surveys using standardized protocols: ECRHS (European Community Respiratory Health Survey, n=1450), SAPALDIA (Swiss cohort study on air pollution and lung disease, n=589) and EGEA (Epidemiological study on Genetics and Environmental Asthma, n=506). 14 variables giving personal characteristics, asthma symptoms, treatment, age of asthma onset, allergic characteristics, lung function and bronchial hyperresponsiveness were considered at both time points.

Results: A model with four latent classes was selected at each time point (prevalence between 14%-36%, mean posterior probability 84%). Two of them were predominantly composed of subjects with active asthma, mainly differing by allergic status and age at onset. Two others were predominantly composed of subjects with inactive-mild asthma, mainly differentiated by allergic status. Most of the population (60%) was assigned to the same asthma phenotype at both time points, although stability varied between phenotypes from 47% for “active adult-onset asthma” to 68% for “inactive-mild non-allergic asthma”).

Conclusion: Asthma phenotypes identified by a clustering approach 10 years apart were comparable. Further analyses will be conducted using Latent transition analysis.

1374 Serum eosinophilic cationic protein (ECP) in adult monozygotic and dizygotic twins

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Aim: To assess whether repeated Latent Class Analysis (LCA) applied in asthma a decade apart leads to the identification of comparable phenotypes, and to characterize the transition between them.

Methods: The LCA was applied twice, 10 years apart, on data from 2399 asthmatic children in 3 epidemiological surveys using standardized protocols: ECRHS (European Community Respiratory Health Survey, n=1450), SAPALDIA (Swiss cohort study on air pollution and lung disease, n=589) and EGEA (Epidemiological study on Genetics and Environmental Asthma, n=506). 14 variables giving personal characteristics, asthma symptoms, treatment, age of asthma onset, allergic characteristics, lung function and bronchial hyperresponsiveness were considered at both time points.

Results: A model with four latent classes was selected at each time point (prevalence between 14%-36%, mean posterior probability 84%). Two of them were predominantly composed of subjects with active asthma, mainly differing by allergic status and age at onset. Two others were predominantly composed of subjects with inactive-mild asthma, mainly differentiated by allergic status. Most of the population (60%) was assigned to the same asthma phenotype at both time points, although stability varied between phenotypes from 47% for “active adult-onset asthma” to 68% for “inactive-mild non-allergic asthma”).

Conclusion: Asthma phenotypes identified by a clustering approach 10 years apart were comparable. Further analyses will be conducted using Latent transition analysis.

1375 Gender differences in bronchial responsiveness: A population-based cohort

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Background: Incidence of adult asthma, particularly non-allergic asthma, is higher in women but underlying mechanisms remain unclear. Cross-sectional studies have shown that bronchial hyper-responsiveness (BHR) is more frequent in women but gender differences in the onset and prognosis of BHR have been little studied.

Methods: Gender differences in BHR were studied in men and women without asthma or asthma-like symptoms participating in the European Community Respiratory Health Survey (baseline 1991-93; n=7521, age 20-44 years). BHR was defined as a 20% decrease in FEV1 for a methacholine dose ≥ 1 mg.

Results: At baseline, BHR was more frequent in women (12.6%) than in men (6.0%) (adjusted odds-ratio (OR): 2.33 95%CI 1.82-2.98). In subjects without BHR at baseline, BHR at follow-up (1998-2000) was observed in 8.2% (139/1649) women and 4.1% (76/1834) men (adjusted OR 2.74; 95%CI 1.92-3.91). Gender difference in BHR onset was significant in never-smokers, smokers and non-atopic subjects but was not observed in atopic subjects. In subjects with BHR at baseline, no gender difference in BHR persistence and prognosis of BHR as regards asthma was observed: in 172 women and 105 men with BHR at baseline, respectively 54.6% vs 48.6% still had BHR at follow-up (p=0.33); 20.4% vs. 23.8% had developed asthma-like symptoms (p=0.50), and 12.8% vs. 15.2% had asthma-like symptoms and BHR (p=0.56). BHR was a significant predictor for asthma development in both sexes.

Conclusions: This study suggests that female sex is a risk factor for the development of BHR during adult life. Further research on the influence of sex-specific factors on BHR is needed to understand the mechanisms underlying the development of asthma in men and women.

148. Tobacco cessation and tobacco cessation services

1376 Genetic factors on quitting habits and smoking characteristics: A twin study

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Introduction: It is well known that quitting has a genetic background; however, no detailed information is available in this field. Our aim was to investigate different quitting and smoking characteristics of monozygotic (MZ) and dizygotic (DZ) twins in order to investigate the genetic contribution.

Methods: Smoking 72 twin pairs (65 Hungarian and 7 American, 44 MZ and 28 DZ; mean age 44±17 years; standard deviation/SD) filled in a questionnaire concerning smoking and quitting habits. The prevalence of concordant answers was calculated from the answers of 9 MZ and 3 DZ twin pairs whose both members quit smoking. Significantly higher rate of concordant answers in MZ twins compared to DZ twins suggested a genetic influence.

Results: No significant difference was observed in the concordant answers concerning quitting attempts and duration of quitting period in MZ versus DZ twins (63% vs. 70%; 2.9±4.0 versus 1.9±1.5 years, p=0.05). Similarly, no significant difference was found in concordant answers regarding the history of quitting, mean difference in first cigarette smoking after wake-up, self-reported tobacco dependence, and certain smoking characteristics (what part of the cigarette is smoked, depth of imbibing the smoke, frequency of taking sniffs; and the frequency of thoughts concerning quitting smoking, harmful effects of smoking on other persons or him/herself, harmful operation of tobacco factories, cost of smoking) in MZ versus DZ twin pairs (p=0.05 for all characteristics).
Conclusions: In conclusion, this small twin study indicates no genetic influence on certain quitting habits, thoughts and smoking characteristics. A larger study sample is warranted.

1377 A pilot study of the acceptability of snus and nicotine pouch in smoking cessation
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New Zealand is aiming to become entirely smokefree by 2025. This goal is endorsed by the Ministry of Health and widely by the tobacco control community. To achieve this goal will require a number of new initiatives both in policy and smoking cessation. We have recently commenced a small pilot study to examine the acceptability of snus (aoral tobacco) and a nicotine pouch (Zonnic) amongst hospitalised smokers who have previously tried and failed to quit with NRT. 100 hospitalised smokers who wished to quit were enrolled and have been followed for at least 3 months. Smokers were given 1 week to try both products and then chose one to use for three months in a further quit attempt.

During the first weeks’ trial the nicotine pouch was more satisfying (using the CES) than snus median score 4.0 (IQR 2-5), 4 (IQR 3-5) p=0.05 and more enjoyable 4.0 (IQR 3-5), 3.0 (IQR 1-4) p<0.01, respectively. During the 2 weeks prior to quitting 50 subjects chose to use the nicotine pouch, 25 chose snus and 25 chose to use neither, except occasionally.

At 3 months, of the 16 who used snus regularly 5 were quit (31%) and a further 3 had smoked less than 2 cigarettes in the last 7 days. Of the 24 who used the nicotine pouch 4 were quit (16.6%) and a further 2 subjects had smoked less than 2 cigarettes.

Amongst smokers with no history of oral tobacco use, the nicotine pouch appears more satisfying and enjoyable and is chosen twice as often as snus, but may be less effective for cessation. Alternatively, those who choose snus may be better able to quit than those who choose znic. A full RCT will be required to confirm these findings.

(This study was funded entirely by the New Zealand Ministry of Health).

1378 Quitting smoking with Champix: Parallel, randomised clinical trial of efficacy for the first time in Iran
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Introduction: Smoking cessation programs were first introduced in Iran in 1997 by the National Research Institute of Tuberculosis and Lung Diseases and up to now, various nicotine replacement therapies have been prescribed. The aim of this study was to evaluate effectiveness of Varenicline for tobacco cessation in this country and compare it with other measures.

Materials and methods: This was a randomized parallel clinical study during 2009-2010.

Participants were divided into three parallel groups randomly. The first group received brief counseling on cessation. The second group received nicotine patches 15 mg/daily for 8 weeks and the third group was prescribed Varenicline one 0.5 mg pill daily for the first 3 days, followed by 0.5 mg twice a day for 4 days and subsequently 1 mg twice daily for 8 weeks.

Results: The study had 272 participants including 160 men (58.8%). Ninety one people were in the first group, 92 individuals in the second and 89 in the third group. At the end of the first month, 128 people from total (47.1%) succeeded in quitting; this included 17 individuals (18.7%) in the first group, 60 (65.2%) in the second group and 51 (57.3%) in the third group (P<0.001). Follow up at 6 month and a year showed 111 people of total (40.8%) and 58 individual (21.3%) remained smoke free which included 12 (13.2%) and 6 (6.6%) in the first group, 47 (51.1%) and 23 (25%) in the second group and 52 (58.4%) and 29(32.6%) in the third group respectively (P=0.000).

Conclusion: Drug treatment can improve success in quitting several fold. Success with Varenicline is slightly better from nicotine replacement treatment.

1379 Smokers’ characteristics, pharmacological treatment and their association with weight gain during smoking cessation
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Smoking cessation is responsible for many deaths. However, the adherence to the treatment is difficult by several factors.

Aim: Investigate if the weight gain during smoking cessation is associated with smokers characteristics or smoking cessation treatment strategies.

Methods: 148 smokers (female=65.5%, age=50.2±11.6y) were evaluated at baseline and after one year during a smoking cessation program. At baseline, all patients were analyzed by general date, anthropometric measurements, motivation stage, nicotine dependence, Hospital Anxiety and Depression Scale (HADS) and pharmacological treatment for smoking cessation. After one year of treatment, the patients were reevaluated for smoking cessation, weight changes. Weight gain above 3.0 kg was considered significant. We used T test, Chi2 and multiple logistic regression.

Results: Among 148 smokers, 81.8% received at least one pharmacological treat ment and 20.2% used bupropion. After one year, 34.4% of patients (60.78% female, age: 51.5±11.3y) were abstinent and they gained more weight [5 (2-10) kg, p<0.001] than patients who continued smoking [0 (0-4) kg]. Only 17.6% of abstinent patients, used bupropion. Among smokers, 41.9% gained weight over 3.0 kg, however we did not find associations of weight gain with HADS scores, intensity of nicotine dependence, motivational status. The multiple logistic regression showed that current smoker had lower chance of weight gain after one year [OR=0.18 (95%CI=0.08-0.40)].

Conclusion: Ours results confirms previous findings of weight gain after smoking cessation and did not identify association between weight gain and any patient characteristics or treatment strategy.

1380 Effectiveness of smoking cessation advice following admission to hospital
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Introduction: Hospitalization offers patients a good opportunity to quit smoking especially when they are admitted with a respiratory illness. The Department of Health (DoH) recommends that all inpatient smokers should be offered support by a smoking cessation officer(SCO).

Aims: • Evaluate if smoking cessation advice is offered to patients admitted with a respiratory illness • Identify a relationship between abstinence and types of smoking cessation aids used

Methods: Prospective follow up of 100 patients in respiratory clinic following hospital admission with a respiratory condition between December 2010 and October 2011. Baseline demographics and data on smoking habits and advice were collected. Chi squared test was used to assess statistical significance.

Results: Median (range) age of patients was 62 years (22 – 97). 52 were male. Of 100 patients 85 were offered cessation advice. 51 (60%) were seen by SCO. At follow up (1 to 3 months post discharge) 36 patients were abstinent. Age, gender or degree of tobacco consumption pre-admission did not influence likelihood of cessation.

SCO review was associated with abstinence (p=0.02). The most effective methods of cessation were willpower (P=0.001) and use of nicotine replacement therapy (NRT, p=0.000).

Conclusions: The majority of patients admitted with an acute respiratory illness were offered cessation advice as recommended by DoH. SCO counselling and NRT are powerful tools and affect success rates. Surprisingly, most quitters in our study did not use additional aids and used hospitalisation alone as an impetus to give up smoking.


1381 Learning platform for smoking cessation project: From beginning to date
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Background: Although 35% of the adults in Turkey are current smokers, the number of trained physicians and smoking cessation (SC) clinics are not enough to meet the demand.

Aim: This national project aimed to create the necessary infrastructure for providing SC therapy all-around the country and to train physicians in this topic. This project was run by Turkish Thoracic Society Tobacco Working Group and supported by a grant from Pfizer Foundation.

Methods: For this purpose, an organization network including field training...
Tobacco cessation clinics in Europe: Data from eSCCAN project
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The eSCCAN project aims to federate smoking cessation clinics in Europe to share and improve practices.

Method: Identification of eSCCAN experts in 26 of the 27 European countries has allowed to organize meetings and internet communication to reach a consensus among the smoking cessation clinics in Europe and to specify their number.

Results: The current estimate is that there is about 2500 tobacco cessation clinics in Europe. A minority of them are centres of counselling to stop smoking without the possibility of prescription; a higher number is made of doctors' offices or pharmacies. The vast majority consists of tobacco cessation clinics with several health professionals and all facilities for smoking cessation.

Examples of good and bad practices have been described on many topics such as rendez-vous delays, that must be less than 3 weeks for a first appointment. Some definitions have met consensus as the definition of healing, and in particular the period which defines a successful cessation. While waiting to close the debate, the recommendation is to record the cessation at 3, 6, and 12 months, with a particular focus at 6 months.

A code and a self-audit in many languages are available on the website for a first evaluation of the activity of the consultations that will enable future improvement.

Conclusions: The project provides real rapprochement eSCCAN knowledge to practices for smoking cessation in Europe that support in each country in Europe less than 10% of smokers, but disseminate knowledge and contribute to the assessment for teaching and research.

Use of radial endobronchial ultrasound for diagnosing peripheral lung lesions – A tertiary centre experience
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Introduction: Small peripheral lung lesions continue to pose a diagnostic dilemma for pulmonologists. Flexible bronchoscopy with fluoroscopy has a limited diagnostic sensitivity (31-56%) for such lesions. Radial endobronchial ultrasound (EBUS) is a relatively new technique that has been used to improve yield, although diagnostic performance has been reported to vary considerably. We describe the characteristics of patients who underwent radial EBUS and outcomes in our centre.

Methods: Retrospective review was performed for 123 patients from Singapore General Hospital with peripheral lung lesions who underwent bronchoscope evaluation with radial EBUS guidance from August 2008 to December 2011.

Results: Median patient age was 64 years. Overall diagnostic yield was 68.3% with no difference for malignant (68.5%) or non-malignant (68%) lesions (p=0.954).

Year-on-year diagnostic yield generally improved with increasing experience: in 2008, yield was 42.9% as compared to 2011 (80%). Data for ultrasound probe location was available for 93 patients. Yield was higher if the probe was within the lesion (78.3%) than when the probe was adjacent to the lesion (40%) (p=0.001). Data for lesion size was available for 118 patients. 40 patients had lesions less than 20mm diameter. Diagnostic yield of such lesions (75.3%) was higher than for larger lesions (64.1%), although this did not reach statistical significance (p=0.169).

Conclusion: Radial EBUS is useful for evaluating peripheral lesions of less than 20mm diameter. Training and experience is important to improve diagnostic yield. We recommend that the ultrasound probe be positioned within the lesion before attempting bronchoscopic biopsy.

Optical coherence tomography for increasing the diagnostic yield of TBNA
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Introduction: Bronchial biopsy techniques of peripheral nodules are associated with poor diagnostic yields. Optical coherence tomography (OCT) can be used to assess tissue microstructure in vivo, however is typically restricted to airway or pleural-based approaches. The aim of this study was to develop a transbronchial OCT catheter, and to investigate the potential of OCT to differentiate nodules from parenchyma with the goal of increasing the TBNA diagnostic yield of peripheral nodules.

Methods: We developed a narrow diameter OCT catheter compatible with standard 21-gauge TBNA needles. Safety and feasibility was demonstrated in 3 swine, in vivo. To determine the accuracy of OCT for differentiating nodules from surrounding parenchyma, OCT was conducted in 35 surgically resected tissue specimens. 2 OCT experts, 2 pathologists, and 2 pulmonologists interpreted the OCT data offline.

Results: Successful imaging was conducted in all swine. Image criteria for differentiating parenchyma from nodule included signal void spaces corresponding to alveoli, and linear regularly spaced specular reflections representing collapsed alveoli. Nodules were found to have a generalized homogeneous appearance. Blinded readers diagnosed the OCT images as nodule or parenchyma with an average accuracy of 95.6%.

Conclusions: We have developed the first transbronchial OCT catheter that is compatible with standard 21-gauge TBNA needles, and have demonstrated that OCT can accurately differentiate nodules from surrounding parenchyma. We anticipate that transbronchial OCT may be useful in increasing the diagnostic yield of TBNA by confirming the needle placement within the target nodule prior to biopsy.
1386 Qualitative and economical analysis of transbronchial lung biopsy with the cryoprobe
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Objective: To analyze the histological quality of transbronchial lung cytobiopsy in patients with interstitial or malignant lung diseases in which a previous transbronchial lung biopsy (TBB) with conventional forces was not diagnostic. A second objective was to analyze the cost of TBB with the flexible cryoprobe compared with surgical lung biopsy.

Patients and methods: From 01.02.2011 until 31.01.2012, 19 TBB with the flexible cryoprobe were performed. Afterwards, we analyze the cost of a TBB with the flexible cryoprobe compared with surgical lung biopsy.

Results: We obtained representative material in 18/19 (95%) patients. Cytobiopsies total specimen area was 20-60 mm² compared to TBB with forces which was done in 13 patients did not show crush artifact in any case. In 15/19 (79%) patients we obtained a definitive diagnosis: 2 malignant tumors and 13 benign disease: 6 usual interstitial pneumonia, 1 nonspecific interstitial pneumonia, 1 desquamative interstitial pneumonia, 1 idiopathic pulmonary fibrosis, 1 follicular bronchiolitis, 1 solitary nodules, 1 respiratory bronchiolitis and 1 organizing pneumonia. In 3 patients we found some pathological findings but a definitive diagnosis was not achieved. The cost of TBB with cryoprobe was $351 € against the cost of surgical lung biopsy which was $1,189 €.

Conclusions: Transbronchial cryobiopsies are larger than TBB with conventional forces with a preserved sample because of the absence of crush artifact. Moreover, cryobiopsies were cheaper than surgical lung biopsy. Hence, transbronchial cryobiopsies could be considered as a prior step or a potentially replacing tool for the open lung biopsy.

1387 Trans-parenchymal nodule access (TPNA) – Real-time image-guided approach to pulmonary nodules
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Background: Currently, pulmonary nodules (PN) are accessed by Transbronchial Needle Aspiration (TTNA) or Transbronchial Needle Aspiration (TBNA). There is a clinical need for improvement of bronchoscopic access to small (<10mm) intraparenchymal PNs such that the high yield of TTNA and the safety of TBNA is a clinical need for improvement of bronchoscopic access to small (<10mm) intraparenchymal PNs in the upper and lower lobes. CT scans were acquired and plans were generated to prescribe a needle-free, straight-line path from a central airway location directly to the target using an image guidance system (LungPoint®). Access through the open lung biopsy was initiated with a TBNA needle followed by balloon dilation and sheath insertion. Advancement of the sheath was guided by overlaying CT-defined targets and tunnels onto the live fluoroscopy images using the system. The sheath enabled target sampling with 2.0mm biopsy forceps through the lumen.

Results: In 10 canines, 31 targets averaging 34mm (21mm – 50mm) from the airway wall and 7.5mm (0.1mm – 21mm) from the pleura, were accessed via TPNA and sampled. Sampling results indicated a yield of 90.4% with no pneumothoraces and minimal bleeding (<2ml).

Conclusions: These canine studies demonstrate that TPNA has the potential to achieve the high yield of TTNA with the low complication profile associated with TBNA.

1388 Combination of CT-guided core biopsy with rapid-on-site-evaluation of imprint cytology enables time and cost savings in diagnosis of peripheral lung tumors
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Background: To perform a biopsy of a peripheral lung nodule is technically more challenging than biopsy of a central lesion. In peripheral lesions, a CT-guided core biopsy was performed after a probable diagnosis was reached by the CT examination. A rapid-on-site-evaluation of imprint cytology was performed on the biopsy sample. The additional imprint cytology was calculated with another 21,07 Euro. The reduced time to diagnosis allowed for cost savings of 890 Euro.

Conclusion: The combination of CT-guided core biopsy and imprint cytology enables a fast and very reliable tumor diagnosis and can save costs in the diagnostic work up of patients with peripheral lung nodules.

1389 Prospective international trial of endobronchial implantation of electromagnetic fiducials for real-time tracking of lung tumors during radiotherapy (RT)
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Introduction: Technologic advance in RT delivery has resulted in dramatic improvement in lung cancer tumor control, but respiratory motion of these tumors still complicates RT. We present our results implanting novel anchored electromagnetic transponders (Varian Medical, Palo Alto, CA) which provide real-time localization and tracking of tumor position during RT.

Methods: 31 patients (pts) underwent thoracic bronchoscopic implantation of 3 transponders (93 total) in small airways in or near the tumor under fluoroscopy ± CT. By using electromagnetic navigation or EBUS, Transponder positions were determined from serial CTs to assess positional stability. Localization and tracking of transponders and tumor was performed using the Calypso System during RT.

Results: There were 14 males/17 females, ages 43-79 (med. 63), with 10/31 tumors in the LUL and 21 in the RUL. There were no complications, no unique skills or tools were required for implantation, and satisfaction with the procedure was high. 29 pts had no significant problems associated with the transponder or procedure. One pt with an apical pleural-based tumor developed a pneumothorax, resolving overnight after chest tube placement. Migration of 1 transponder at appx 1 wk was attributed to implantation in a larger airway; pt was asymptomatic.

Conclusion: Implantation of electromagnetic anchored transponders is feasible and safe. This technology should enable highly accurate delivery of radiotherapy.

150. Physiological monitoring during sleep and in neuromuscular disease in children

1390 Assessment of diaphragm thickness variations by ultrasoundography in patients with Duchenne muscular dystrophy (DMD)
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Variations of diaphragm thickness (DT) during different respiratory maneuvers can be measured by B-mode ultrasonography (US). In order to verify if this parameter provides useful insights for functional assessment in DMD, we measured DT by a 7.5 MHz US linear probe in the 9th or 10th right intercostal space in 39 DMD patients (age 16±3.4 yrs. FVC 53±24.8%pred) in supine position (rest-expiration during quiet breathing; QB) and maximal inspiratory pressure (MIP) at residual volume. The contribution of the abdominal compartment to tidal volume (Vabd%) was assessed by optoelectronic plethysmography during QB and an inspiratory capacity (IC) maneuver.

Patients were subdivided into 3 groups according to age (G1: n=11, age<14; G2: n=13, 14<age<18; G3: n=15, age>18 yrs). MIP was significantly higher in G2 compared to both G1 and G3 (figure, left). The variation of DT during the MIP maneuver, expressed as % change of DT at rest, was significantly greater in G3.
compared to G1. Patients belonging to G3 group were also characterized by lower Vab% during subjects volume variations of AB led RCP (negative phase shifts, figure 1) independently on age. A similar behavior was found in G1 DMD patients, but not in older subjects (G2, G3 and G4) where RCP was the leading component (<p<0.05).

In conclusion, in DMD patients lying supine the action of the inspiratory rib cage muscles progressively increases with age relative to the diaphragm. Accurate monitoring of TAA during spontaneous breathing is a valid indicator of diaphragm function progress in DMD.

**1392**

Which are the most informative parameters to follow the respiratory decline in Duchenne muscular dystrophy? Sonia Khirn1, Adriana Ramirez2, Guillaume Aubertin1, Michèle Bouli6, Chrystelle Chemouny3, Veronique Forin1, Brigitte Fauroux1, 5 INSERM UMR S-038, AP-HP, Hôpital Armand Trousseau, Paris, France; 1ADEC Assistance, ADEC Assistance, Saintes, France; 1Pediatric Pulmonology Department, AP-HP; Hôpital Armand Trousseau, Paris, France; 4Respiratory Physiology Department, AP-HP; Hôpital Armand Trousseau, Paris, France; 6Pediatric Rehabilitation Department, AP-HP; Hôpital Armand Trousseau, Paris, France

Rationale: Duchenne muscular dystrophy causes progressive respiratory muscle weakness. Few information is available on the natural evolution of respiratory parameters in both Duchenne muscular dystrophy.

Objectives: In order to identify respiratory parameters associated with the earliest decline, lung function, blood gases, respiratory mechanics, and respiratory muscle strength were measured in 48 boys with Duchenne muscular dystrophy (mean age 12.7±3.4 years, range 7.6–19 years), over a period of 10 years.

Main results: Only four parameters showed an important decline with age. Gastroc pressure during cough was below normal in all patients with a mean 5.7±3.8 cmH2O decline per year. Sniff nasal inspiratory pressure tended to increase between the age of 10 years followed by a rapid decline (mean decrease 4.8±4.9 cmH2O or 5.2±4.4% predicted per year). Absolute forced vital capacity values peaked around 13-14 years of age and remained mainly over 1 liter but predicted values showed a mean 4.1±6.4% decline per year. Diaphragmatic tension time index increased above normal after the age of 14 years old with a mean increase of 0.2±0.04 year per year.

Conclusion: Repeated gastric pressure during cough, sniff nasal inspiratory pressure, and forced vital capacity measurements provide simple tools to assess the progression of respiratory muscle weakness in young boys with Duchenne muscular dystrophy. Endurance indexes decline at a later age. These indexes may help to monitor treatment effects.

**1393**

Inefficient cough in Duchenne muscular dystrophy (DMD)

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In DMD, impaired cough secondary to muscle weakness leads to serious respiratory complications, namely atelectasis, ineffective airway clearance, pneumonia and tracheal intubations. In order to study which factors influence and determine inefficient cough in DMD we studied 36 DMD patients and 15 healthy controls (C; age: 16.3±5.4 yrs). Peak cough flow (PFC) was measured at the mouth while rib cage (RC), abdominal (AB) and total chest wall (CW) volume variations were measured by opto-electronic plethysmography during quiet breathing and maximal cough (supine position). PFC was <160 L/min in 15 patients (inefficient cough, age:17.6±5.4 yrs, FVC 33.7±20% predicted) and >270 L/min in 9 (efficient cough, age:16.1±4.3 yrs, FVC 70.8±34% predicted). Tidal volume (Vt) was similar in L, E and C. In L, RC, AB and CW inspired volumes preceding cough were significantly lower than controls and inspired AB volume was lower than E (panel A). Thoraco-abdominal asynchrony during cough, quantified by labored breathing index (LBI), and percentage abdominal contribution to VT (%ΔVAB) were respectively higher and lower in I group (panel B and C).

In conclusion, in DMD inefficient cough is characterized by impaired inspiration, thoraco-abdominal asynchrony and lower abdominal contribution to volume variations due to diaphragmatic weakness. %ΔVAB, that does not require patient’s collaboration, seems to be a good predictor of inefficient cough.

**1394**

Adiposity but not severity of obstructive sleep-disordered breathing correlates with morning plasma TNF-α levels in Greek children

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Background: Sleep-disordered breathing (SDB) has been associated with increased frequency of excessive daytime sleepiness (EDS). In adults, increased TNF-α plasma levels probably mediate this association, but conflicting results have been reported in children. We hypothesized that: i) the higher the severity of SDB in childhood, the higher the frequency of EDS and morning TNF-α plasma levels; ii) subjects with high TNF-α levels are more likely to have EDS.

Methods: Children without and with snoring underwent polysomnography, EDS and plasma levels measurements. The 3 groups did not differ regarding TNF-α

In conclusion, SDB in children is associated with increased plasma TNF-α levels, mainly in those who have severe SDB and consequently high EDS.
levels (0.63 ± 0.2 vs. 0.65 ± 0.2 vs. 0.57 ± 0.13 pg/mL; p < 0.05). TNF-α levels were associated significantly with body mass index z-score (p < 0.05), but not atH or SpO2 nadir (p > 0.05). Subjects with high TNF-α levels (> 0.57 pg/mL; i.e. median in controls) were not elevated risk for EDS compared to those with low levels. (OR [95% CI] adjusted for obesity: 1.9 [0.6-6.4]).

Conclusions: Increasing severity of SDB is related to increasing frequency of EDS but not with elevated TNF-α plasma concentrations which are positively correlated with the degree of adiposity. Children with high TNF-α levels are not at increased risk for EDS.

1395
Low morning serum cortisol levels in children with adenotonsillar hypertrophy and obstructive sleep apnea
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Adenoidal and tonsillar tissue in children with obstructive sleep apnea (OSA) has enhanced expression of glucocorticoid receptors (Goldbart 2005). Although this finding suggests a favorable profile for topical steroid therapy in children with OSA, its pathogenic role in adenotonsillar hypertrophy is unknown. It is possible that overexpression of glucocorticoid receptors in pharyngeal lymphoid tissue reflects low endogenous cortisol levels. We hypothesized that children with OSA and tonsillar hypertrophy have lower morning serum cortisol levels compared to healthy control subjects.

Methods: Consecutive children with snoring and participating without snoring underwent polysomnography, grading of tonsillar size and measurement of morning serum cortisol.

Results: Children with moderate-to-severe OSA (n=17; 6.1 ± 2.2 yo; AHI 14.7 ± 10.6 episodes/h) had significantly lower morning serum cortisol levels than subjects with mild OSA (n=14; 6.8 ± 2.3 yo; AHI 2.6 ± 1.2 episodes/h) or control participants without snoring (n=14; 6.5 ± 2.5 yo; AHI 0.7 ± 0.2 episodes/h): 16.4 ± 8.7 vs. 23.3 ± 4.2 or 22.3 ± 5.3 mcg/dL; p < 0.05. In contrast, children with moderate-to-severe OSA (n=13; 5.1 ± 1.1 yo; AHI 11.1 ± 5.6 episodes/h) had similar cortisol levels relative to subjects with mild OSA (n=13; 6.8 ± 2.4 yo; AHI 2.4 ± 1.2 episodes/h) or control participants without snoring: 25.6 ± 8.1 or 20.2 ± 1.1 or 22.3 ± 5.3 mcg/dL; p = 0.05.

Conclusions: Low morning serum cortisol in children with OSA and tonsillar hypertrophy might be responsible for the enhanced expression of glucocorticoid levels in pharyngeal lymphoid tissue.

1396
Sleep disordered breathing in children with trisomy 21 and pulmonary hypertension
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Introduction: Children with trisomy 21 (T21) have a significantly high prevalence of sleep disordered breathing (SDB), specifically obstructive sleep apnea (OSA). Children with T21 are also at risk for pulmonary arterial hypertension (PAH). It is unclear if PAH per se confers additional risk for OSA in this population.

Aim: To compare the prevalence of SDB in T21 children with PAH and without PAH and with controls.

Methods: This was a retrospective study where PSG data on all non-obese children at the Hospital for Sick Children, Toronto with T21 and/or PAH referred over a 3 year period, were reviewed and compared with PSG data in age-matched controls. The main outcome measure was the obstructive apnea-hypopnea index (OAHl).

Results: PSG of 33 children aged 0.2 – 8 years with a BMI < 25 kg/m2 were reviewed and compared in 4 groups; 1) controls (n=8), 2) children with PAH (n=9), 3) children with T21 (n=10), and 4) children with both T21 and PAH (n=6). In children with both T21 and PAH, there was a significantly higher OAHl (p=0.01) and a trend for lower oxygen saturations and a higher nCO2 when compared with the other groups (see figures below).

Conclusions: Children with both T21 and PAH are at increased risk of severe OSA. All children with T21 who are known to have PAH should undergo sleep surveillance with PSG. Future research may be directed towards understanding the interaction of T21 and PAH predisposing to OSA.

151. New mechanisms in non-neoplastic and neoplastic lung diseases

1397
Reliability of EGFR mutations detection in NSCLC brain metastases by two different allele-specific PCR methods
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Reliable detection of EGFR mutations in lung cancer metastases requires highly sensitive and robust molecular method. Our aim was to assess effectiveness of two highly sensitive PCR methods in detection of EGFR activating mutations in FFPE samples of brain metastases from 142 NSCLC patients. Isolated DNA was analyzed for EGFR exon 19 deletions and exon 21 L858R mutations by real-time PCR PNA-LNA PCR clamp and allele-specific PCR (ASP-PCR). If discrepant, results were re-evaluated by TaqMan genotyping. Direct sequencing analyses are ongoing. All samples were successfully analyzed. In 37 samples (26%) DNA was of low quality and PCR pre-amplification was performed prior to PNA-LNA PCR clamp analysis. In total 11 out of 142 samples (8%) proved positive for EGFR activating mutations. 6 samples (55% of detected) were positive for exon 19 deletions (n=3) and L858R substitution (n=3) as assessed by both PNA-LNA PCR clamp and ASP-PCR. ASP-PCR, but not PNA-LNA PCR clamp, detected 3 further L858R mutations, whereas 1 L858R substitution and 1 rare A859T mutation were detected by PNA-LNA PCR clamp only. None of discrepant L858R substitutions were confirmed by TaqMan genotyping. A different approach to molecular diagnostics represented by two highly sensitive methods employed in our study might be responsible for observed discrepancies.

1398
The role of the regulated retrotransposon transcriptome in asthma
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Rationale: Genetic studies identified over 200 asthma susceptibility genes that associate with the asthmatic pathology. In the light of the novel functions for mobile DNA elements, we propose that complex diseases, such as asthma, may result from transposed and transposable elements (TEs) which integrate in asthma susceptibility genes or in their regulatory elements.

Objectives: To investigate whether TEs may cause asthma. Therefore, we performed (i) in-silico analysis of TEs in selected asthma susceptibility genes which could potentially function as transcription modulators; (ii) establish CAGE libraries (open analysis of gene expression) using human lung tissue of asthma patients and of healthy controls; and (iii) analyze the transcriptome of the lung tissue CAGE libraries.

Methods: The gene sequence of twelve asthma susceptibility genes (DPF10, CFYF2, HLA-G, GPR5, SFRSS, PIF11, ADAM33, PDCD1, CHI3L1, ORML1, PDE4D, DNN1B) were analyzed in silico for the presence of TEs. In addition, we analyzed the 100 000 5’-upstream bp region in order to localize TEs that may potentially act as alternative promoters/enhancers.

Results: In silico analysis showed that the TE content in the 12 analyzed gene

250s
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Chronic obstructive pulmonary disease (COPD) is influenced by environmental and genetic factors. An important fraction of COPD cases harbor a major genetic determinant, inherited ZZ (Glu342Lys)- α1-antiproteinase deficiency (AATD). Severe, ZZ AATD is associated with a predisposition to early onset, rapidly progressive COPD where emphysema is a major component. We hypothesized that gene expression pattern differs in end-stage COPD with and without AATD. Tissues from explanted lungs of end-stage AATD-related (ZZ, n=3) were treated with α1-antiproteinase augmentation therapy and “normal” (MM, n=3) COPD were used for microarray gene expression analysis. A total of 162 genes were found to be differentially expressed (p-value ≤ 0.05 and |FC| ≥ 2) between MM and ZZ COPD patients. Of these, 134 genes were up-regulated and 28 were down-regulated. When compared to healthy individuals, a subgroup of genes, zinc finger protein 165, snail homolog 1 (Drosophila), and Krüppel-like transcription factors (KLFs) were found to be up-regulated in ZZ COPD patients only.

1400 Regulation of microRNA-mRNA target pairs in a model of bronchopulmonary dysplasia

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Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease of premature neonates characterized by arrested pulmonary alveolar development. Objective: Because microRNA (miRNAs) may regulate the translation of messenger RNAs (mRNAs), we used a computational approach to identify miRNA targets that may be involved in BPD. Methods: Neonatal mice were exposed to 80% oxygen (O2) or room air (RA) for either 14 or 29 days. Lung histology was assessed using standard techniques. Comprehensive miRNA and mRNA profiling was performed using lung tissue from each group. Potential direct miRNA targets of these miRNAs were systematically predicted through miRNA-mRNA correlations and computational mapping in miRBase. Functional significance was investigated using Gene Ontology (GO) term enrichment analysis for miRNA regulatory networks using the DAVID and MetaCore databases.

Results: At both 14 and 29 days, the lungs of O2 mice displayed histological changes consistent with BPD. Between the two time points we identified 2,714 miRNAs and 66 mRNAs that were dynamically regulated by O2 exposure. All but one of the miRNAs were up-regulated. We identified 581 dynamically regulated, direct miRNA targets of these miRNAs by computational mapping in miRBase. Gene ontology enrichment and pathway analysis revealed that hyperoxia modulated genes involved in a variety of lung developmental processes, including cell cycle, cell adhesion, inflammation and angiogenesis. Conclusion: A murine model of BPD is characterized by altered expression of Wnt/β-catenin signaling may be involved in airway inflammation and fibrosis. Overexpression of Wnt antagonists may contribute to this process, implicating potential therapeutic targets for the treatment of COPD.

1403 ADAM33 protein found in bronchial brushings and biopsies is increased in bronchial carcinomas

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Background: The asthma and COPD susceptibility gene, ADAM33, is selectively expressed in mesenchymal cells and the activity of soluble ADAM33 has been linked to angiogenesis and airway remodeling. Aims: We hypothesized that ADAM33 mRNA & protein are differentially expressed in bronchial biopsies from healthy airways and bronchial carcinomas. Methods: Paired primary human bronchial fibroblasts (n=4) from healthy and tumor tissue were grown +/- TGFβ2 to induce myofibroblast differentiation. Fibroblasts,
bronchial biopsies (n=12) and brushings (n=12) were analysed for ADAM33 expression using quantitative RT-PCR and western blotting. Immunohistochemistry for ADAM33 was performed on bronchial biopsies.

**Results:**

TGFS-α caused induction of α-SMA and suppression of ADAM33 mRNA expression in normal and tumor fibroblasts. ADAM33 mRNA expression tended to be decreased in tumor biopsies whereas ADAM33 protein expression was significantly increased (bands of 45 and 75 kDa). In bronchial brushings ADAM33 mRNA was not detectable. However, there was a single band at ~75kDa for ADAM33 and also specific staining for ADAM33 in the epithelium of bronchial biopsies.

**Conclusions:** Similar to cells from healthy and asthmatic volunteers TGFS-α suppressed expression of ADAM33 mRNA in normal and tumor fibroblasts. ADAM33 protein was increased in bronchial tumor biopsies suggesting potential roles in tumorigenesis and growth. The presence of ADAM33 protein in bronchial brushings and biopsies in the absence of ADAM33 mRNA expression in brushings suggests that the mesenchyme is the source for ADAM33 protein in the epithelium.

* R.M. was supported by ERS short-term research training fellowship in 2010/2011 in Southampton, UK.

**1404**

### Independent validation of prognostic value of 22 microRNAs (miRs) in stage I-II lung adenocarcinoma (AC)

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**Background:** About 50% of NSCLC patients (pts) will develop distant metastases following pulmonary resection. Currently, apart from clinical stage at diagnosis, there are no reliable factors to select the high risk pts for adjuvant chemotherapy. We previously demonstrated prognostic value of 22 miRs in frozen tissue samples of early stage SqCLC, and the feasibility of their expression assessment in formalin fixed paraffin embedded (FFPE) samples (Skrzypski et al. J Clin Oncol 2010; 28:15s). In this study, we validated the prognostic value of these miRs in an independent cohort of early AC pts.

**Methods:** FFPE tumor samples were obtained from 82 stage I-II AC pts who underwent radical pulmonary resection, 44% of whom developed distant metastases. Median follow-up of pts who did not develop metastases was 5.53 years (range, 3.01-8.9 years). miRs were isolated from tumor tissue with RecoverAll kit (Ambion). Expression of 22 miRs previously found to be related to the risk of metastases was analyzed by RT-PCR assay (Appliedbiosystems). Raw data were normalized vs. the expression of U6. Individual miRs were correlated with distant metastases-free survival (MFS).

**Results:** MiR-22**2** (p=0.0003) and miR-222 (p=0.002) were significantly related to MFS. Using the median of the miR-222 expression as a cut-off value, the median MFS was 2.12 years in the high risk group, and not reached in the low risk group (HR=1.95). Using the median of the miR-222 expression as a cut-off value, the median MFS was 2.56 years in the high risk group, and not reached in the low risk group (HR=1.78). **Conclusions:** MiR-222 and miR-222 are strong predictors of distant relapse in operable early AC.

**152.** Microbiological advances in the diagnosis of tuberculosis

**P1405**

### Comparison of molecular and immunological methods for a rapid diagnosis of smear-negative tuberculosis

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**Background:** A rapid diagnosis or exclusion of pulmonary tuberculosis (pTB) in pTB suspects with negative acid-fast-bacilli (AFB) sputum smears is at times still challenging in clinical practice.

**Methods:** We compared in retrospect results of Xpert MTB/Rif (single sputum or BAL specimen) nucleic acid amplification with a Mycobacterium tuberculosis-specific bronchoalveolar-lavage (BAL) Elispot in suspects of pTB with negative AFB sputum smears at a TB referral center in Germany.

**Results:** In 96 suspects of pTB with negative AFB sputum smears admitted from 04/2010-10/2011 in our clinic, pTB was confirmed by culture in 10 cases and clinically suspected in 9 cases. Sensitivity, specificity, positive and negative likelihood ratio were 60%, 97%, 30, 0.41 for culture confirmed cases and 42.1%, 97%, 21, 0.59 for all TB patients for the Xpert MTB/Rif and 89%, 62.6%, 2.1, 0.32 for culture confirmed cases and 89.4%, 62.6%, 2.4, 0.17 for all TB patients for the M. tuberculosis specific BAL-Elispot. BAL-Elispot identified 10 out of 11 patients with pTB (including 3 out of 4 with culture confirmed TB) with a negative Xpert MTB/Rif test.

**Conclusion:** A positive result of a Xpert MTB/Rif test on a sputum or BAL specimen has a very high likelihood for the diagnosis of active TB, however the sensitivity is insufficient to rule out pTB with a negative result. BAL-Elispot identifies the majority of TB cases in suspects of pTB with negative AFB sputum smears and negative Xpert MTB/Rif test but the specificity of the BAL-Elispot is suboptimal for a confirmed diagnosis.

**P1406**

### Diagnostic role of micro-MGIT culture of BAL samples in sputum smear-negative pulmonary tuberculosis

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**Introduction:** In view of the diagnostic difficulties associated with sputum- negative pulmonary TB (PTB), we aimed at exploring if bronchoalveolar lavage (BAL) samples can be subjected to near-microscopy and molecular-mycobacterial culture (by Mycobacterial Growth Indicator Tube method) to achieve improved diagnosis of this condition.

**Methods:** Patients presenting with clinico-radiological features suggestive of pulmonary tuberculosis and whose sputum smears were negative for acid-fast bacilli (AFB) or who could not expectorate sputum were prospectively enrolled in this study. BAL samples collected from them were subjected to smear-microscopy for AFB and micro-mGHT culture. BAL samples were also inoculated on Lowenstein- Jensen (LJ) slants.

**Results:** A total of 105 patients (74 males) were recruited in the study, with a mean (±SD) age of 51 (± 15) years. The diagnosis of PTB was made in 52 patients on the basis of clinico- radiological presentation, with or without microbiological confirmation. Thirty- four patients (65.4%) had microbiologically confirmed PTB. Of them, AFB was detected in 12 BAL samples, while culture- positivity was noted in 24 and 27 patients by the LJ and MGIT methods respectively. Inter- test agreement between the LJ and MGIT methods was found to be significant (κ= 0.66; p<0.001). However, the mean time to positivity was significantly lower for the MGIT method than for the LJ method (p<0.001).

**Conclusion:** Examination of BAL samples by smear-microscopy and micro-MGIT culture can, therefore, provide a rapid and definitive diagnosis of PTB in sputum-negative patients.

**P1407**

### Effective variable-number tandem repeats loci for discrimination of Mycobacterium tuberculosis isolated from Korea

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**Introduction:** The variable-number tandem repeats (VNTR) typing is a promising method to discriminate M. tuberculosis isolates in molecular epidemiology.

**Objectives:** The purpose of this study was to evaluate already known VNTR loci and to select best combination of VNTR loci set for discrimination Korean TB strains.

**Methods:** The 307 clinical isolates collected from throughout Korea were genotyped using IS6110 RFLP, and analyzed the number of VNTR copies for the 32 VNTR loci including Supply-15, Supply-24 and JATA-15 (except QUB-18; MIRU-02, -04, -10, -16, -20, -23, -24, -26, -27, -31, -39, -40, ETR-A, -B, -C, QUB-11a, -11b, -15, -26, Mubh-04, -21, VNTR-3322, -3336, -3360, -4120, -4156. And then, allelic diversity (h) and the Hunter-Gaston discriminatory index (HGDI) were calculated to evaluate discriminatory power of locus and combination of VNTR loci.

**Results:** As a results of analysis of the 32 VNTR loci, we found that 12 loci (MIRU-26, -31, QUB-11a, -11b, -26, Mubh-04, -21, VNTR-3322, -3336, -3820, -4120, -4156) showed high discrimination power (each h values of them was over 0.6). This new 12-locus combination for Korea TB strains was designated as a KT-12. The discriminatory index (HGDI) of IS6110 RFLP and VNTRs of Supply-15, Supply-24, JATA-15, and KT-12 was 0.9992, 0.9980, 0.9987, 0.9992 and 0.9997 respectively. Also the percentage of clustered cases was 16.6%(51/307), 21.8%(67/307), 16.9%(52/307), 14.3%(44/307), 6.8%(21/307) respectively.

**Conclusions:** The newly proposed VNTR typing system, KT-12 loci can be effective tool for M. tuberculosis genotyping in Korea where the Beijing strains are predominant.
P1408 Evaluation of real time polymerase chain reaction, adenosine deaminase and interferon gamma in tubercular pleural effusions
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Introduction: Pleural effusions are a common manifestation of tuberculosis. Real Time Polymerase Chain Reaction (RT-PCR), Adenosine Deaminase (ADA) and Interferon gamma release assay (INF) provide faster results than Ziehl Neelson (ZN) staining and Culture on LJ medium. RT-PCR is superior to conventional PCR in sensitivity, specificity with lower contamination and reduction in time to result.

Aims and Objectives: To evaluate the sensitivity of RT-PCR. ADA and INF in cases of pleural effusions due to tuberculosis.

Methods: RT-PCR was performed in 168 patients of tubercular pleural effusions. All patients had positive Mantoux test with high protein and lymphocyte percentage.

RT-PCR was performed by detecting amplification reaction for the insert element IS6110 of the Mycobacterium tuberculosis complex (Biostub-QT, Biostools Labs, Spain) using a real-time centrifugal amplification system (Rotor-Gene 3000, Corbett Research, Australia). ADA was estimated by enzymatic method (BQ Kits, San Diego, USA) and INF was measured using Quantiferon TR Gold kit from Cellstest Ltd, USA on Automated ELISA Reader (TECAN, Miltenyzer).

Results: RT-PCR was positive in 154 of the 168 cases of tubercular pleural effusions (Sensitivity 91.67%). ADA showed high positivity in 162 of 168 cases (sensitivity 96.42%). INF showed sensitivity of 69.64% (positive in 117 of 168 cases).

The sensitivity of ZN staining in tubercular pleural effusion was 13.10%, Culture for AFB by LJ medium was 31.55% and BACTEC was 57.14%.

Conclusion: Real time PCR provides rapid diagnosis of tubercular pleural effusions. The diagnostic efficiency could be increased by combining RT-PCR with ADA.

P1409 Rapid detection of Mycobacterium tuberculosis from clinical specimens using a new target
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Introduction: Auramine O fluorescent stain was found to be more sensitive than Ziehl Neelsen stain and weakly acid fast bacteria (e.g: Nocardia species). The aim of this study was to develop a new sensitive and specific method for detection of M. tuberculosis. The aim of this study was to develop a new sensitive and specific PCR method for detection of M. tuberculosis directly from respiratory specimens.

Methods: The identification of M. tuberculosis isolates was confirmed using standard biochemical tests. Primer 3 plus software was used to design primers from CYP141. The expected size of the amplicon was 173 bp. We collected spuata from 247 suspected patients of different cities of Iran.

Results: With the exception of M. tuberculosis complex, no amplification was obtained with DNA from other mycobacteria, potentially pathogenic bacteria in the respiratory tract and human cells. These results give evidence that CYP141 can be used as a target for direct detection of M. tuberculosis from respiratory specimens.

Discussion: We obtained positive results with a trace amount of template DNA, as little as 1pg. Rv3121 or CYP141 exists in all M. tuberculosis isolates used in this study. The high overall specificity (97.8%) and sensitivity (85.7%) of this target (MOTT) and weakly acid fast bacteria (e.g: Nocardia species). The aim of this study was to modify the time of decolorization by 0.5% acid alcohol in order to increase the specificity without affecting the sensitivity of the stain. Smears were prepared from 25 bacterial cultures classified into 4 different groups. Group A comprises Mycobacterium tuberculosis complex, group B comprises 15 Mycobacteria other than tuberculosis (MOTT), group C comprises Nocardia farcinica and group D comprises one Gram positive and one Gram negative bacteria. All smears were stained with Auramine O fluorescence stain (IML-Red, Germany). 6 smears from each bacterial isolates were decolorized by 0.5% acid alcohol for (1, 2, 3, 4, 5, 10 m) to each smear separately, then all smears were counterstained with K permanganate for 1 m. All group (B) bacterial isolates were stained 100% fluorescence after 5 minutes decolorization time but the fluorescence of group (B) isolates were reduced to 73.3% after 5 minutes decolorization time and to 53.3% after 10 minutes. Group (C) showed weak fluorescence after 1 and 2 minutes which completely decolorized after 3 minutes. In conclusion, Mycobacterium tuberculosis complex was resistant to decolorization with 0.5% acid alcohol for 10 minutes while some MOTT were decolorized when using the same time.

P1411 Detection of fluoroquinolone resistance associated mutations in Mycobacterium tuberculosis by use of sequencing and TaqMan probes
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Introduction: Mutations conferring resistance of MTT to fluoroquinolones occur in two short discrete segments of gyrA and gyrB genes. The aim of the amino acids at positions 88, 90 and 94 in gyrA plays a crucial role in the acquired resistance to fluoroquinolones. The aim of investigations is to evaluate the method of real time PCR with dual TaqMan probes for rapid detection of MTT resistance to fluoroquinolones.

Methods: Resistance to ofloxacin of MTT was determined by reference technique. gyrA and gyrB genes were amplified and autosequenced. The real-time PCR with dual TaqMan probes was developed to detect mutations in triplets 90, 94 of the gyrA gene.

Results: The gyrA codons 90, 91, 94 were reported to be the most frequently mutated codons worldwide, the same tendency was registered in Belarus: point mutations were predominately localized at codons 90 and 94 and rarer - 91. Mutations occurred at codon 90 resulted in Ala→Val replacements, at triplet 94 Asp→Gly or Asp→Asn, at codon 91 - Ser→Pro. The designed dual TaqMan probes for real-time PCR allowed detecting mutations in triplets 90, 94 of gyrA gene. Samples with mutations were characterized by above-threshold florescence on JOE-channel and subthreshold florescence on FAM-channel, while samples without mutations displayed above-threshold florescence on FAM-channel and subthreshold florescence on JOE-channel. The results obtained by real-time PCR with dual TaqMan probes showed high level of coincidence with sequencing data (94%).

Conclusion: The dominant mutations in 90, 94 triplets gyrA can be rapidly and effectively detected by PCR with dual-probe TaqMan probes.

P1412 Resazurin microtitre assay (REMA) plate – A simple, rapid and inexpensive method for detection of drug resistance in Mycobacterium tuberculosis Sudharrth Kunte, Alaka Karmarkar, Sujata Dharmashale, Swapnara Hatolkar
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Introduction: The sensitivity of REMA for the respective drugs was found to be 94.4%, 93.75%, 93.3% and 66.6%. The specificity of REMA for the respective drug was found to be 100%, 100%, 45.5% and 35.3%. The cost of REMA Plate method came out to be half of that required for Proportion Method.

Conclusions: REMA can be considered as one of the most rapid and inexpensive method to find out drug resistance to INH and RIF and can be of great advantage in the diagnosis of MDR-TB. ETM and STR, two drugs known to be difficult to test showed a low specificity.
**P1413**

Evaluation of real time polymerase chain reaction in tubercular mediastinal lymphadenopathy

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**Introduction:** Mediastinal lymphadenopathy is a common manifestation of tuberculosis. Several other conditions such as Sarcoïdosis and lung cancers also cause mediastinal lymphadenopathy. Radiology alone does not provide a diagnosis of TB in such cases. Conventional methods such as culture on L3 medium give results after several weeks while ZN stain for AFB has low sensitivity. We studied the sensitivity of Real Time Polymerase Chain Reaction (RT-PCR) on samples obtained by Trans Bronchial Needle Aspiration (TBNA) through fiberoptic bronchoscopy.

**Aims and Objectives:** To evaluate the sensitivity of RT-PCR in cases of mediastinal lymphadenopathy due to tuberculosis.

**Methods:** RT-PCR was performed in 39 consecutive patients of mediastinal lymphadenopathy who underwent fiberoptic bronchoscopy and TBNA of the mediastinal nodes. Final diagnosis of all patients was based on Histopathology, ZN staining and BACTEC culture for AFB.

RT-PCR was performed by detecting amplification reaction for the insert element IS6110 of the Mycobacterium tuberculosis complex (Biotub QT, Biotools Labs, Spain) using a real-time centrifugal amplification system (Rotor-Gene 3000, Corbett Research, Australia).

**Results:** Of the 39 cases of mediastinal lymphadenopathy, 21 were due to tuberculosis. In 11 cases the cause was Sarcoïdosis and 7 cases were due to malignancy. RT-PCR was positive in 19 of the 21 cases of tuberculosis ( Sensitivity 90.48%). There was 1 false positive RT-PCR in a case of lung malignancy. The Specificity of RT-PCR in tuberculosis was 94.74%

**Conclusion:** Real time PCR is valuable in the diagnosis of mediastinal lymphadenopathy due to tuberculosis with a sensitivity of 90.48% and specificity of 94.74%.

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**P1414**

**Xpert MTB/RIF assay for rapid detection of Mycobacterium tuberculosis and rifampicin resistance**

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**Introduction:** Xpert MTB/RIF is a novel molecular diagnostic point of care test for rapid detection of MTB and its susceptibility to rifampicin (RIF).

**Objective:** This study was performed to evaluate the performance of Xpert MTB/RIF assay in detection of MTB and resistance to rifampicin from sputum specimens taking positive culture for MTB and phenotypic resistance to rifampicin as reference standards.

**Materials and methods:** 126 consecutive patients of pulmonary tuberculosis presenting to the hospital from December 2010 to January 2012 were enrolled for the study. Their sputum samples were subjected to concentrated ZN microscopy, culture on solid (LI) and liquid (MGIT) media. All positive cultures were identified as MTB complex using SD-TB Ag MPT 64 Rapid immunochromatographic test and indescriminating susceptibility testing performed by MGIT SIRE.

**Result:** Of the 126 cases included in the study, 83 were smear-positive and 43 were smear-negative. Of patients with culture positive samples, 20 of 126 (15.9%) were found to have multdrug resistance on indirect drug susceptibility testing with MGIT SIRE. With positive culture as the reference standard, MTB/RIF assay when done detected 98.7% of smear positive cases and 72.1% of smear negative cases. The test correctly identified all 20 of rifampicin resistant culture isolates and 105 of 106 rifampicin susceptible isolates for a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 99%, 95.2% and 100% respectively.

**Conclusion:** Xpert MTB/RIF assay is a reliable technique for rapid detection of Mycobacterium tuberculosis and Rifampicin resistance from pulmonary specimens.

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**P1415**

**The prevalence of pyrazinamide resistance in multidrug resistant tuberculosis cases in the Netherlands**

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**Introduction:** Pyrazinamide is very important in the treatment of multidrug resistant tuberculosis (MDR TB). Unfortunately, studies on the prevalence of pyrazinamide resistance in MDR TB cases are scarce and mainly come from non-European countries.

**Aims and objectives:** Our aim was to determine the prevalence of pyrazinamide resistance in MDR TB cases from the Netherlands.

**Methods:** We retrospectively analyzed pyrazinamide resistance in all MDR TB cases from the Netherlands found in 2007-2011. Drug susceptibility testing was performed using the Mycobacterial Growth Indicator Tube (MGIT) method. Also in every resistant isolate the pncA gene was sequenced. Resistance was determined using a diagnostic algorithm described recently by our group incorporating both methods (Simons, S.O., et al. JCM 2012: 50:428-34).

**Results:** 61 cases of multidrug resistant tuberculosis were seen in the Netherlands from 2007-2011. Pyrazinamide resistance testing was possible in 59 cases. In 17 MDR TB cases pyrazinamide resistance was observed (29%). 16 out of these 17 cases carried a nonsynonymous mutation in the pncA gene.

**Conclusions:** Our data suggest that among MDR TB cases in the Netherlands pyrazinamide resistance is around 29%. Strategies are required to determine the optimal diagnostic algorithm in this population.

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**P1416**

**Comparative analysis of detection of Mycobacterium tuberculosis and rifampicin resistance determination through microbiological and molecular methods for pulmonary tuberculosis patients with presence or absence of sputum**

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**Introduction:** The majority of studies on diagnostics of pulmonary tuberculosis (PTB) used only sputum that appears at later stages of disease and don’t use bronchoalveolar lavage (BAL) fluid obtained by bronchoscopy. At the same time these patients are epidemiologically dangerous even at the early stages of disease. The aim of our study was to compare the possibilities of microbiological and molecular genetics methods for Mycobacterium tuberculosis (MTB) detection and rifampicin resistance identification (RIF-R) in new cases of PTB through sputum or BAL fluid examination. We conducted a double-blind randomized retrospective investigation. The aetiology of PTB has been proven by receiving the culture growth or histological examination of lung tissue with Ziehl-Neelsen staining. A total of 134 specimens (32 sputum and 102 BAL fluid) from 133 patients gave positive results by Real-Time PCR (kit “AmpliSencMTB-FL”) and by sequencing of rpoB gene (kit “AmpliSencMTB-RIF-seq”). We received growing of MTB culture in only 23 sputum and 56 (54.9%) BAL fluid compared to the molecular genetics investigations. We found RIF-R in 12 (38.7%) sputum and 37 (36.3%) BAL fluid by all methods. In addition to the culture method we managed to detect RIF-R in 15 sputum and 25 BAL fluid samples (plus one insignificant mutation). Due to the higher sensitivity of molecular genetics methods we not only found out MTB in proven cases of PTB more likely than culture method, but also higher level of RIF-R that did not demonstrate a difference between patients with presence or absence of sputum.

**P1417**

**Assessment of molecular assays for detection of MDR Mycobacterium tuberculosis resistant to second-line injectable drugs**

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With the emergence of MDR-TB and XDR-TB rapid and accurate second-line drug susceptibility testing became essential. The [GenoType® MTBDRsl] (Hain Lifescience, Germany) gives the possibility to identify mutations in the rrs, gyrA and embB genes. The aim of the present study was to assess the sensitivity of this molecular assay for the identification of M. tuberculosis resistant to second-line injectable drugs (SLIDs), as, to our knowledge, detection of rrs mutations is not sufficient for this purpose. 40 MDR M. tuberculosis strains, also resistant to SLIDs, were chosen from our culture collection. 20 SLIDs-resistant strains were adopted as control. Three DNA targets were investigated: the rrs gene, the embB promoter region and the embA gene. The [GenoType®] was used to detect rrs mutations and SSCP and sequencing were performed for all three genes. All kanamycin and capreomycin-resistant cultures carried an A1404G substitution in the rrs gene and were detected with all the molecular assays, but one of the strains also had an embB mutation. 8 kanamycin-resistant strains carried various embA mutations, the most common being the C141T substitution, and thus could not be identified with the [GenoType®]. No mutations were found in the embA gene. One of the SLIDs-susceptible strains carried a C12T mutation. Therefore 20% of M. tuberculosis strains resistant to kanamycin could not be detected with the [GenoType®]. Mutations in the embB promoter region are found in kanamycin-resistant M. tuberculosis strains at high rates and should be included in molecular assays for detection of SLIDs resistance.

**P1418**

**Modern molecular direct tests for rapid identification and drug susceptibility testing of Mycobacterium tuberculosis**

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Molecular tests are widely used for detection of M. tuberculosis (MTB) in clinical samples in laboratories around the world. At present, there are molecular tests allowing to perform MTB detection and DST to antituberculosis drugs simultaneously.
We performed a comparative analysis of three molecular tests: GeneXpert MTB/RIF (Cepheid, USA), GenoType MTBDRplus (Hain LifeScience, Germany) and TB-Biochip MDR (LLC "BIOCHIP", Russia).

All in all 151 sputum samples were investigated. 32 of them were smear- and culture-positive, and 19 of them were smear-negative but culture-positive. Co-occurrence of the results of MTB detection by molecular tests with the culture test in Racine, USA and in Becton Dickinson, USA were 92.8%, 78.4% and 49.02% respectively. For GeneXpert MTB/RIF, TB-Biochip MDR and MTBDRplus respectively. For the smear-negative and growth-positive sputum samples results coincided in 80.9% and 52.4% of cases for GeneXpert MTB/RIF and TB-Biochip MDR respectively. Results of molecular and bacteriologic DST to rifampicin (RIF) (isoniazid (BIN)) coincided in 100%, 97.4% and 100% of cases for GeneXpert MTB/RIF, "TB-Biochip MDR" and MTBDRplus respectively. Our data show, that GeneXpert MTB/RIF is the fastest real-time test with the highest sensitivity, but we can get the information about MTB sensitivity only to RIF. As to TB-Biochip MDR and MTBDRplus tests, they are also simple, reliable and establishing of DST to RIF and INH, but the sensitivity of MTBDRplus is not enough to analyze smear-negative samples.

P1419

Population-based study of fluoroquinolone-resistance in clinical isolates of Mycobacterium tuberculosis in Novosibirsk Oblast, Russian Federation

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Background: Fluoroquinolones (FQ) are used for treatment of many bacterial infections frequently. These drugs are being used for treatment of MDR-TB in Novosibirsk Oblast (NO) since 2003.

Aims: To evaluate prevalence of primary drug resistance of M. tuberculosis to FQ in NO. To estimate contribution of common prescription of FQ treatment of non-TB infections to resistance selection in mycobacterial population.

Methods: Minimal inhibitory concentrations (MIC) of ofloxacin (OFL) were determined for 344 isolates of M. tuberculosis from 344 patients with newly diagnosed TB. This selection consisted from 165 isolates obtained in 2000-2002 and 179 in 2006-2010. DST was conducted on all isolates and based on results they were divided additionally in to the following groups - 141 fully susceptible to first-line anti-tuberculosis drugs isolates, 83 MDR isolates and 120 resistant other than MDR.

Results: An increase in MIC of OFL (6,0-32,0 mcg/ml) was detected in the MDR-group (7,2%, 95%CI:3,4-14,9) exclusively and only among isolates obtained in 2006-2010 (3,4%, 95%CI:1,5-7,1). FQs have not been prescribed to 6 patients with FQ-resistant MTB (MIC of OFL > 40 mcg/ml) within the period prior to establishing of TB diagnosis. 3 of them had had a contact with an MDR-TB patient. The calculated prevalence of primary FQ-resistance of M. tuberculosis in NO was 6,4%, 95%CI:2,9-13,2 (result of the sampling of 94 isolates obtained in 2006-2010).

Conclusions: These findings indicate that emerging FQ-resistance in MBT strains in NO is the result of treatment of patients with MDR-TB rather than from FQ prescriptions to general population for non-TB infections.

P1420

Substantial time reduction in diagnosis of Mycobacterium tuberculosis rifampicin and isoniazid resistance by the application of a DNA strip hybridization assay in clinical samples

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The MTBDRplus (Hain LifeScience, Nehren, Germany) is a molecular assay detecting mutations involved in M. tuberculosis rifampicin (RMP) and isoniazid (INH) resistance, approved for application on culture isolates and smear-positive (AFB+) specimens. We evaluated its performance as a routine diagnostic assay directly on clinical specimens.

Methods: Consecutive AFB+ and selected AFB− specimens, from high risk patients for drug resistance, were assayed. The results were compared to conventional drug susceptibility testing (DST). For time reduction estimation we counted the days elapsed before patient’s first positive culture was available.

Results: 475 specimens were analyzed. Interpretable MTBDRplus results were obtained for 331/400 (82.7%) AFB+, 33/70 (47) AFB− and 1/5 (20%) microscopically suspicious specimens. We identified 13 MDR, 28 INH resistant, 2 RMP resistant, and 2 rpo polypharmaceuticals. Disagreement between DST and MTBDRplus mainly involved strains with inhA mutations (68) conflicting resis- tance to low INH concentrations2. The sensitivity, specificity, PPV and NPV values for RMP and INH resistance detection were 100%, 99%, 96%, 92%, 8%, 100% and 86, 6%, 96, 94% respectively. Substantial reduction in drug susceptibility diagnosis was recorded (14±6±2 days).

Conclusions: The MTBDRplus assay was informative for the great majority of AFB+ cases, highly accurate for screening RMP and INH resistance and its application achieved considerable reduction in diagnostic delay.

P1421

Dual TaqMan probes for the detection of rifampicin resistance in Mycobacterium tuberculosis

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Mutations (SNP) at codons 526, 531 of rpo gene of MTB are considered to be biomarkers of resistance to rifampicin (RIF). The aim of the study was to develop 96-well plate qPCR platform with dual TaqMan probes for the prediction of RMP resistance in MTB.

Methods: A total number of 122 DNA extracts from MTB cultures were studied. SNPs in 516, 526, 531 codons of rpo gene were detected by autosequencing and qPCR with dual TaqMan probes (labeled with FAM and JOE for identification of wild and mutated codons correspondingly).

Results: We present a 96-well PCR plate method for identification of SNPs in rpo gene of MTB. Each 96-well PCR plate is organized as follows: 1) 12 DNA extracts can be investigated collectively; 2) four wells are used for each DNA extract to identify MTB and mutations in 516, 526, 531 codons; 3) one set of controls per 6 DNA extracts is provided including positive, negative (with and without mutations), and no-template controls for each control tested. The entire assay includes the following steps: 1) filling wells with DNA-extracts and PCR reaction mixtures using repeater pipette; 2) amplification and data bioanalysis including: a) detection of fluorescence threshold using method of negatives with 20% tolerance; b) allele discrimination analysis based on detection of differences in JOE and FAM fluorescence. The results obtained with this real time PCR design agreed well with DNA sequencing data. Out of 122 DNA extracts (488 reactions) 8 samples were false negative (7%) versus sequencing data. This 96-well PCR plates uses 48 DNA extracts of 20 DNA reactions in 6 lines, and represents an adequate method for the specific and rapid detection of RMP resistance in MTB cultures.

P1422

Line probe assay (LPA) based rapid detection of multiple drug resistant (MDR) mycobacterium tuberculosis (MTB)

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Objective: Rapid confirmation of diagnosis of MTB and MDR-MTB in clinical samples by Line probe assays based on Reverse DNA hybridization(RDH)

Methods: RDH is useful for detection of mutations related to drug resistance in Mycobacterium tuberculosis. The sample size of 50 AFB staining positive sputum samples was taken. Of these 30% were cases known to be MDR cases as detected from culture tests and 79% were fresh smear positive cases on treatment for TB. The Line probe assays were developed to cover common drug resistant mutations with rifampicin, INH, and aminoglycosides. The genes probed were rpoB, katG, gyrA, gyrB, rrs, eis, the MTB complex and NTN. The end point was detected was by avidin biotin labeled nested PCR products from patient samples.

Results: All the 50 smear positive samples were detected as MTB or NTN positive by the LPA assay. All the known MDR cases showed drug resistance related mutations in the LPA. About 30% had mutations in the gyrA gene and all were observed in clinically known MDR cases; 46% of mutations were seen in the rpo gene and 56% in the katG region. The efficacy of the line probe when related to culture tests was greater than 90%.

Conclusion: The LPA assay relates well with both MTB mycobacterial presence and Drug resistance.

References:

Cigarette smoke upregulates IL-8/CXCL8 expression by augmenting mRNA stability via p38 MAPK-induced MK2 phosphorylation which was accompanied by the phosphorylation of MAPK-activated kinase 2 (MK2), a known downstream substrate of the p38 MAPK. In both BHSMC and human alveolar macrophages, pharmacological inhibition of p38 MAPK only acutely accelerated the decay of IL-8 mRNA levels upon stimulation with CSE or acrolein and subsequent blockade of mRNA neo-synthesis with actinomycin D. Conversely, pharmacological inhibition of extracellular-signal-regulated kinase 1/2 (ERK1/2) signalling did not affect mRNA stability but inhibited both CSE- and acrolein-induced steady-state levels of IL-8 mRNA, suggesting a transcriptional effect. In sum, p38 MAPK/MK2 signalling appear to be an important post-transcriptional mechanism underlying CSE-induced IL-8 mRNA upregulation.

Cigarette smoke is the most important risk factor for the development of Chronic Obstructive Pulmonary Disease (COPD). A large body of evidence exists indicating that cigarette smoke is able to activate the Epidermal Growth Factor Receptor. We have previously established that aconitase cigarette smoke extract (CSE) stimulates CXCL8 and VEGF release from normal human lung fibroblasts (NHFL) and airways smooth muscle cells (ASM) and that these effects are mediated by the α,β-unsaturated aldehydes contained in the CSE such as acrolein. Here we examined the effect of pharmacological inhibition of EGFR on CXCL8 and VEGF release induced by CSE and acrolein. We found that the EGFR inhibitors AG1478, gefitinib and PD153035 inhibit CSE- and acrolein-induced CXCL8 release in both NHFL and ASM, but do not affect neither TNFα-induced CXCL8 release nor CSE-induced VEGF release. We have previously shown that CSE-evoked CXCL8 and VEGF release was accompanied by a rapid p38 MAPK phosphorylation mimicking by acrolein. Because p38 MAPK phosphorylation is one of the possible downstream pathways activated by EGFR, we examined the effects of EGFR inhibitors on p38 MAPK phosphorylation. We observed that all three EGFR inhibitors failed in modifying p38 MAPK phosphorylation evoked by CSE. In sum, pharmacological inhibition of EGFR suggests that EGFR is involved in CXCL8 release through a p38 MAPK independent mechanism. Given the pivotal role of CXCL8 and VEGF as neutrophils chemoattractant and angiogenic factor respectively, this study sheds light on the different mechanisms through which cigarette smoke can orchestrate inflammation and vascular remodeling in the lung.

Cigarette smoke (CS) as a major source for oxidative stress in the lungs, is the main cause of chronic obstructive pulmonary disease (COPD). Patients suffering from COPD are more susceptible to viral infections resulting in acute exacerbations. Viral infections induce expression of immunoproteasomes (IP) via IFNγ-signaling. This specialized form of proteasome is destined to improve antigen presentation and the control of viral infections. The role of IP in viral lung infections is unknown. Expression levels of IP-subunits LMP2 and LMP7 were evaluated in wildtype (wt) as well as LMP2+ and LMP7+ deficient mice in whole lung homogenates. Of note, we observed pronounced expression of IP-subunits in wt lungs compared to other organs. Immunohistochemical analysis of lung sections revealed that IP positive staining was observed in cells adjacent to airways, but also in alveolar regions. To study regulation of IP in vivo, we analyzed expression of IP in different lung cell lines. IFNγ induced pronounced expression of IP in both lung epithelial and fibroblasts cells, as detected by qRT-PCR and western blotting. In COPD patients and in PBT-cells from HC subjects stimulated with CSE. CSE causes the release of chemokines but reduces IgE/antigen-induced degranulation and cytokine release. Interestingly, CSE was found in CSE. Both CSE and acrolein induced p38 mitogen-activated protein kinase (MAPK) phosphorylation -induced CXCL8 release through a p38 MAPK independent mechanism. Given the pivotal role of CXCL8 and VEGF as neutrophils chemoattractant and angiogenic factor respectively, this study sheds light on the different mechanisms through which cigarette smoke can orchestrate inflammation and vascular remodeling in the lung. Chronic obstructive pulmonary disease (COPD) is a multicomponent disease characterized by emphysema and/or chronic bronchitis. COPD is mostly associated with cigarette smoking. Many inflammatory cells are present in the airways of patients with COPD. Cigarette smoke contains over 4,700 chemical compounds, including free radicals and LPS (a Toll Like Receptor 4 agonist) at concentrations which may contribute to the pathogenesis of diseases like COPD. Toll-like recep-
P1428 Role of interferon-γ in tumor necrosis factor-α-mediated increase of lung microvascular endothelial cells

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Background: Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease in which tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are respectively and have been suggested to play pathogenic roles. The effect of these agents on angiogenesis in the lung tissues of COPD is unknown.

Objective: To examine the effects of these mediators on lung endothelial cells (ECs).

Methods: NR2f knockout mice were exposed to cigarette smoke (CS) for 4 weeks, and the down-regulated genes referring to vascularity in the whole lung were identified by microarray analysis. To confirm the protein levels, which were indicated in the microarray data, cell lines, namely human umbilical vein microvascular endothelial cells (HUVECs) and human microvascular endothelial cells (HMECs) were used. The protein levels of TNF-α and IFN-γ were performed, thereafter ECs were submitted to an examination of protein levels expression using immunoblotting or immunocytochemistry.

Results: Microarray analysis data have shown that the mRNA expression of angiogenin-like protein 1 (AmotL1) decreased in response to CS when compared to no exposure to CS. TNF-α enhanced vascular endothelial cell growth factor (VEGF) production by cultured lung fibroblasts, however, vascularity was decreased when treated with IFN-γ. In addition, IFN-γ induced tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors on ECs and attenuated the expression of AmotL1 localized to endothelial cell-cell junctions.

Conclusions: These results suggest that IFN-γ acts as anti-angiogenesis by regulating the expression of TRAIL receptors and AmotL1 on ECs, which were induced by the enhanced VEGF production by TNF-α-stimulated lung fibroblasts.

P1429 Second hand smoke exposure impairs CD39 expression and function in the lung

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Chronic second hand smoke (SHS) exposure is the main risk factor for non-smokers to develop chronic obstructive pulmonary disease COPD. The mechanisms behind the chronic inflammation and lung destruction are not completely understood.

In response to injury vascular and blood cells release ATP that is implicated in regulating immune responses. In the present report, we have shown that chronic SHS exposure induced a down-regulation of CD39 expression in the whole lung tissue on mRNA and protein levels. Moreover, CD39 expression was decreased in the lungs from COPD patients. In addition, CD39 expression in the whole lung tissue on mRNA and protein levels. Moreover, CD39 expression was decreased in the lungs from COPD patients. Cigarette smoke extract in vitro almost abolished CD39 and CD73 expression in the alveolar macrophages and vascular endothelial cells. Second hand smoke exposure impairs ectonucleotidase expression in the lungs and leads to accumulation of extracellular ATP that confers increased proinflammatory responses leading to the development of emphysema.

Funded by AHA 0735388N, 11GRNT7520020, FAMRI CIA 072053, Emphysema Division of Pulmonary Medicine, Allergy, and Rheumatology, Iwate Medical University School of Medicine, Morioka, Japan

P1430 Chronic obstructive pulmonary disease (COPD) is one of the most prevalent, and among smokers with COPD. CD98 was measured on AM using flow cytometry. We showed that SHS exposure downregulated CD98 expression on AMs of healthy smokers and COPD patients.

Methods: Sprague Dawley rats were exposed to SHS in a smoking chamber (total particulate matter levels 115 mg/m³). The expression levels of CD39 and CD73 in the alveolar macrophages and vascular endothelial cells. Second hand smoke exposure impairs ectonucleotidase expression in the lungs and leads to accumulation of extracellular ATP that confers increased proinflammatory responses leading to the development of emphysema.

Funded by AHA 0735388N, 11GRNT7520020, FAMRI CIA 072053, Emphysema Division of Pulmonary Medicine, Allergy, and Rheumatology, Iwate Medical University School of Medicine, Morioka, Japan

P1431 Lectins improve efferocytosis via changes to cytoskeletal remodeling: Relevance to COPD

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Objective: To examine the effects of these mediators on lung endothelial cells (ECs).

Methods: NR2f knockout mice were exposed to cigarette smoke (CS) for 4 weeks, and the down-regulated genes referring to vascularity in the whole lung were identified by microarray analysis. To confirm the protein levels, which were indicated in the microarray data, cell lines, namely human umbilical vein microvascular endothelial cells (HUVECs) and human microvascular endothelial cells (HMECs) were used. The protein levels of TNF-α and IFN-γ were performed, thereafter ECs were submitted to an examination of protein levels expression using immunoblotting or immunocytochemistry.

Results: Microarray analysis data have shown that the mRNA expression of angiogenin-like protein 1 (AmotL1) decreased in response to CS when compared to no exposure to CS. TNF-α enhanced vascular endothelial cell growth factor (VEGF) production by cultured lung fibroblasts, however, vascularity was decreased when treated with IFN-γ. In addition, IFN-γ induced tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors on ECs and attenuated the expression of AmotL1 localized to endothelial cell-cell junctions.

Conclusions: These results suggest that IFN-γ acts as anti-angiogenesis by regulating the expression of TRAIL receptors and AmotL1 on ECs, which were induced by the enhanced VEGF production by TNF-α-stimulated lung fibroblasts.

Second hand smoke exposure impairs CD39 expression and function in the lung

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Chronic second hand smoke (SHS) exposure is the main risk factor for non-smokers to develop chronic obstructive pulmonary disease COPD. The mechanisms behind the chronic inflammation and lung destruction are not completely understood.

In response to injury vascular and blood cells release ATP that is implicated in regulating immune responses. In the present report, we have shown that chronic SHS exposure induced a down-regulation of CD39 expression in the whole lung tissue on mRNA and protein levels. Moreover, CD39 expression was decreased in the lungs from COPD patients. Cigarette smoke extract in vitro almost abolished CD39 and CD73 expression in the alveolar macrophages and vascular endothelial cells. Second hand smoke exposure impairs ectonucleotidase expression in the lungs and leads to accumulation of extracellular ATP that confers increased proinflammatory responses leading to the development of emphysema.

Funded by AHA 0735388N, 11GRNT7520020, FAMRI CIA 072053, Emphysema Division of Pulmonary Medicine, Allergy, and Rheumatology, Iwate Medical University School of Medicine, Morioka, Japan

P1432 Enhanced cytotoxic function of NK and NKT-like cells associated with decreased CD94 (Kp43) in the airway in COPD

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NK and NKT-like cells represent a small but important proportion of effector lymphocytes that we have previously shown to be a major source of pro-inflammatory cytokines and granymes. We hypothesized that NK and NKT-like cells would be increased in the airway in COPD and that this would be accompanied by a reduction in expression of the inhibitory receptor CD94 (Kp43) and increased expression of the cytotoxic potential by production of granymes A and B and using a cytotoxicity assay. In blood from COPD subjects, there were no significant changes in NK or NKT-like cell numbers or expression of granyme A or cytotoxic potential vs controls. There was however, increased expression of granyme B and decreased expression of CD94 by both cell types vs controls.

In the airway in COPD, NK and NKT-like numbers were increased, associated with increased NK cytotoxicity, increased expression of granyme B and decreased expression of the inhibitory receptor CD94. Treatment strategies that target NK and NKT-like cells, their cytotoxicity and production of inflammatory mediators in the airway may improve COPD morbidity.

P1433 The role of IL-17 and lymphoid follicles in the pathogenesis of COPD

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Chronic Obstructive Pulmonary Disease (COPD) is one of the most prevalent respiratory diseases in the world. There is no definitive treatment to arrest the progressive loss of lung function characteristic of COPD, partly due to a lack of understanding of the underlying cellular pathological mechanisms. In individuals with severe COPD, there is an accumulation of adaptive immune cells as well as an increase in the frequency of lymphoid follicles in the lung; however, the role of lymphoid follicles in driving the disease and the factors that promote their formation are largely unknown. In addition, individuals with COPD exhibit elevated levels of IL-17, a cytokine that is associated with autoimmunity and was recently shown to promote lymphoid neogenesis. We have modeled different...
severities of COPD by incremental instillation of LPS and elastase in mice. We observed an increase in the levels of IL-17A following repeated challenges, which coincided with the progressive drop in lung function as well as the appearance of lymphoid follicles. IL-17A production was in part triggered by the engagement of Toll Like Receptor 3 implicating a role for an endogenous danger signal in COPD. Neutralization of IL-17A at specific times after the initiation of disease ameliorated the impaired function and affected B Cell lineage and pro-angiogen Activations. Our data indicates that IL-17A is involved in COPD progression by induction of lymphoid follicles and regulation of both innate and adaptive immunity.

Rationale: Although adaptive immune responses are critical for combating distant airway infections in COPD, the structural basis for alveolar antigen uptake has remained poorly investigated. This study investigates the interface between alveolar lumen and the adaptive immune system at different severities of COPD.

Methods: Lung resections (n=31) from mild (GOLD I), moderate-severe (GOLD II-III), and very severe (GOLD IV) COPD patients were used to study detailed histological assessment of components of the adaptive immune system in distal lung. Never-smokers and non-COPD smokers served as controls (n=15).

Results: COPD patients showed increased numbers and size of lymphoid aggregates compared to controls and in non-smokers. Immunohistochemistry for common lymphoid markers showed, increased numbers of B cells, T cells and macrophages. These aggregates were mainly composed of B cells (98%) with a minor contribution of T cells (2%) and macrophages (2%). However, the total epithelial TLR7-immunoreactivity was upregulated in COPD patients in comparison to controls and non-smokers.

Conclusions: Whether the altered expression reflects a natural adaption to the increased pathogen burden in advanced COPD or is part of a dysfunctional immune-regulation in COPD remains to be determined.

P1435 Diverse and altered distribution patterns of TLR5 and TLR7 in the distal lung of COPD patients

Methods: GOLD I (n=6), GOLD II-III (n=13), GOLD IV patients (n=8), and controls (n=15) were enrolled in this study. Immunohistochemical staining was used to identify TLR5 and TLR7 positive cells.

Results: TLR5 immunoreactivity was identified in sub-epithelial glands, airway smooth muscle, CD68+ macrophages, CD138+ plasma cells, CD208+ type II pneumocytes and the small airway epithelium. In control subjects and mild COPD (GOLD I) TLR5 was expressed in the alveolar and small airway epithelium and the alveolar lumen. In moderate-severe (GOLD II-III) and severe COPD (GOLD IV) alveolar and small airway wall matrix components were stained with a hyaluronan binding protein. All stainings were corrected for total surface area and data expressed as mean % of stained area.

Conclusions: These results indicate that remodeling in the alveolar and SA wall in COPD show marked similarities and both relate to FEV1.

P1436 Metabolomic fingerprinting in the identification of biomarkers in COPD patients

Methods: Metabolomic fingerprinting is able to achieve the identification of novel biomarkers the comprehensive characterization of the entire metabolome of a disease. The main objective is to use it to understand the pathological basis underlying COPD and its relationship to the severity and phenotypic characteristics.

Results: Observational case-control study involving COPD patients and controls without COPD or cardiovascular history. COPD patients were grouped in chronic bronchitis and emphysema, and at different stages of GOLD. Different platforms are required to capture all metabolites in one sample of plasma and separation techniques such as gas chromatography coupled to mass spectrometry (GC-MS).

Conclusions: Using metabolomic fingerprinting in plasma we could identify markers and differentiate phenotypes and early stages in COPD.

P1437 Comparable matrix alterations in the alveolar and small airway wall of COPD patient lungs

Results: Using metabolomic fingerprinting in plasma we could identify markers and differentiate phenotypes and early stages in COPD.

Conclusions: Using metabolomic fingerprinting in plasma we could identify markers and differentiate phenotypes and early stages in COPD.

P1438 Corticosteroid insensitivity in airway smooth muscle cells of severe asthma and COPD: Modulation by IFN-γ

Methods: Aper-nuclear expression in the small airway epithelium irrespective of the study group. However, the total epithelial TLR7-immunoreactivity was upregulated in GOLD IV patients compared to never smokers (p=0.009). TLR7 expression was also detected in S100B+ nerve cells, CD68+ macrophages, B- and T-lymphocytes, and CD56+ NK cells.

Conclusion: Both epithelial TLR5 and TLR7 are upregulated in advanced COPD. Whether the altered expression reflects a natural adaption to the increased pathogen burden in advanced COPD or is part of a dysfunctional immune-regulation in COPD remains to be determined.
Conclusions: ASCMs of SA, smokers and COPD display CS insensitivity. IFN-γ impairs the suppressive effect of Dex on CXCL8 in the healthy and asthmatics but improves it in smokers and COPD, suggesting differential mechanisms underlying CS insensitivity in SA and smokers/COPD.

P1439
Inhaled corticosteroids (ICS) attenuates epithelial mesenchymal transition (EMT) in COPD: A key to understanding long term benefits?
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Introduction: We recently published that EMT is an active process in COPD airways. Our knowledge about the effects of ICS on this process in COPD is very limited.

Objective: To assess the effects ofICS on EMT in endobronchial biopsies (ebb) from COPD patients.

Methods: A double-blinded, randomized, placebo-controlled study assessed the effects of inhaled fluticasone propionate (FP, 500μg twice daily) on EMT in 34 COPD patients. Ebb were assessed for EMT related reticolar basement membrane (Rbm) fragmentation and immunostained for the EMT signatures S100A4 (a fibroblast epitope), matrix-metalloproteinase-9 (MMP-9) and epithelial activation marker, epidermal growth factor receptor (EGFR).

Results:

Comparison at baseline and after treatment (FP, n=23 and placebo, n=11)
Markers Before (FP) After (FP) Before (Placebo) After (Placebo)
% Rbm fragmentation 19.1 (0.2-42.8) % 2.6 (0.88-6.6) 24.0 (6.6-100) 26.9 (2.5-48.5)
S100A4 positive cells in Rbm per mm Rbm 25.8 (2.455-3.9) 12.3 (0.6-24.9) 19.8 (2.931.6) 17.4 (0.3-35.5)
S100A4 positive cells in Rbm per mm of Rbm 44.4 (15.3-92.6) 20.8 (2.6-60.7) 23.1 (14.82.9) 29.3 (3.6-48.1)
MMP-9 positive cells in Rbm clefts per mm of Rbm 0.6 (0.0-22.4) 1.1 (0.0-4) 1.3 (0.27)
EGFR % ciliated

Data expressed as medians and ranges. *No significant difference at baseline. **Significant difference after treatment with FP (p<0.03).

Conclusions: This is the first study to report that ICS have potent anti-EMT effects in COPD. This may be a mechanistic link between ICS treatment and long term reduction in smoking-related lung cancer seen in COPD.

P1441
One size does not fit all – Impact of the one liter tidal volume breathing protocol on indices from nitrogen multiple-breath washout in children
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Background: Nitrogen multiple-breath washout (N2MBW) is a useful tidal breathing lung function test to assess ventilation inhomogeneity (Vi), e.g. in Cystic Fibrosis (CF) patients. One liter tidal volume (VT) breathing protocols are regarded to improve comparability of results between subjects breathing at different VT and are widely used in adults. The impact of protocols using fixed VT on results in children is unknown. We assessed whether breathing at fixed VT impacts N2MBW indices in school-aged children.

Methods: Ten children with CF and 16 healthy children performed six N2MBW tests using a validated setup (Exhalyzer D, Eco Medics, Switzerland). Children performed three baseline N2MBW at free tidal breathing and three N2MBW at increased VT with a target of one liter using an incentive. Outcomes were size and variability of lung clearance index (LCI), functional residual capacity (FRC), Scdol and Sacin.

Results: All 26 children achieved six N2MBW. Mean (SD) VT at free tidal breathing was 0.5 (0.1) L, at fixed VT 1.2 (0.2) L. Comparing free tidal breathing with the one liter VT N2MBW, LCI increased on average (95% CD 2.3 (0.6-3.9) in CF children and 1.4 (0.5-2.3) in healthy children. LCI increased by more than one LCI unit in 9 out of 10 CF children and in 14 out of 16 healthy children. FRC decreased, Scdol and Sacin increased significantly. Variability within tests and between subjects increased for all MBW outcomes.

Conclusion: Fixed tidal breathing protocols impact N2MBW indices as shown for the one liter VT protocol in school-aged children. Underlying physiological mechanisms and applicability in adult patients require further study.

P1442
Epithelial cell regulation of immunity in cystic fibrosis
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Introduction: Despite clinical importance, the adaptive immune system in cystic fibrosis (CF) lung disease has been sparsely studied.

Methods: We isolated CF primary human bronchial epithelial cells (PBEC) and assessed their modulation of monocyte-derived dendritic cell (moDC) function and downstream T cell activation, hypothesising that epithelial cells skew immunity to favour chronic infection and lung damage in CF. Healthy monocytes were cultured with the conditioned medium from 6 steady-state CF patient PBEC during moDC differentiation with IL-4 and GM-CSF.

Results: Compared to control moDC, epithelial cell conditioned moDC were tolerogenic and macrophage-like (CD1a, [darr] CD86, [darr] CD14 and [darr] CD1a), reducing low T cell proliferation and interferon-γ production in an allogeneic mixed lymphocyte reaction (MLR) with T cells from healthy donors.

Conclusion: This study is the first to report that CF epithelial cells modulate moDC function and favour chronic infection and lung damage in CF. We provide evidence that the lung epithelium may be a key regulator of the adaptive immune system in CF.

154. Cystic fibrosis (adults and children): new basic and clinical physiology research

P1440
Connexin 37 and Connexin 43 genotypes in correlation to cytokines in induced sputum and blood in cystic fibrosis (CF)
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Background: We have provided evidence in previous studies that cytokines (IL-8, TNF alpha, LBP) measured in whole blood correlate well with lung function in delta 508 homozygous patients. GAP junction proteins (connexins) might be of importance for the influx of blood cells into the lung. Our aim was to assess the relationship between connexin genotypes, cytokines (IL-8, TNF-alpha and LBP) in induced sputum and blood and lung disease.

Methods: 24 patients homozygous for delta F 508 (median age 20.5 y, m/f 14/10, BMI 20.35 kg/m2, Stbowman score 75, FEV1 (%R) 83%) were examined. Sequence analysis was performed for GAP junction protein α1 (GJA1/Connexin 43) and gap junction protein α4 (GJA4/connexin 37). Cytokines were assessed in blood and induced sputum (IS) by chemiluminescence (DPC Biermann, Bad Homburg, Germany).

Results: Here we present the first preliminary data: For 18 patients cytokine and gap junction protein analysis was performed for GAP junction protein α1 (GJA1/Connexin 43) and gap junction protein α4 (GJA4/connexin 37). Cytokines were assessed in blood and induced sputum (IS) 154. Cystic fibrosis (adults and children): new basic and clinical physiology research

Figure 1. Steady state moDC phenotype and function altered by PBEC derived soluble factors

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lymphocyte reaction (MLR). Stimulation of PBEC or direct stimulation of mDC with clinically isolated Burkholderia cepacia whole cell lysate gave a mature, highly stimulatory mDC phenotype while Pseudomonas aeruginosa induced poor maturation and a less potent T cell response.

Conclusion: CF epithelial cells secrete factors which contribute to immune tolerance. CF pathogens may have a variable ability to overcome this regulation and induce an immune response which may favour chronic infection by Pseudomonas aeruginosa.

P1443 Proteases from anaerobic bacteria cleave naturally occurring innate antiproteases in cystic fibrosis

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Introduction: Cystic fibrosis (CF) results in chronic bacterial pulmonary infection leading to an irreversable decline in lung function and ultimately respiratory failure. There is evidence now that CF infection is polymicrobial and that anaerobic bacteria which are not usually detected by routine culture are responsible for at least in part for pathogenic infection (1).

Aims: We aim to study if proteases from P. melaninogenica, the most common anaerobic bacteria found in the CF lung (2), cleave the host innate human antiproteases namely, alpha one antitrypsin (AAT), secretory leukocyte protease inhibitor (SLPI) and elafin.

Method: P. melaninogenica is grown and incubated at 37°C in Luria Bertani Broth (LB) broth, and Basal Anaerobic Media (BAM) broth under strict anaerobic conditions in an anaerobic recumbent. Recombinant SLPI, Elafin and native AAT were included for selected time points with supernatant and cleavage products visualised by SDS-PAGE electrophoresis and Western Blotting analysis using specific antibodies raised against these antiproteases.

Results: P. melaninogenica produces proteases on Day 4.5,6 of incubation and they have distinct cleavage patterns and these cleavage products cleave naturally occurring antiproteases.

References:

P1444 Pseudomonas aeruginosa counteracts the host defense functions of MIG/CXCL9

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Introduction: Cystic fibrosis (CF) is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. A number of studies have been performed to investigate whether CFTR dysfunction in CF is primarily a result of the genetic defect or due to chronic bacterial infection and inflammation.

Aim: The aim of this study was to provide support for intrinsic alterations in CF. Specifically to determine whether accumulation of CFTR within the endoplasmic reticulum (ER) of circulating neutrophils from patients with CF leads to ER stress responses including the release of ER calcium (Ca2+) stores. This study focused on the ER-resident chaperone, GRP78 and ATF6, a transcription factor that coordinates the unfolded protein response (UPR).

Methods: Neutrophils were purified from whole blood and the cytosols were analysed using Western blotting for ER stress markers ATF6 and GRP78. Intraacellular Ca2+ was determined using a fluorometric assay.

Results: Western blots revealed that markers of ER stress, GRP78 and cleaved ATF6, were increased in neutrophil cytosols of patients with CF homogygous for the AF508 mutation, when compared to healthy controls (n=8 for both groups). In addition, densitometric analysis of immunobands confirmed significant up-regulation of both GRP78 and active ATF6 in CF neutrophils compared to control cells (p<0.05). Intraacellular Ca2+ was increased in the CF neutrophils compared to healthy controls.

Conclusions: Our data demonstrates for the first time activation of the UPR in vivo in neutrophils isolated from individuals with CF, which may in part explain the exaggerated inflammatory response of these cells.

P1447 Cytokine and chemokine release in response to Pseudomonas aeruginosa (PA), by bronchial epithelium of the native airway and transplanted lung of paediatric cystic fibrosis (CF) lung transplant recipients

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Introduction: Infection and inflammation are implicated in the pathophysiology of Bronchiolitis Obliterans Syndrome (BOS), the major cause of mortality following lung transplantation. It is unclear if the cytokine and chemokine release by Cystic Fibrosis (CF) airway epithelium in response to pathogens differs from that of the transplanted lung.

Aims: We hypothesised that there is no difference in the cytokine and chemokine release in response to Pseudomonas aeruginosa (PA), by the epithelium of the native CF airway and the transplanted lung.

Methods: 5 children who had lung transplantations for CF (Great Ormond Street Hospital for Children, London, UK), were studied. Bronchoscopic brushings from above and below the airway anastomosis were cultured to differentiated ciliated epithelium in an air-liquid interface (ALI). The epithelium was exposed to late exponential cultures of PA (105 CFU per ml). The culture supernatants were harvested at baseline and 5 hours post PA exposure. The cytokines and chemokines in the culture supernatants were measured using a multiplex ELISA based protein array (SECTOR Imager 6000, MSD).

Results: There were no differences in baseline levels of cytokines and chemokines. 5 hours after exposure to PA, the release of chemokines - CCL2, CCL5, CCL13, CXCL8 and the cytokines - IL1β, IL13 and TNFα, by the native CF epithelium was significantly higher (p<0.01) compared to that from the transplanted lung.

Conclusion: The differential cytokine and chemokine release in response to pathogens may be contributory to the exaggerated inflammatory response of the CF epithelium.
P1448
Ciliary function of the nasal and bronchial epithelium in children with cystic fibrosis

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Background: Normal ciliary function is essential in pulmonary defence. It is unclear if there is any difference in ciliary function between the nasal and the bronchial epithelium, in children with Cystic Fibrosis (CF).

Aims: Our aim was to determine if there is any difference in ciliary function between the nasal and the bronchial epithelium, in children with CF.

Methods: 9 children with CF (2 males, median [IQ] age: 14.1 [12.8-15.7] years, median [IQ] duration post transplant: 12 [9-15.5] months), who had lung transplant at the GOS Hospital for Children (London, UK) were studied. Nasal brushings and bronchoscopic bronchial brushings from the lower airway above the anastomosis were studied using digital high speed video camera to determine the ciliary beat frequency (CBF) and beat pattern, as described previously. (Thomas B. et al. Eur Respir J. 2009;34:401-4).

Results: There was no significant difference in CBF or beat pattern between the epithelium of the nose and the lower airway above the anastomosis. Sputum IgG and IgA antibody concentrations remained under the detection limit of the assay in most samples, and were significantly increased above the detection limit of the assay in all subjects, and were significantly increased in Pa+ as compared to Pa- patients. As expected serum IgA levels were elevated in Pa+ as compared to Pa- patients.

Discussion: There was no significant difference in CBF or beat pattern between the nasal and the bronchial epithelium in paediatric CF lung transplant recipients. Supported by an unconditional grant by Gilead Sciences, Inc and the Sophia fund: 'steun door Zeevaart.'

P1449
Detection of antibodies against Pseudomonas aeruginosa in the sputum of cystic fibrosis patients: A pilot study

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Chronic Pseudomonas aeruginosa (Pa) infection plays a pivotal role in disease progression in patients with cystic fibrosis (CF). The aim of this cross-sectional study was to test whether anti-Pa antibodies can be detected in the sputum using common serological methods.

During routineambulatory visits blood and spontaneously expectorated sputum samples were obtained from 29 adult CF patients (11 chronicallyinfected with Pa [Pa+]. 10 non-infected [Pa-] and 8 intermittently infected [Pa+/-]). Anti-Pa antibodies (IgA and IgG) in serum and in sputum supernatant were measured with ELISA originally developed for measuring anti-Pa antibodies in serum (Genesisc Diagnostics). Data are presented as means ± SEM.

As expected serum IgA levels were elevated in Pa+ as compared to Pa- patients (20.3±9.5 vs. 6.0±1.5 pg/ml, respectively, p<0.05). Sputum IgA levels were above the detection limit of the assay in all subjects, and were significantly increased in Pa+ compared to Pa- patients (20.6±5.6 vs. 8.5±1.1 pg/ml, respectively, p<0.05).

In Pa+- patients sputum IgA levels were similar to that of Pa- patients (p>0.05). In all subjects serum and sputum IgA levels showed a close correlation (r=0.525, p<0.01). The sensitivity and the specificity of the assay in sputum were 70% and 72%, respectively, as compared to 44% and 90% in serum. Sputum IgG antibody concentrations remained under the detection limit of the assay in most cases. In conclusion, sputum anti-Pa IgA antibody levels are elevated in patients with chronic Pa infection. The sensitivity of the assay is even greater in sputum than in serum raising the possibility that sputum could be maternally of choice for the early detection of Pa.

P1450
Tracking disease progression in cystic fibrosis using bronchiectasis, trapped air and quality of life

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Background: Progression of cystic fibrosis (CF) is characterized by bronchiectasis (BE) and trapped air (TA) on CT. We hypothesize that progression of BE, and TA results in a lower Health Related Quality of Life (HRQoL), assessed by the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Objective: To evaluate associations between changes in BE, TA, and CFQ-R over time.

Methods: Cohort study (July 2007-January 2012). Clinical stable CF patients, with two routine bi-annual chest CTs, and CFQ-Rs. CT scans were anonymous and randomly scored, using CF-CT BE and TA scores. Scores are expressed as % of maximum score. CFQ-R was completed by children (aged 6-13 years) and adolescents (aged ≥ 14 years). Score-range 0-100, higher scores indicate better HRQoL. For changes in CF-CT BE, TA score, CFQ-R respiratory-symptoms domain scores, their correlations, and to test the hypothesis we used Student’s paired t-test, Spearman’s correlation coefficient, and linear regression model, adjusted for age and gender.

Results: CF patients (n=40): mean age T1 11.9 years, T2 13.8 years. In two years there was a significant increase in CF-CT BE scores (p<0.03) and CF-CT TA scores (p<0.03), but not in CFQ-R scores. At T1, CFQ-R BE scores (p<0.01, r=0.49) and CF-CT TA scores (p=0.05, r=0.34) correlate with CFQ-R scores. At T2, similar correlations were found: CF-CT BE (p<0.01, r=0.41), CF-CT TA (p=0.02, r=0.37). Change in CF-CT BE and TA scores did not correlate to change in CFQ-R scores.

Conclusion: BE and TA correlates to HRQoL. Modest progression of BE and TA did not result in impairment of HRQoL.

P1451
Lung clearance index (LCI) and hyperinflation in children with cystic fibrosis (CF)

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Introduction: LCI is used to detect early CF lung disease.1, 2, 3 However, there are few data relating changes in LCI to lung volumes, and extent of hyperinflation, in children with CF. Therefore, we aimed to look at the association between LCI (derived from multiple-breath nitrogen washout (MBNW) and two indices of hyperinflation (i) residual volume/total lung capacity (RV/TLC), and (ii) the difference between FRC determined by plethysmography (FRCp) and MBNW (FRCMBNW). Methods: Children with CF completed MBNW and plethysmography as part of their annual review. All tests were performed, analysed and reported according to ATS/ERS recommendations. The difference between FRCp and FRCMBNW was expressed as a % of FRCp, and called FRCdiff. Results were examined using Spearman’s rank correlation coefficient.

Results: 37 children with CF (aged 5-17) completed lung function tests. A significant correlation was found between LCI and RV/TLC (r=0.516, p=0.001) (Figure), and between LCI and FRCdiff (r=0.433, p=0.011).

Discussion: The adoption of LCI as an ideal marker for early lung disease requires that it should correspond to established markers of abnormalities in lung function.4 Our findings showed comparable decline in LCI and indices of hyperinflation in children with CF.

References:
P1452

Short term effects of chest physiotherapy in children with cystic fibrosis assessed by a new lung function test
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Background: No lung function test exists that is able to assess short-term effects of physiotherapeutic treatment (PT) in children with Cystic Fibrosis (CF). We recently developed a tidal single-breath washout (SBW) using two tracer gases to measure ventilation inhomogeneity (VI).

Aims: We assessed whether this new SBW test is able to measure short-term effects of PT and inhalation.

Methods: Children with CF (n=25) between 6 and 16 years performed lung function assessments prior to and after inhalation and PT. Assessments consisted of a double tracer gas SBW (DTG-SBW) and spirometry. DTG contained sulfur hexafluoride (SF6) and helium (He), and was induced during tidal breathing. A side-stream ultrasonic flowmeter measured molar mass. DTG-SBW outcome was percentage of expired volume where expired molar mass equals inspired molar mass, reflecting inspired ratio of SF6 and He (IPDTG).

Results: After intervention IPDTG decreased from 65.6±25.8% to 59.7%±(±25.4) resulting in a mean difference of -7.3% (95%CI -12.9 to -1.8) and MEF25.75 increased from 1.41 L/s to 1.62 L/s resulting in a mean difference of 0.19 L/s (95%CI 0.02 to 0.37). In a post-hoc subgroup analysis we found that the DTG-SBW is more suited to detect changes in VI in patients with mild CF lung disease (n=14, FEV1 z-score <−2), whereas spirometry indexes increased only in patients with moderate CF lung function (n=11, FEV1 z-score <−2).

Conclusion: The DTG-SBW seems to be a promising test to detect short-term effects of physiotherapy and inhalation.

P1453

Peripulmonary airflow and severity of CF lung disease – A cross-sectional study from childhood to late middle age
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Background: Ventilation inhomogeneity (VI) measured by multiple-breathe washout (MBW) is a characteristic feature of cystic fibrosis (CF) and correlates more closely than spirometry with HRCT structural lung damage (Thorax 2008;63:129). MBW provides both global indices of VI such as the lung clearance index (LCI) and specific indices of VI arising in the conductive (Scond) and the acinar (Sacin) part of the conducting airways. DTG-SBW outcome was percentage of expired volume where expired molar mass equals inspired molar mass, reflecting inspired ratio of SF6 and He (IPDTG).

Methods: The LCI, Scond and Sacin were measured by SF6 MBW in 71 CF subjects aged 7.1-55.4 yrs (median 17.4) with FEV1 % pred (median 86). Data are given as z-scores (Respiration 2009;78:339). It is unknown how Sccond and Sacin reflect overall lung disease severity over a wide age range.

Results: The LCI, Scond and Sacin were measured by SF6 MBW in 71 CF subjects aged 7.1-55.4 yrs (median 17.4) with FEV1 % pred (median 86). Data are given as z-scores (Respiration 2009;78:339). It is unknown how Sccond and Sacin reflect overall lung disease severity over a wide age range.

Conclusions: These cross-sectional findings suggest that LCI is more useful than Scond in monitoring CF lung disease. Scond may, however, be used as an early marker of lung involvement.

Cystic fibrosis pulmonary function in adult patients with cystic fibrosis
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Introduction: Habitual physical activity has important clinical implications in Cystic Fibrosis (CF) and has therapeutic effects on sputum clearance, respiratory muscle strength and quality of life. While recent studies have shown that aerobic fitness is related to survival, that physically active CF patients have higher physical performance and lower metabolic rate at rest, the role of physical activity in improving muscle strength in terms of oxidative capacity.

Methods: Eleven stable CF patients (mean SD age 32 (9) yrs; FEV1 2.7 (0.8) L; IC 8.0 (0.9) L), were studied at rest, during symptom-limited incremental exercise test (CPET) and during 6MWT. We assessed daily physical activity using both SW (SenseWear, SW) that subjects wore for 4 consecutive days from waking until going to bed including weekends, and the Habitual Activity Estimation Scale Questionnaire (HAESQ).

Results: There was no difference between the weekdays and weekends recordings in any activity variable. We found no agreement in physical activity measured by SW vs HAESQ. By contrast, we found a close relationship between SW step count and VO2peak (r2=0.60; p<0.001) and SW energy expenditure vs VO2peak (r2=0.78; p<0.005) at CPET. Distance at 6MWT was not correlated to any physical activity variables, either at SW or HAESQ.

Conclusions: Adults CF patients have similar habitual physical activity levels at weekdays and weekends. Activity levels measured by the subjective methods and by the objective monitoring, i.e., SW vs HAESQ, seems to provide different information on the level of daily physical activity. Physical activity is related to degree of airflow obstruction and to the maximum exercise capacity.

P1454

Prolonged oxygen kinetics during submaximal cardiopulmonary exercise testing (CPET) in adult patients with cystic fibrosis (CF) and their relationship with indices of oxidative capacity
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Background: Patients with cystic fibrosis demonstrate reduced exercise capacity. As the submaximal exercise testing overcomes many of the limitations of maximal exercise testing, indices of submaximal exercise capacity like time constant (t-on) of oxygen uptake (VO2peak) and the slope of recovery after maximal CPET as it is expressed by the ratio of oxygen consumption to time (VO2/t slope)

Results: The main finding is that t-on in control group is significantly lower (29.3±5.38 s) than t-on in CF group (42.5±6.15 s, p<0.05). Moreover, a statistically significant negative correlation is found between t-on and indices of oxidative capacity of maximal CPET such as: VO2peak (r=-0.53, p=0.049), AT % (r=-0.645, p=0.013) and VO2/t slope (r=−0.576, p=0.031).

Conclusion: Oxygen kinetics of submaximal CPET in adult patients with cystic fibrosis are prolonged and they are correlated with indices of oxidative capacity during maximal CPET.

P1456

Acute exercise in cystic fibrosis patients increases neuropsychological pulmonary inflammation
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Background: Neuropsychological inflammation mainly from recurrent bacterial infection characterizes cystic fibrosis (CF) Airways. Repeated inflammatory insults may lead to progressive lung function decline. Acute exercise is reported to trigger a systemic inflammatory response, but inflammation pattern has been poorly studied.

Methods: 12 subjects with mild to moderate stable CF (FEV1<50% of p.v.) underwent a constant load exercise test at 80% of their maximal load. Sputum and blood were sampled before and 1 hour after exercise and analysed for differential leukocyte counts.

Results: 6 females and 6 males completed the study with a mean FEV1 of 72.2% and a mean exercise time of 4.6 minutes. No desaturation was reported. Table 1 summarizes the differential leukocytes counts in blood and sputum. Exercise Arises a 2.2 fold increase in airway neutrophils (p=0.019) and 1.4 fold increase in blood neutrophils (p=0.01)

Conclusion: We demonstrate that acute exercise increases the peripheral and airway inflammation.

Table 1

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Eosinophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum pre-exercise</td>
<td>2.47±0.8</td>
<td>0.06±0.04</td>
<td>0.03±0.01</td>
</tr>
<tr>
<td>Sputum post-exercise</td>
<td>5.5±1.8</td>
<td>0.37±0.27</td>
<td>0.06±0.02</td>
</tr>
<tr>
<td>Blood pre-exercise</td>
<td>5.8±0.8</td>
<td>0.13±0.04</td>
<td>1.65±0.1</td>
</tr>
<tr>
<td>Blood post-exercise</td>
<td>7.6±0.9</td>
<td>0.13±0.04</td>
<td>1.54±0.15</td>
</tr>
</tbody>
</table>

Conclusion: We demonstrate that acute exercise increases the peripheral and airway inflammation.
way inflammation in stable CF subjects. This burst of neutrophils might have a dual role in which it might improve local defense against infections and participate in airway destruction through release of elastase and other mediators. The modulation of this inflammatory response by exercise training has to be explored.

P1457 Heart rate variability response to submaximal exercise in children with cystic fibrosis

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Background: Rehabilitation or physical activity can improve chronic respiratory disease as a Cystic Fibrosis. Nevertheless, because autonomic dysfunction is common in CF, heart control may be affected in response to exercise.

Objective: To assess the cardiac autonomic control using heart rate variability (HRV) analysis before and after a six-minute walking test (6MWOT).

Methods: We studied lung function at baseline and HRV before and after 6MWOT in children’s with CF and matched healthy control group.

Results: Thirty children in the CF group (6 male) mean age: 12±2.7 years, with obstructive disease (FEV1/FVC: 0.83±0.11, FEV1: 71.4±2.11%pred) and 12 healthy children (6 male), mean age 11.4±2.4 years, with normal lung function (FEV1/FVC: 0.93±0.12, FEV1: 91.6±17.4%pred) were evaluated. Baseline HRV was different between CF and CG in LFnu: 53.18±15.01 vs. 32.79±7.91, p = 0.0003; HFnu: 25.4±1.84 vs. 53.19±9.36, p = 0.0018; HFnu: 47.3±1.48 vs. 68.34±6.87, p = 0.0009; and LF/HF: 1.25±0.72 vs. 0.49±0.18, p < 0.0066. After the 6MWOT was observed significant differences between groups for LF(Fnu/2): 846.69 vs.754.81 vs. 345.58±197.18, p=0.027, LFhu: 35.44±8.06 vs. 25.88±6.20, p=0.0024; LFnu: 34.2±16.27 vs. 34.9±8.71, p=0.0000; HFnu: 27.42±17.73 vs. 48.13±33, p=0.0003; HFnu: 40.45±15.8 v. 65.59±8.18, p<0.0003; and LF/HF: 1.94±1.7 vs. 0.53±0.21, p=0.0001.

Conclusion: Children with CF had higher sympathetic drive at baseline and after a submaximal exercise test compared to the CG, suggesting a sympatho-vagal dysfunction.

155. The best posters on quality of life and coping styles in COPD

P1458 TELEMOLD project: A telemonitoring system that combines oximetry and physical activity quantification to improve long term oxygen therapy

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Background: Standard assessment to long term oxygen therapy (LTOT) prescription involves periodic clinical tests (arterial blood gas, 6-min walk test and nocturnal oximetry) carried out in several hospital visits. However, there is some evidence that oxygen demand during daily activities may not be correctly estimated by such tests, when compared to continuous ambulatory oximetry.

Aim: To evaluate the clinical usefulness of a home telemonitoring system in LTOT optimization.

Methods: Thirty five respiratory failure patients (29 with LTOT, 6 under evaluation for LTOT) followed in an University Hospital were real-time monitored with an oximeter sensor (Nonin Avan 4000 system) and an accelerometer (BioPlux motion). Signals were sent via Bluetooth to a mobile phone and then via 3G or GPRS to a server. Continuous and secure access to data through an Internet site was established.

Results: Each patient was monitored in average 7.6±4.5 (range 2-19) days, in a total of 83.0±66.9 (4.8-228.8) hours. Percentage of valid records was in average 65.4±24.1% (0-100%). Percentages of rest, activity and sleep records per patient were, in average, 28.4±21.3%, 65±5.5% and 59.3±24.6%, respectively. Significative desaturation during rest, activity and sleep was found on 2, 26 and 9 patients, respectively. Patient’s user-friendliness was fairly good (75.8% reported it as easy/very easy).

Conclusion: Our study suggests that a telemonitoring system combining oximetry and physical activity evaluation may improve LTOT through a more adequate oxygen flow prescription, namely during daily activities. This project was funded with a grant by Fundação Vodafone Portugal.

P1459 Quality of life in patients receiving home oxygen therapy (HOT) for chronic respiratory diseases (CRD)

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Introduction: Health related quality of life (HRQOL) is impaired in chronic obstructive pulmonary disease (COPD). Less is known about impacts of HOT on health status in patients with CRDs. We hypothesized that health status would be impaired independent of underlying respiratory disease, and physical and mental health status would be lower than population norms.

Methods: Patients receiving HOT from 3 hospitals in South Australia completed Australian Karnovsky Performance Scale (AKPS), Short Form 36 (SF36) and Chronic Respiratory Questionnaire (CRQ). Scores were compared to population norms. Correlations were made with Sperman (skewed) or Pearson (normal distributions). Differences in scores between CRD types were evaluated by Student T-test.

Results: Data were available from 197 patients (mean age=74±4; SD=9 yrs; 62% male; 155 (78.6%) with COPD, 32 (16.2%) pulmonary fibrosis (PF), and 10 (6.2%) other CRDs). No differences in HRQOL were seen between COPD and IPF. SF36 emotional dimensions were similar to population norms. Physical health dimensions were substantially lower than population norms. Patients’ AKPS performance was on average “requiring occasional assistance” (64.8; SD=12.1). CRQ dyspnoea (3.4; 1-6) and fatigue (3.29; 1-7) scores indicated moderate impairment; emotional function (4.4; 1-5) and mastery (4.4; 1-5) were not impaired. CRQ domains (except emotional function) were highly correlated with AKPS and SF36 dimensions (p<0.001).

Conclusions: Patients receiving HOT for respiratory diseases had severe physical disability, which correlated closely with dyspnoea and fatigue, but their mental and emotional status were similar to population norms.

P1460 Influence of patient activation and health literacy on quality of life among patients with COPD

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Background: While many factors contribute to the health status of patients with COPD little attention has been given to the influence of patient activation (PA) and health literacy (HL).

Objectives: The purpose of this analysis was to examine the influence of PA and HL on quality of life (QOL) among a sample of patients with COPD.

Methods: This was a cross-sectional analysis of baseline data from patients with COPD eligible for pulmonary rehabilitation enrolled in a self-management clinical trial. PA was measured using two questions: confidence on when to seek medical care (ACT1) and frequency of taking a list of medications to doctor visits (ACT2). HL was measured using three questions: confidence in filling out forms, frequency of help needed to read hospital materials, or problems learning about medical condition. QOL was measured using generic (SF-12) and disease-specific (Chronic Respiratory Questionnaire [CRQ]) instruments.

Results: Of 218 patients the majority reported being confident/very confident when to seek medical care (ACT1=79.8%) and taking a list of medicines (ACT2=68.1%). The association between levels of PA and QOL was examined separately using linear regression: ACT1 was directly and significantly associated with CRQ, and SF-12 physical and mental composite scores. In contrast ACT2 was only significantly, but inversely associated with CRQ. There was no association between levels of HL and any measures of QOL.

Conclusion: These results suggest that a component of patient activation (ACT1) is associated with improved QOL and may offer a specific target for intervention to enhance activation and outcomes.

Funding: National Institutes of Health-NHLII R18 HL092955.
symptoms, 8 showed mild depression, and 6 moderate depression. None showed severe depression. Mean PCS and MCS were 46.4 (±10.4) and 47.5 (±9.6) respectively. PCS and MCS values lower respect to mean value of Italian general population were found in 22 and 17 subjects, respectively. A negative relationship was found between BDI-II and PCS (p=0.02). BDI-II was linearly correlated to BODE (r=0.0001) but not to GOLD stage. MCS was inversely correlated to BODE (p=0.02), but not to GOLD Stage. MCS was not related to BODE and to GOLD Stage. Among individual components of BODE, only MRC was a good and direct predictor for depression (p=.007), and an inverse predictor for both MCS (p=.007) and PCS (p=.0002). In conclusion, a greater dyspnea perception, regardless of disease severity, is associated with higher depression score and poorer QoL.

P1462
Self-efficacy and quality of life in COPD patients
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Background and purpose: Chronic obstructive pulmonary disease (COPD) is a complex chronic multi-component disease. Understanding the mechanisms of health related quality of life (HRQL) impairment should help identifying targets of pulmonary rehabilitation (PR). Research has shown positive correlations between self-efficacy and outcome in patients with COPD (Kojic MK. Int J Nurs Practice 2011; 17:1-8, Arnold R et al. Behav Med, 2005 31:107-15). This study sought to evaluate the relative role of self-efficacy and socio-demographic variables in the prediction of HRQL in COPD patients.

Methods: A total of 103 COPD patients (60% males, mean aged 70±14 years) presented dyspnea perception, regardless of disease severity, is associated with higher depression score and poorer QoL.

Results: Stepwise multiple regression analysis revealed that age and self-efficacy were correlated with HRQL (R²=0.27). These findings suggest that the HRQL is negatively correlated with age (b =0.30) and positively correlated with self-efficacy (b =0.36), independent of gender, level of education, and marital status. Conclusions: In a chronic diseases such as COPD, it is important to work in improving confidence in the patient’s ability to follow a self-care regimen by increasing self-efficacy, especially in older patients, as it may positively affect quality of life. Therefore, clinicians should include careful assessment of self-efficacy in their routine evaluation of patients before entering a pulmonary rehabilitation program.

P1463
Validation of CAT as an independent assessment tool in pulmonary rehabilitation (PR) for chronic obstructive pulmonary disease (COPD)
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The benefits of PR in COPD are well recognised but the practical assessment of patients undergoing PR can be complex. The COPD assessment test (CAT) is a recently introduced simple, validated 8-item questionnaire designed to assess the impact of COPD symptoms on quality of life (QOL). We hypothesized that CAT could be used as a screening tool and outcome measure to assess QOL in COPD. 60 patients with COPD enrolled in 8 weeks outpatient PR between January 2011 and October 2011 were studied. Patients completed CAT score, chronic respiratory disease questionnaire (CRQD), hospital anxiety and depression (HAD) at baseline and at 8 weeks. Functional status (6 min walk test (6MWT) and incremental shuttle walk test (ISWT)), dyspnoea (MRCD) and body mass index (BMI) were measured.

52 COPD patients completed the 8 weeks PR and data were available for 37 patients with mean (SD) age 67.8 (9.2) yrs and FEV1 49.6 (20.7) % predicted. There was a significant difference in 6MWT (47.03m), ISWT (47.84m), MRCD (3.03 points), CRQD (-3.02 points), Anxiety (1.5 points), depression (0.69points) and CAT (3.63 points) post PR. CAT correlated closely with CRQD at baseline and following PR whereas there was good correlation only with ISWT, anxiety and depression post PR.

CAT is an independent, simple and highly responsive outcome measure that can also be utilized for screening patients with COPD for PR.

P1464
Developing a patient reported experience measure for COPD
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Introduction: The patient experience and patient outcomes are metrics for quality improvements in healthcare. There is now available patient reported experience measure (PREM) for COPD.

Study Aim
The aim of the study is to create a valid and reliable PREM for patients with COPD.

Methods: Sixty four people with COPD across the community of North East London, North Central London and Essex and 19 with recent hospital experience were interviewed to capture their patient journey with COPD. Analysis of the interview data was by a two layer approach: content and then by affective (emotive or felt) responses.

Results: Eighteen different affective responses were described by patients and were grouped as positive, negative or ambivalent. Positive responses included: hope, gratitude, comfort/reassured, acceptance, optimism, altruism, happy and respect. Negative responses included scared, anxiety, fear, frustration, worry, feeling depressed, denial and embarrassment: ‘selfmotivation’ and control were contextual and could be either positive or negative. The community patient groups’ experience centred around five categories identified in the content analysis: ‘journey to Diagnosis’; ‘Smoking’; ‘Usual Care’; ‘Exacerbation (flare-up)’ and ‘My Everyday Life’. The hospital patient experience was categorised as: ‘Going to Hospital’; ‘On Arrival to Hospital’; ‘On the Ward’; ‘Discharge from hospital’ and ‘Follow-up care’. Items on patients’ affective responses were generated from the categories to develop a PREM-COPD scale.

Conclusion: Completion of the testing of the PREM-COPD will result in a valid and reliable instrument to be used to measure self-defined important patient experiences when using healthcare services.

P1465
Correlations between disease-specific and generic health status questionnaires in patients with COPD
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Purpose: Aims of this longitudinal study were to determine whether and to what extent a disease-specific health status questionnaire correlates with generic health status questionnaires at 4 different time points in patients with advanced COPD; and to determine the correlation between the changes in these questionnaires during 1-year follow-up.

Methods: Demographic and clinical characteristics were assessed in 105 outpatients with advanced COPD. Disease-specific health status (Saint George’s Respiratory Questionnaire, SGRQ) and generic health status (EuroQol-5-Dimensions, EQ-SD) were measured at baseline. Agreement in direction of change was assessed.

Results: Eighty patients (80.0%) were included for analysis (61.9% male, age 65.7±9.2 yrs, FEV1 34.2 (13.7%) pred) SGRQ total score and EQ-SD index score, AqQol total score and SF-36 PCS score were moderately to strongly correlated (r = 0.49 ± 0.00). The correlation of the changes between SGRQ and EQ-SD, AqQol and SF-36 PCS and SF-36 Mental Component Summary measure (SF-36 MCS) score were weak or absent (r = 0.13 ± 0.27). The direction of changes in SGRQ agreed slightly with the direction of changes in EQ-SD, AqQol and SF-36 PCS score (Cohen’s Kappa = 0.11 ± 0.18, p<0.05).

Conclusions: Disease specific health status questionnaires and generic health status questionnaires should be used together to gain complete insight in health status and changes in health status over time in patients with advanced COPD.

P1466
Psychiatric comorbidity in COPD and its determinants
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Background: Depression and anxiety are prevalent in patients with chronic obstructive pulmonary disease (COPD); however, their etiology and relationship to the clinical features of COPD are not well understood.

Objectives: To evaluate the prevalence of psychiatric comorbidity (depression and anxiety) in COPD patients and to examine possible associations with demographic and clinical characteristics as well as health-related quality of life of these patients.

Design and methods: A total of 100 clinically stable COPD patients answered the St. George’s Respiratory Questionnaire (SGRQ) (assessing HRQoL), the Hos-
pital Anxiety and Depression Scale (HADS), Modified Medical Research Council (MMRC) Dyspnea Scale. Socio-demographic information, lung function, and other clinical data were collected.

Results: The prevalence of depression was found to be 40%, while that of anxiety was 29%. Patients living alone, having a longer duration of COPD diagnosis, lower BMI and more severe disease (as measured by FEV1% of predicted) had more depressive and anxious symptoms. The significant independent predictors of both anxiety and depression were higher MMRC score and worse quality of life.

Conclusion: We found that patients with COPD had high prevalence of depressive and anxious symptoms. Clinical and physiologic measures were less important determinants of psychiatric comorbidities in COPD than dyspnea and quality-of-life.

Therefore, screening and treatment of these psychiatric comorbidities in patients with COPD may lead to significant improvements in patients’ quality of life.

P1465
Impact of a pulmonary rehabilitation program on psychopathology of patients diagnosed with COPD

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Introduction: Psychological comorbidities such as anxiety and depression are common in COPD. Recent studies suggest a decrease in both anxiety and depression in patients with COPD after participating in a rehabilitation program. However, there is insufficient literature on changes in general psychopathology after RP.

Aims and objectives: To examine the changes in general psychopathology of patients with COPD after participating in a rehabilitation program.

Methods: The participants were patients (80 men and 21 women) with pure COPD who attended a three-month RP. The patients' psychopathology was assessed at the start and by the end of the PR, using the Symptom Checklist-90-R (SCL-90-R), which is a self-report questionnaire widely used in both normal and distressed populations. In order to determine COPD severity a spirometric evaluation before and after bronchodilatation was performed.

Results: Means of anxiety and of FEV1% of predicted were 64.15±8.13 and 43.51±21.53, respectively. Statistically significant changes (Paired t test) were observed at the end of the PR on the following scales: somatisation (0.70 VS 0.45, p<0.01), obsessive-compulsive (0.75 VS 0.48, p<0.01), interpersonal sensitivity (0.44 VS 0.35, p<0.05), depression (0.81 VS 0.48, p<0.01), anxiety (0.63 VS 0.35, p<0.05), hostility (0.53 VS 0.31, p<0.01), phobic anxiety (0.33 VS 0.17, p<0.01), paranoid ideation (0.43 VS 0.33, p<0.05). However, there was no statistical difference regarding the psychosomatic scale (0.15 VS 0.13, p>0.05).

Conclusions: A pulmonary rehabilitation program may improve psychopathological symptoms, particularly those of the neurotic spectrum, of COPD patients.

P1468
Health status and coping skills of carers of patients receiving home oxygen therapy for respiratory diseases

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Introduction: Carer burden is well-documented for a range of chronic diseases. Burdens for those who care for people with chronic respiratory diseases (CRD) requiring home oxygen therapy (HOT) have not been reported but would be expected to have a similarly high burden.

Methods: Consecutive patient-carer dyads were enrolled over three years from 3 metropolitan hospitals if the patient was receiving HOT for a CRD. Baseline demographic observations and validated questionnaires were collected for Carers: health-related quality of life with Short Form-36 (SF36); Self-Esteem (SE) and Mastery (MS) Scales; Anticipated & Received Social Support (ARSS) and Carer Overload (CO) Scales, and Experiences and Impacts of Fatigue Scale (ICFS).

Results: All measures were completed by all 197 carers enrolled. Score results are expressed as mean, SD. Most (68.5%) were female and married (88.3%).

Their mean age (67.12 yrs) was significantly lower than their patient (74.5±6 yrs) (p<0.001). Carer SF-36 dimension scores were similar to normative values for age and gender. They had high SE (43.05±8) and MS (60.9%), had no perceived overload (7.9; 2.5), and were not unduly fatigued.

Conclusions: In this population, patients receiving HOT have carers (mostly marital partners) who generally perceive little undue burden, either physically or emotionally.

Funded by an Australian NHMRC Project Grant.

P1469
Coping styles in patients with COPD before and after pulmonary rehabilitation

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Background: Pulmonary rehabilitation (PR) improves physical and psychological symptoms in COPD patients. To date, it remains unknown whether coping styles change following comprehensive PR. This study assessed retrospectively coping styles in COPD patients before and after PR programme.

Methods: Coping styles were assessed in 303 COPD patients (53.1% men) before and after 36 PR sessions using the Utrecht Coping List (UCL). Additionally, lung function, St. George’s Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Scale (HADS-A and HADS-D) and six-minute walking distance (6MWD) were recorded.

Results: Mean age was 62.4±8.4 yrs; FEV1; 47.9±19.5% pred; SGRQ total score 56.2±15.4 pts; 6MWD 441.6±112.2 m; HADS-A 7.4±4.2 pts and HADS-D 7.1±4.1 pts. Mean change scores following PR were SGRQ total score -6.3±12.9 pts; HADS-A -1.7±3.6 pts; HADS-D -1.6±3.7 pts (all p<0.001) and 6MWD 28.9±51.2 m (p>0.05). The level of active confronting coping style increased (p<0.05), while the levels of avoidance (p<0.05), passive reaction pattern and reassurring thoughts coping styles decreased following PR (both p<0.001). Palliative reaction, seeking social support and expressing emotions coping styles did not change (p>0.05).

Conclusions: Comprehensive PR results in significant change in coping styles of COPD patients. Further studies are needed to evaluate the outcome of interventions actively targeting coping style domains.

P1470
An evaluation of the needs of carers of people with COPD

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Introduction: Many COPD patients are dependent on carers. Whilst the role of caring can be very demanding, surprisingly little is known about the needs of carers of COPD patients and hence this was the main aim of this study.

Methods: 21 patient-carer dyads recruited from databases at Repatriation General Hospital completed questionnaires and carers attended focus group meetings.

Results: Carers (mean age 71.1, SD 9.8) completed the Short-Form 36 (SF36); Physical Component Score (PCS) 41.1, SD 11.4; Mental Component Score (MCS) 44.9, SD 9.2), and Hospital Anxiety and Depression scale (HADS: Anxiety 8.9, SD 3.3; Depression 5.1, SD 3.3). Patients (mean age 75.2, SD 7.6) completed the Chronic Respiratory Questionnaire (Dyspnoea 3.5, SD 1.2; Fatigue 3.5, SD 1.5; Emotional 4.3, SD 1.3; Mastery 4.5, SD 1.4, SF36 PCS 25.7, SD 7; MCS 47.1, SD 11.9) and HADS (Anxiety 7.5, SD 3.4; Depression 6.5, SD 4). The thematic analysis of focus group transcripts indicated that carers emphasised physical and emotional impacts of their duties and identified social and work-related handicap as consequences. Carers believed that physical and/or emotional problems (either theirs or their patient’s) as well as a lack of knowledge were significant barriers to their role. A lack of inclusion in patient treatment plans, particularly following hospital discharge, was also noted. Respite support, peer debriefing, counselling and respiratory disease education were identified as areas that would assist carers with their role.

Discussion: Carer burden, handicap, lack of inclusion and knowledge were identified as issues that remain under-supported. The findings suggest the potential value of carer recognition, support and upsilling in COPD treatment planning.
P1471 A self-management programme of activity coping and education (SPACE) for COPD: Patients perspective
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Introduction: We have developed a self-management programme ‘SPACE for COPD’ and as part of it’s wider evaluation a nested qualitative study was conducted exploring patient’s perspectives of self-management before and after completing the programme.

Method: Semi-structured interviews were carried out with participants randomised to ‘SPACE for COPD’ prior to starting SPACE and 6 weeks later. Interviews were transcribed verbatim and thematic analysis was performed by NVivo (Version 8). A third researcher analysed a sub-group of interviews to ensure agreement over themes.

Results: Four main themes describe patient’s beliefs and expectations prior to starting ‘SPACE for COPD’ - role of self-management, barriers to exercise, facilitators to exercise, role of healthcare professionals. Patients had differing perspectives of self-management and were focussed on maintaining current activity levels. All desired more knowledge about COPD. Analysis of follow-up interviews identified themes - changing perceptions, the impact of SPACE for COPD, barriers to exercise, facilitators to exercise, the manual as a motivator. The experience of using SPACE was positive and many described the motivating effect of the manual. Education was an important component of the intervention and self-management skills were demonstrated. At baseline patients anticipating positive results had been encouraged to initiate exercise and at follow-up positive results had been observed, this further reinforced exercise behaviour. Barriers to exercise identified at baseline remained at follow-up.

Conclusion: ‘SPACE for COPD’ has enabled patients to learn more about their condition and become more active.

P1472 Do illness beliefs predict depression and quality of life after pulmonary rehabilitation?
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Introduction: Several studies have demonstrated the relevance of illness beliefs for health-related outcomes in chronic diseases. Patients form beliefs about possible causes, controllability and consequences. These illness beliefs are linked to anxiety, depression, coping strategies. Aim: Aim of this study was to examine the role of subjective illness beliefs in chronic obstructive pulmonary disease (COPD) patients on later depression and health-related quality of life after pulmonary rehabilitation (PR).

Methods: 96 COPD inpatients (GOLD II/III; 56 female; M=61.3 yrs±7.8) were tested for measures such as exercise capacity (6MWD) and forced expiratory volume in one second (FEV1% pred.) before and after PR. Additionally, assessment of illness beliefs (Illness Perception Questionnaire-Revised (IPQ-R)), health-related quality of life (HRQL;SF36) and depressive symptoms (Hospital Anxiety and Depression Scale (HADS)) before and after rehabilitation were collected. Results: Biomedical variables showed a significant improvement after PR: 6MWD ±66.5m; p<0.01 (admission 294.11±636m and FEVI ±4.67±8.43% pred.; p<0.05 (baseline FEVI 33.52±12.53% pred.). Results of hierarchical multiple regression analyses, after controlling for demographic variables and illness severity, indicated that COPD-patients’ beliefs about their illness before PR predicted depressive symptoms (β=0.46; p<0.001) and health-related quality of life (β=0.29; p<0.05) after treatment.

Conclusion: Patients’ illness beliefs before PR strongly influence later health-related quality of life. COPD-patients may benefit from interventions aimed at changing maladaptive illness beliefs to improve outcome of treatment.

P1473 Evolution of functional capacity and health status 2 years after a pulmonary rehabilitation programme
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Background: Pulmonary rehabilitation programs (PRP) have been shown to improve exercise capacity and health status and to reduce dyspnoea and healthcare resource use, in patients (pts) with chronic lung disease. These benefits have been shown to last for up to 9 months, however appear to decline by 12 months. Aim: Evaluate functional exercise capacity and health status after PRP in pts followed in “respiratory failure day hospital”.

Methods: Retrospective study of pts integrated in a PRP. After PRP, pts who kept a physically active lifestyle (at least 3 walks of 30 minutes/week) were included in the active group (AG). The others were considered as control group (CG). Were evaluated demographic characteristics, pulmonary pathology, six-minute walk test (6MWT) and St’s George’s respiratory questionnaire (SGRQ).

Results: Thirty-two pts were included. 24 in the AG and 8 in the CG. 81% of the pts had chronic obstructive pulmonary disease, with mean FEV1 of 42%. Immediately after PRP, there was a significant improvement in the 6MWD and SGRQ global score, in both groups. After completing PRP, there was a decline in the mean 6MWD when evaluated at 6 months, 1 and 2 years as well as in SGRQ score. However, after 2 years, the AG continued to show an average improvement of 15m in the 6MWD and at least 4 points in SGRQ comparing with pre-PRP, although in the CG, there was a clinically significant decline in 6MWD (-34m) and SGRQ score (13 points).

Conclusion: Despite the progressive decrease of benefits after completing PRP in the AG, these are still significantly positive 2 years after training, which does not happen in the CG. Active lifestyle seems to contribute to maintain the benefits of PRP.

P1474 Health-related quality of life in hypercapnic COPD patients during an admission for acute exacerbation
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GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Netherlands

Introduction: Little is known about Health Related Quality of Life (HR-QoL) during an admission in COPD patients with chronic hypercapnic respiratory failure (CHRF) after an episode of ventilation for acute exacerbation. The Maugeri Respiratory Failure (MRF-28) and Severe Respiratory Insufficiency (SRI) questionnaires were specifically developed for patients with stable CHRF.

Methods: Hospitalized patients still hypercapnic > 48 hours after ending mechanical (invasive or non invasive) ventilation filled in the SRI, MRF-28 and Chronic Respiratory Questionnaire (CRQ), Groninger Activity Restriction Scale (GARS) and Hospital Anxiety and Depression Scale (HADS). Concurrent validity was evaluated by comparing both questionnaires with the CQ. Construct validity was determined by assessing correlations between the different domains of the MRF-28, SRI, CQ and both generic physical and psychological questionnaires measured during admission.

Results: N=163 COPD patients (67 men; age 63 yrs; FEV1 0.67L±0.26L). Total scores and all domains of MRF-28 and SRI correlated (p<0.01) with the CQ and with its respective domains. Physical domains of all 3 questionnaires correlated strongly with the GARS (r=0.77, 0.74 and 0.52, respectively) and psychological domains of the SRI and CRQ with the HADS (r=0.79 and 0.76).

Conclusions: This study shows that SRI and MRF-28 are valid questionnaires in hospitalized patients with CHRF who are still hypercapnic 48 hours after ending mechanical ventilation for an acute COPD exacerbation. As the SRI is more elaborate with also a psychological domain we recommend this questionnaire in this specific group of severe COPD patients.

P1475 Health related quality of life and family burden in ALS patients. Differences over time
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The aim of this study was to investigate the health related Quality of Life (HR-QoL) in ALS patients and the burden on their families over time.

Methods/Patients: The SF-36 was used for HR-QOL estimation in 15 ALS patients and the Family Burden Questionnaire for assessment of objective and subjective burden as well as adaptation strategies in 15 caregivers, with a 6 months interval. Demographic characteristics of all subjects and patients ALSFS were recorded.

Results: Patients were aged (64.4±11.4 years) with ALSFS 77.6±8.4. All SF-36 domains had low scores except for pain and no statistical difference was observed after 6 months. Moderate/severe burden was objectively recognized by 42.8% of caregivers in employment, 60% in social activities, 40% in finances and 64.3% in household management, although the subjective burden was lower in most domains. After 6 months the objective and subjective burden was almost consistent. A significant negative correlation was observed between caregivers’ subjective burden in social activities, employment, patient’s physical function (r=0.596, p<0.019) and social function=r=-0.905, p<0.013) respectively. Caregivers’ adaptation strategies changed over time in passivity (50% vs. 33.3%), ambivalence (66% vs. 60%), guilt (66.7% vs. 80%), resignation (16.7% vs. 26.7%), hopefulness (33.3 vs. 53.3%) and in reorientation of their life (33% vs. 26.7%). Hopefulness was significantly correlated with patients’ social function (r=0.684, p<0.001).

Conclusion: ALS patients had low QOL. Families experienced a considerable
amount of burden in all examined domains but also rather negative feelings which seem to replenish over time and re-organize their life to support the patient.

156. Lung transplantation: studies in candidates and recipients

P1476 Results of a phase 2b multi-center trial of ALN-RSV01 in respiratory syncytial virus (RSV)-infected lung transplant patients
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ALN-RSV01 is a small interfering RNA targeting RSV replication. A Phase 2a randomized controlled trial in 25 RSV-infected lung transplant patients undergoing nebulized ALN-RSV01 or PBO daily for 3 days was previously conducted in which ALN-RSV01 led to a significant decrease in new or progressive bronchiolitis obliterans syndrome (BOS) at Day 90 (p=0.027). We have now performed a Phase 2b multi-center, randomized, double-blind, PBO controlled trial in 87 RSV-infected lung transplant patients to examine the impact of ALN-RSV01 on the incidence of new or progressive BOS at Day 180. RSV positive patients were randomized (1:1) to receive nebulized ALN-RSV01 or PBO daily for 5 days, alongside the institution’s standard-of-care. Patients were prospectively stratified for: 1) days from symptom onset to treatment; and 2) pre-infection BOS grade. Of the 39 patients enrolled, 21 were RSV positive, of which 45 were randomized to receive ALN-RSV01 and 42 to receive PBO (intent-to-treat (ITT) population). Ten patients were without confirmed RSV by central laboratory testing, thus a total of 77 patients (ALN-RSV01, n=44; PBO, n=33) comprised the ITT population. Baseline viral load was balanced between both treatments. ALN-RSV01 was generally safe and well tolerated. There was a decrease in new or progressive BOS at Day 180 in ALN-RSV01-treated patients compared to PBO in the ITT population (13.6% vs. 30.3%, p=0.056), which was statistically significant by prospectively defined Last Observation Carried Forward (p=0.028) and Per-Protocol (p=0.025) analyses. ALN-RSV01 had a treatment effect of 54.6% in all of the pre-specified populations.

P1477 The impact of desensitization therapy prior to lung transplantation
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Introduction: Limited data exists on the impact of allosensitization on wait time and waitlist mortality in lung transplantation. No published data exists on the impact of desensitization therapy in lung transplant patients.

Aim: Determine the impact of desensitization therapy on wait time and waitlist mortality.

Methods: We performed a retrospective cohort study based on chart review of all patients listed for lung transplant between 1/1/2007 and 12/31/2010 at The Methodist Hospital. Groups were compared by Chi square test. P-values of 0.05 were considered statistically significant.

Result: Excluding retransplant listings, 299 patients were listed for lung transplant. 30(10%) had panel reactive antibody (PRA) <25%, while 269 (90%) had PRA ≥25%. Median wait time was significantly longer in those with PRA ≥25% (181 days vs. 45 days, p<0.0001). Waitlist mortality was also significantly higher in those with PRA ≥25% (26.7% vs. 8.6%, p=0.0001). Of the patients with PRA ≥25%, 16 (53.3%) underwent desensitization with intravenous immunoglobulin and plasma exchange +/- rituximab. Of the patients undergoing desensitization therapy, 10 (62.5%) were transplanted, 4 died waiting (25%), and 2 (12.5%) are still waiting. Of the patients with PRA ≥25% that did not receive desensitization therapy, 7 (50%) were transplanted, 4 (28.6%) died waiting, and 3 (21.4%) are still waiting.

Conclusion: PRA ≥25% was associated with a longer wait time and higher waitlist mortality. Desensitization therapy did not improve waitlist time or waitlist mortality when compared to allosensitized patients that did not undergo desensitization. Study is limited by being a retrospective, single center study with low numbers of patients.

P1478 Multiple breath washout in bronchiolitis obliterans syndrome following paediatric lung transplantation
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Aim: Bronchiolitis obliterans syndrome (BOS) is a significant cause of morbidity and mortality following lung transplantation. Lung Clearance Index (LCI) measured by multiple breath washout (MBW) detects early structural lung damage in other paediatric obstructive lung disease. The aim was to determine the pattern of LCI values in children with BOS.

Methods: Retrospective analysis of MBW and spirometry data from subjects transplanted between 2002-2010 (date of annual MBW testing introduction). BOS staging was defined using published “all age” reference equations. LCI in BOS 0, 0p and 1 were compared.

Results: 50(56%) subjects had MBW performed (n=162): mean (SD range) 3.1 (1.85-1.13) times over a mean (SD range) follow up 1069 (613; 196-2613) days. Abnormal LCI values (>1.75) were common post-transplant (63/144 tests, 55%). LCI was increased in subjects with BOS. All those with persistent LCI >10 (n=8) died from severe BOS. Two distinct BOS patterns were seen: gradual vs very rapid FEV1 decline. Despite infrequent testing, earlier LCI signal was seen in some (1/8) but not all 8 subjects (e.g. not those with rapid FEV1 decline).

Conclusion: LCI is frequently abnormal post lung transplantation. LCI is significantly elevated in BOS, and appears to increase with BOS severity. An early signal of subsequent outcome may exist but optimal frequency of testing is yet to be determined.

P1479 Assessment of the restrictive allograft syndrome in patients after lung transplantation
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Background: Chronic lung allograft dysfunction (CLAD) is the leading cause of long term mortality after lung transplantation. The rare but constant finding of fibrotic changes has led to the hypothesis that bronchiolitis obliterans syndrome (BOS) is not the only manifestation of chronic rejection after lung transplantation.

Aims: The purpose of our study was to evaluate the recently reported criteria for the diagnosis of Restrictive Allograft Syndrome (RAS) in our post-lung transplantation patient population.

Methods: We retrospectively analyzed the lung function tests from 162 patients after lung transplantation from 2000 to 2011 with a conditional survival of 180 days. Established criteria for BOS were used for the definition of CLAD. RAS was defined as a detectable, irreversible decline of more than 10% of the best post-transplant total lung capacity (TLC). CT-scans were evaluated for the detection of possible causes for the TLC-decline.

Results: In our study 68 (42%) patients were diagnosed with CLAD, and 22 (14%) of these patients met the criteria for RAS after exclusion of 13 patients with other causes for a TLC-decline. Mean post-transplant survival was 2873 ± 318 days. Abnormal LCI values (≥1.5) were detected in 50/56 (89%) subjects had MBW performed (n=162): mean (SD: range) 3.1 (1.85-1.13) times over a mean (SD range) follow up 1069 (613: 196-2613) days. Abnormal LCI values (>1.75) were common post-transplant (63/144 tests, 55%). LCI was increased in subjects with BOS. All those with persistent LCI >10 (n=8) died from severe BOS. Two distinct BOS patterns were seen: gradual vs very rapid FEV1 decline. Despite infrequent testing, earlier LCI signal was seen in some (1/8) but not all 8 subjects (e.g. not those with rapid FEV1 decline).

Conclusion: LCI is frequently abnormal post lung transplantation. LCI is significantly elevated in BOS, and appears to increase with BOS severity. An early signal of subsequent outcome may exist but optimal frequency of testing is yet to be determined.
vival after lung transplantation and reduces health related quality of life (HRQOL). **Aims:** The study was performed to find parameters correlating with low exercise capacity of patients with advanced CLAD. **Methods:** In this single-center prospective study, all patients with advanced CLAD (FEV1 <50% baseline) in our out-patient clinic were screened between 1.7.2011 and 15.11.2011 by exercise capacity, HRQOL (using SF 36, St. George, HADS), body composition, blood gas analysis, pulmonary function testing, respiratory muscle function and chest x-ray. The patients with low exercise capacity (LEC-CLAD) were defined as 6MWT < 50% predicted or use of oxygen or wheelchair/rollator. Results: 319 of 785 patients (40%) had LEC-CLAD and 53 had the diagnosis of advanced CLAD. A single patient refused consent to this study. 52 patients were included. 19 needed oxygen or had a 6 min walk test (6 MWT) fewer than 50% predicted (LEC-CLAD). Patients with LEC-CLAD demonstrated lower forced vital capacity (FEV1 <50%) in terms of acute rejection (AR), lymphocytic bronchiolitis (LB), infections, BOS and survival. All 193 patients transplanted for emphysema between 1993-2011 and surviving more than 60 days post transplant, were included (53 SLTs(x singly) and 140 SLTS(double)). AB, LB and BOS are diagnosed according to the ISHLT criteria. Multivariate analyzes were done using SAS software. Patients with LEC-CLAD demonstrated a decrease in activity and social function. **Conclusion:** Advanced CLAD is an inhomogeneity cohort of patients showing different exercise tolerance of reduced lung function. We were able to demonstrate pronounced hypventilation in patients with worse toleration and pathologic respiratory muscle function.


Lung transplantation (LTx) is an accepted therapeutic option for patient with end-stage emphysema. These emphysema patients can be subdivided in blue blowers and pink puffers, although most patients have characteristics of both groups. BMI is an important tool in distinguishing these subgroups. A low BMI is associated with a poor nutritional status which may predict a poor outcome after LTx. We aimed to investigate the outcome of emphysema patients with a low pre-transplant BMI (<20) in terms of acute rejection (AR), lymphocytic bronchiolitis (LB), infections, BOS and survival. We observed: 193 patients transplanted for emphysema between 1993-2011 and surviving more than 60 days post transplant, were included (53 SLTs(x singly) and 140 SLTS(double)). AB, LB and BOS are diagnosed according to the ISHLT criteria. Multivariate analyzes were done using SAS software. Patients with a lower BMI (<20) had a significant better 10-years survival compared to patients with a BMI between 18-20 for the total population (p=0.01) (figure). Prevalence of BOS was significantly lower within the lower BMI group, independent from other covariates (table). There is a statistical association between the prevalence of BOS, infection and LB (table).

We conclude from this single centre observation that emphysema patients with a BMI below 20 have a better outcome in terms of BOS and mortality and this should therefore no longer be regarded as contra-indication for LTx.

P1482 Systemic oxygenation affects post-transplantation edema formation and pulmonary artery hypertension in an ex vivo animal model Sara Klein, Stefan Dhein, Luisa Bauer, Franziska Schlegel, Sven Lehmann, Markus Barten, Friedrich-Wilhelm Mohr, Hartmuth Bittner. Heart Center Leipzig, Clinic for Cardiac Surgery, Leipzig, Germany

**Introduction:** By using an ex vivo model of isolated perfused and ventilated rabbit lungs we investigated the influence of systemic oxygenation on pulmonary function during simulated transplantation. **Methods:** Lungs of New Zealand White rabbits were flush-perfused with Perfadex® Solution, followed by an ischemic storage for 4h on ice. Thereafter ventilation and reperfusion for 2h were continued to simulate a transplantation situation (oxygenated group, pulmonary artery pO2=120mmHg). In another series the perfusate inflow was gassed with nitrogen to simulate the typical situation with deoxygenated pulmonary artery blood and not reanastomized private vessels(deoxygenated group, pulmonary artery pO2=50mmHg). Hemodynamic and ventilatory parameters were continuously detected. **Results:** After 2h reperfusion time the oxygenated group showed a significant lower PAP and lung weight compared to the deoxygenated group (p<0.05). PAP and lung weight steadily increased after reestablishment of lung perfusion (PAP 8.78±0.89 to 11.5±1.06cmH2O; lung weight 22.1±1.32 to 35.4±4.23g). This development was significantly influenced by the intravascular pO2 (P ≤ 0.05 to 8.02±0.63cmH2O; lung weight 17.9±1.54 to 21.6±2.29g; p<0.05). **Conclusions:** Oxygenation of the lung perfusate during simulated transplantation attenuates post transplant edema formation and decreases pulmonary arterial hyperpenterosion. This suggests that systemic oxygenation may delay the surgical situation, revascularisation of bronchial arteries after lung transplantation might initiate effective impacts in the early phase after lung transplantation.

P1483 Extracorporeal life support (ECLS) as a bridge to lung transplantation (LTx) | David Ruttens, Toufan Bahrami1, Anna Reed2, Mohamed Amrani1, Prashant Mohite1, Ajay Moza1, Heike Krueger1, Martin Carby2, Andre Simon1. 1Department or Cardiothoracic Transplantation and Mechanical Circulatory Support, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, Harefield, Middlesex, United Kingdom; 2Department of Respiratory Medicine, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, Harefield, Middlesex, United Kingdom

**Purpose:** Death on the waiting list remains high in patients awaiting LTx. ECLS as a bridge may increase patient’s survival. We present our initial experience. **Materials and methods:** Between Feb. 2010 and Dec. 2011 100 patients underwent LTx at our institution. 7 (7%) recipients were supported with ECLS prior to LTx. Outcome, donor and recipient parameters were analysed. **Results:** Donor age was 24(20-47) (median [interquartile range]); gender – F/M: 5/2, cause of death: intrinsic hamorrhage 3, hypoxic brain injury 2, bacterial meningitis 2; duration of donor mechanical ventilation was 2(2;2) days; PaO2/FiO2 ratio: 63.6±58.15;69.45±1.5Kpa. One patient died during the support.

**Table 1. Recipients’ demographics and perioperative data**

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<tr>
<td>Death on the waiting list</td>
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</table>

**Results:** ECLS as a bridge to LTx is a feasible option of treatment providing good early results. Longer weaning from mechanical ventilation, hospital and ICU LOS after transplantation should be expected.

P1484 Superior lung preservation with a polyethylene glycol based solution in a porcine lung transplant model | Anne Olland1, Arne Neynck1, Malika Benhamede1, Thomas Boogmans2, Albreka Stana1, Karin Elbay2, Shaharyar Wouters1, Geert Verleden1, Izzie Namer1, Dirk Van Raemdonck2,3. 1Laboratory for Experimental Thoracic Surgery, Catholic University Leuven, Leuven, Belgium; 2CNRS UMR 7237, UMR 7177, Strasbourg University, Strasbourg, France; 3Laboratory for Pneumology, University Hospital Gasthuisberg, Leuven, Belgium. *Biophysics and Nuclear Medicine Department, University Hospital, Strasbourg, France; 3Thoracic Surgery Department, University Hospital Gasthuisberg, Leuven, Belgium; 4Anesthesiology Department, University Hospital Gasthuisberg, Leuven, Belgium

**Objectives:** Scot15® is a low-K+ preservation solution including polyethylene glycol (PEG) as a colloid for protection of vascular endothelium during cold ischemia. PEG was previously demonstrated to have “immunomodulation” properties. The aim of this study was to assess whether these properties would be beneficial in a pig lung transplant model.

**Material:** Domestic pig donor lungs were flushed either with Scot15®[S;n=6] or Perfadex®[P;n=6] and stored on ice for 22 hours. The left lung was transplanted in a recipient animal observed during 6 hours after reperfusion. Pulmonary vascular resistance (PVR) and partial arterial oxygen tension (PaO2) were measured hourly. Lung biopsies were taken for HRMAS detection of the respective colloid in the lungs. Bronchoalveolar lavage (BAL) was taken to assess neutrophilic alveolar recruitment. At the end of reperfusion, wet to dry weight ratio (W/D) was measured as a marker of lung edema.

**Results:** HRMAS showed presence of PEG in the lungs in [S] before and during storage (8.78±0.43 to 8.02±0.63cmH2O; lung weight 17.9±1.54 to 21.6±2.29g; p<0.05).

**Conclusions:** Scot15® as a colloid for protection of vascular endothelium during cold ischemia.
The prevalence of SDB is high in lung transplant recipients, and sleep was associated with symptoms of sleepiness as measured by ESS. Interestingly, neither the occurrence of SDB nor the quality of body mass index was associated with less inflammatory reaction in lung grafts preserved with Scot15®.

**Patients and Methods:** Between March 2011 and February 2012 we included 28 clinically stable lung transplant recipients (16 men, time range after LTX 6±8.3 years, BMI: 26±8.3 kg/m² and FEV1 69±12 and 43±8 vessels/mm²), suggesting a role for denervation of the lung in the impairment of exercise capacity after bilateral lung transplantation.

**Results:** Age and body mass index (BMI) of men and women were similar (age: 56±9 years vs. 54±9 years, BMI: 26±3 kg/m² vs. 25±6 kg/m², n=30). The prevalence of acute rejection was observed by logistic regression analysis, even after adjustment for FEV1 and gender in multivariate analysis we found a statistically significant correlation between the exercise capacity and HCVR.

Conclusion: There is a remarkable difference in ventilatory response to carbon dioxide between male and female bilateral lung transplant recipients, suggesting a role for denervation of the lung in the impairment of exercise capacity after bilateral lung transplantation.

**Background:** Only few studies reported findings on CO2 rebreathing in long-term bilateral lung transplant recipients. Bilateral lung transplantation causes denervation of the donor lung. This might have an impact on control of breathing as measured by the hypercapnic ventilatory response (HCVR). The influence of gender on HCVR and the relation to exercise capacity is unknown yet.

**Objectives:** To study HCVR and the relation to exercise capacity after bilateral lung transplantation.

**Methods and patients:** Minute ventilation, respiratory rate and HCVR were studied in 24 bilateral lung transplant recipients (12 male). HCVR was measured according to the Read protocol. Exercise testing was performed to evaluate the maximum level of workload. This was expressed as percentage of the corresponding reference value.

**Results:** Age and body mass index (BMI) of men and women were similar (age: 56±9 years vs. 54±9 years, BMI: 26±3 kg/m² vs. 25±6 kg/m², n=30). The prevalence of acute rejection was observed by logistic regression analysis, even after adjustment for FEV1 and gender in multivariate analysis we found a statistically significant correlation between the exercise capacity and HCVR.

Conclusion: There is a remarkable difference in ventilatory response to carbon dioxide between male and female bilateral lung transplant recipients, suggesting a role for denervation of the lung in the impairment of exercise capacity after bilateral lung transplantation.
Progressive and irreversible fibroproliferative process leads to BOS. The presence of mesenchymal cells, the primary source of fibrotic cells, has been described in BAL fluid of LTR as predictive of BOS onset (Badri et al, 2011). CD44 cell surface glycoprotein has been found increasingly expressed by graft infiltrating lymphocytes, macrophages and AR fibroblasts with active OB. CD44 has been associated to an invasive fibroblast phenotype. Inhibition of mTOR, responsible of cell over-proliferation has been found effective in treating fibrotic process. Aim of this work is to assay CD44 expression in fibroblastoid cells derived from colony-forming units (CFU) of mesenchymal cells isolated from BAL of LTR patients with BOS. BOS 0p, 1 and 2 to evaluate its implication in fibrotic process. In addition, in the same cells expression of the active form of mTOR has been assayed to specifically target pharmacological treatment.

Results: BOS 1 and 2 patients showed moderate to strong expression of both CD44 and mTOR in 80% and weak in 20% BOS 0p subjects displayed moderate to high expression in 5% cells, weak signal in 60% and no detection in 35% cells. We also found that cells isolated from BOS 0p had a significantly \( p < 0.01 \), ANOVA lower proliferation rate compared to other cultured fibroblastoid cells. Conclusion: These results open new perspectives in the identification of a specific fibroblastoid phenotype linked to BOS grades and to target a therapeutic treatment.

157. Pulmonary circulation: clinical aspects of PAH, PTE and CTEPH

P1491

Oxidized-polymers of Z-AT are associated with exaggerated pulmonary inflammation post lung transplantation

Sam Alam1, Karthik Santhanakrishnan2, Jas Parmar2, Ravi Mahadeva1.

Aim of this work is to assay CD44 expression in fibroblastoid cells derived from colony-forming units (CFU) of mesenchymal cells isolated from BAL of LTR patients with BOS. BOS 0p, 1 and 2 to evaluate its implication in fibrotic process. In addition, in the same cells expression of the active form of mTOR has been assayed to specifically target pharmacological treatment.

Results: BOS 1 and 2 patients showed moderate to strong expression of both CD44 and mTOR in 80% and weak in 20% BOS 0p subjects displayed moderate to high expression in 5% cells, weak signal in 60% and no detection in 35% cells. We also found that cells isolated from BOS 0p had a significantly \( p < 0.01 \), ANOVA lower proliferation rate compared to other cultured fibroblastoid cells. Conclusion: These results open new perspectives in the identification of a specific fibroblastoid phenotype linked to BOS grades and to target a therapeutic treatment.

P1492

Characterization and hypertocyte-like differentiation of mesenchymal stem cells derived from adipose tissue of immunodeficient mice

Samir Alam, Veronika Klaassen, Jana Hübler, Nieder Mollen, Bruno Christ.

Aims and objectives: To isolate CDSCs from mouse adipose tissue and verify their potential for differentiation to explore their use for alleviating the shortage of liver transplantation donors to treat AATD.

Methods: MSCs were isolated from immunodeficient mice and cultured to 90% confluency. After DNA demethylation, a differentiation medium was applied and cellular morphology was assessed by microscopy after 0, 7, 14 and 21 days. Flow cytometry was used to detect mesenchymal (CD13, CD29, CD44, CD105) and haematopoietic (CD34, CD45) cell surface markers to estimate the percentage of differentiated cells. Gene expression of the hypertocyte-specific markers transferrin, albumin, CR1, CD26 and CYP3A1 was measured by semi-quantitative reverse transcription polymerase chain reaction.

Results: During differentiation, the morphology of MSCs changed from a spindle shape into a more polygonal aspect. Mesenchymal markers were expressed at each time point, whereas haematopoietic markers were hardly detectable after 21 days. The relative gene expression of the hepatic markers was increased at each time point.

Conclusion: MSCs derived from mouse adipose tissue may differentiate into hypertocyte-like cells in vitro. Conversely, human MSCs derived from mesenchymal tissue of a syngeneic mouse model of AATD can now be analysed.

P1493

Creatine supplementation attenuates systemic and pulmonary effects of acute lung injury induced by pulmonary ischemia-reperfusion in rats

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Creatine supplementation (CS) prevents prothrombin and therapeutic effects for some muscular, cardiovascular and neurological disorders. In case of temporary ischemia, CS improves the capacity to generate ATP reducing cell damage. Ischemia and reperfusion (IR) injury is partially attributed to decreased intracellular ATP turnover, but also to increased oxidative stress and reduced IGF-1. Thus, this study evaluated the effects of 5 days of CS prior 90 minutes ischemia of left pulmonary artery followed by 120 minutes of reperfusion in 40 male Wistar rats divided in 4 groups: Sham-operated, CS+Isham, Ischemia/Reperfusion, Creat+Isham/Reperfusion. Lung mechanics, exhaled nitric oxide, cellularity in systemic circulation and in bronchoalveolar lavage (BAL), neutrophils and edema in lung tissue, total proteins in BAL, the levels of IL-\( \beta \)-ta, IL-4, IL-6, IL-17, KC, MCP-1 and TNF-alpha in serum and in bronchoalveolar lavage were evaluated by ELISA, as well as the expression of IGF-1, iNOS and caspase-3 in lung tissue. Compared with IR group, CS supplementation (CS+IR group) resulted in a reduction of exhaled nitric oxide (p<0.05), tissue damping (GTIS) and tissue elastance (HTIS) (p<0.05), total cells and neutrophils number in systemic circulation, in BAL and also in lung tissue (p<0.01), BAL levels of total proteins (p<0.05) and edema index in lung tissue (p<0.05), and systemic and pulmonary IL-\( \beta \)-ta (p<0.05). In addition, CS resulted in increased expression of IGF-1 in lung tissue. CS presents protective effects for the development of pulmonary and systemic manifestations of acute lung injury caused by pulmonary IR.

P1494

The development of pulmonary hypertension after first episode of acute pulmonary embolism and related risk factors

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Background: Part of patients with acute pulmonary embolism(PE) will develop into pulmonary hypertension(PE) including chronic pulmonary thromboembolic hypertension(CTEPH). Related risk factors need to be addressed to guide clinical practice.

Objectives: To investigate the incidence of PH after PE and related risk factors.

Methods: Consecutive patients diagnosed as acute PE admitted to our institute from 2006 to 2010 were included. All the patients were followed till Dec 2011. During the follow-up, patients with PH showed in echocardiogram, defined as an increased systolic pulmonary artery pressure (PAP) over 50mmHg, received right heart catheterization to confirm the diagnosis of CTEPH.
Results: 612 patients were included and the median follow-up period was 36 months. All-cause mortality was 17.3%. 15 patients developed into PH and 10 were diagnosed as CTEPH. The 1-, 2- and 5-year cumulative incidences of PH were 1.0% (95% CI: 0.2%-1.8%), 1.3% (95% CI: 0.3%-2.3%) and 3.5% (95% CI: 1.5%-5.5%) respectively. Patients with varicose vein of lower limbs (HR 5.480, 95% CI 2.795-10.793) and existence of PH at the beginning (HR 10.743, 95% CI 2.315-49.852) had higher risk in developing into PH.

Conclusion: CTEPH is a serious complication in a significant number of PE cases. History of varicose vein of lower limbs and estimated sPAP over 50mmHg at the first episode of PE seem to predict the risk of CTEPH in long-term follow-up.

P1495
Measurement of gas transfer components using nitric oxide in post pulmonary endartecctomy (PEA) chronic thromboembolic hypertension (CTEPH) patients
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Introduction: Reduced TLCO is frequently observed in CTEPH patients. Previous work has used single breath for NO to differentiate the diffusing membrane capacity (Dm) and capillary blood volume (Vc); the components of TLCO. It has been suggested, that TLNO is a more accurate reflection of Dm, due to greater affinity for haemoglobin and independence from Vc. This study uses new technology to measure Dm and Vc, using NO, in a cohort of post PEA CTEPH patients. The aim of the study is to compare the relative contribution of Dm and Vc to the reduction in TLCO.

Methods: We studied 24 CTEPH patients (14 male, 10 female, mean age 56±15) post PEA. Full lung function were performed and TLNO and Dm were measured using single breath for NO and CO on a PFTpro system (Viasys). Vc was calculated using the equation 1(DLCO=1(Dm×[(CO×Vc)]/NO)×Vc). Patients with co-existing parenchymal lung disease were excluded from the study. Correlations between variables were looked at using Pearson’s.

Results: Both Dm and Vc demonstrated a significant correlation with TLCO. Vc is more affected than the alveolar component Dm. The new technology offers a simple patient friendly procedure allowing measurements of Dm and Vc. This has the potential for improving our understanding of the different components of gas transfer. Further work is warranted in this area.

P1496
Circulating microRNA signature and its novel involvement in pathogenesis of chronic thromboembolic pulmonary hypertension
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Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease characterized by multiple etiology and mechanism. Circulating miRNA is partially derived from cells affected by disease and therefore can serve as potential biomarker and reflect the pathogenesis of this disease. In present study, we compared miRNA expression in plasma from 10 CTEPH patients and 10 healthy control subjects by microarray, and fourteen miRNAs were indentified to be differentially expressed.

Selectively, five of the differentially expressed miRNAs were further validated in an independent 40 pairs of subjects by stem-loop qRT-PCR, among which let-7b and miR-22 were downregulated to about 25% in CTEPH patients. Endothelin-1 (ET-1) and transforming growth factor beta receptor 1 (TGFBR1) was the direct targets of let-7b by reporter assay, and plasma ET-1 level was reversely correlated to let-7b. TGFBR1 was further required for induction of ET-1 in endothelial cells.

P1497
Persistent lung perfusion defect is a risk factor for recurrent venous thromboembolism after pulmonary embolectomy
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Introduction: Up to 50% of patients with pulmonary embolism (PE) still have lung perfusion defects after 6 months of anticoagulant treatment, but little is known about the risk of recurrence in patients with persistent perfusion defect after an acute PE.

Aim of the study: To assess the risk of recurrent venous thromboembolism (VTE) in patients with persistent lung perfusion defects after a first episode of PE.

Patients and methods: Consecutive patients given at least 3 months of anticoagulant for an objectively proven first episode of acute PE were included. Ventilation/perfusion (V/Q) lung scan was performed 6 to 12 months after the diagnosis of PE. Objectively proven recurrent deep vein thrombosis (DVT) and PE were registered during follow-up. Persistent perfusion defects were defined as a pulmonary vascular obstruction > 10% on the V/Q lung scan.

Results: 318 patients (mean age 58±13 years) with an acute PE were included. 63 (19.8%, 95% CI, 15.4-24.2%) had persistent perfusion defects. During follow-up (median duration: 51 months [25th 75th percentiles: 27 - 73 months]), 71 patients (22%) had a recurrent episode of VTE. In multivariate analysis, persistent defect (HR 2.22; 95% CI, 1.3-3.75; p = 0.0048), unprovoked PE (HR 3.48; 95% CI, 1.96-6.19; p = 0.0001), persistent risk factor for VTE (HR 2.64; 95% CI 1.08-6.48; p = 0.03001) and age (60 to 75 years; HR 1.88; 95% CI, 1.0-3.61; p = 0.0112) were identified as independent risk factors for recurrent VTE whereas prolonged anticoagulation was a protecting factor (HR 0.19; 95% CI, 0.07-0.54; p = 0.0001).

Conclusion: Persistent perfusion defect is an independent risk factor for recurrent VTE after a first episode of PE.
Involvement of the pulmonary micro-vasculature in chronic thromboembolic pulmonary hypertension (CTEPH) 

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Conclusion: Other significant.

P1498

Two inventive protocols are useful to reduce the artifacts in rPA.

Introduction: Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH. However, a limited subset of CTEPH-patients present with persistent PH after PEA.

Aims: To assess microvascular lesions and clinical characteristics in CTEPH-patients with persistent PH after PEA.

Methods: We analyzed lung histology available from 8/10 patients with persistent PH after PEA and compared them with 10 randomly selected CTEPH-patients with successful PEA.

Results: Histopathology from 8 persistent PH patients revealed thrombotic lesions, intimal fibrosis and medial hypertrophy in peripheral small muscular pulmonary arteries of all analyzed lungs. 7/8 persistent PH patients displayed moderate pulmonary venous involvement, including intimal fibrosis of small pre-septal venules, foci of capillary multiplication, and hemosiderosis. All cases presented hypertrophy of bronchial systemic arteries. Hemodynamic data, exercise testing and medical history exhibited non-significant but by-trend discriminating values between the persistent PH and the successful PEA group for PVR (119±154 dynes s cm^-5 versus 825±98 dynes s cm^-5), DCO (63±6% versus 75±4%), 6-minute walking distance (6MWD) (272±64m versus 415±33m), history of vascular implants (6/10 versus 0/10), and presence of subpleural septa on chest scanner (6/10 versus 2/10).

Conclusion: We report conspicuous remodeling of the pre- and post-capillary microvasculature in CTEPH-patients with persistent PH after PEA. Group-related discrepancies of PVR, DCO, 6MWD, vascular implant-history, and one radio logic criterion were observed in CTEPH patients with persistent PH, as compared with CTEPH-patients with successful PEA.

P1499

Inventive protocols of CT pulmonary angiography (CTPA) avoid artifacts in pulmonary embolism (PE).

Methods: Aims: To investigate the incidence of recurrent VTE in patients with first episode acute pulmonary embolism(PE) and related risk factors

Patients and methods: 24 consecutive patients suspected PE underwent CTPAs using a 64-detector MDCT. Each protocol was started with a 3 ml/sec-injection of 100ml of CM (300mg/Iml) via vein in upper limb. Three protocols followed the above CM injection, protocol-1 (P-1) with immediate exposure, protocol-2 (P-2) with exposure after 10 sec.-delayed, and protocol-3 (P-3) with exposure after injection of 30ml saline (3ml/sec). We observed artifacts regarding rPA, subclavian veins, calciﬁcation, and motion. Then an artifact-observed score (AOS) was given 0 to 4 as artifact grade.

Results: Each average of AOS in rPA was 1.80 in P-1, 0.25 in P-2, and 0.13 in P-3. The AOS in P-1 was higher than the others, in P-2 (p=0.04) and in P-3 (p=0.001). Each average of AOS in subclavian veins and motion artifact did not differ from P-1 to P-3. The CM-density of all regions of interest in P-1 were higher than the others significantly.

Conclusion: Invasive protocols are useful to reduce the artifacts in rPA.

They may improve detectability of thrombi in rPA in CTPA.

P1500

Sleep-disordered breathing in acute pulmonary embolism: A dangerous comorbidity?


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Background: Sleep-disordered breathing (SDB) is a common comorbidity in patients with acute pulmonary embolism (PE) but its prognostic relevance in PE is unclear. Therefore, we conducted a prospective cohort study to clarify if the presence of SDB is associated with an adverse outcome in acute PE.

Methods: 106 consecutive PE patients were prospectively evaluated by portable monitoring (PM). Nocturnal polysomnography was performed in all subjects who have been diagnosed by PM to have an apnoea-hypopnoea index (AHI) > 15 or evidence of increased daytime sleepiness. All-cause mortality was registered after a mean observation period of 12 months.

Results: Neither central sleep apnoea nor periodic breathing were observed. Mild obstructive sleep apnoea (OSA) was diagnosed in 35.8% of patients. 12.3% of subjects suffered from moderate to severe OSA (AHI > 15/h). The incidence of sleep apnoea among study participants was significantly higher in patients with moderate to severe OSA compared to subjects with an AHI > 15/h (8.3% vs. 2.4%, p = 0.003).

Conclusion: OSA is a common comorbidity to PE and might be associated with an increased mortality in survivors of acute PE.

P1501

Red cell distribution width (RDW): A new predictor for chronic thromboembolic pulmonary hypertension

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Introduction: Our aim is to investigate whether RDW might be a predictor of CTEPH in pulmonary embolism patients or not. This study is a retrospective cohort study. A total of 203 consecutive patients with acute PE were included. Minimum follow-up period was 10 months. We collected each patient's baseline characteristics including RDW, Troponin-T and CRP. Receiver operating characteristic (ROC) analysis was performed to determine the optimal RDW cut-off levels to predict CTEPH. CTEPH frequency in PE patients (n=203) was 7.9% (n=16). RDW was higher in CTEPH patients than the patients without CTEPH (17.0±4.46; 14.6±1.82) (p=0.015). The optimal cutoff value of RDW for predicting CTEPH was 14.65. The area under the curve of RDW for prediction of CTEPH was 0.735 (CI: 0.600-0.869). In cases with RDW levels>14.65, the specificity and sensitivity for CTEPH were 62% and 75%, respectively. Negative predictive value of RDW at cutoff 14.65 for CTEPH was 96.7%. At multivariate regression analysis, RDW, hazard ratio: 1.58 (95% confidence interval: 1.09-2.30) was a predictor of CTEPH (p=0.016). High RDW levels was an independent predictor of CTEPH in PE patients. Therefore, RDW levels may provide a potential market to predict CTEPH in PE patients.

P1502

The incidence of venous thromboembolism recurrence in patients after first episode acute pulmonary embolism and related risk factors.

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Background: Early identification of recurrent venous thromboembolism(VTE) in patients with first episode acute pulmonary embolism(PE) and related risk factors is important in clinical practice.

Methods: Consecutive patients with acute PE from 2006 to 2010 were enrolled. Baseline clinical data was collected and patients were followed up for years. The primary endpoint is symptomatic recurrent VTE and the second endpoint is death.

Results: 612 patients were included. The median follow-up period was 36 months and all-cause mortality was 17.3%. The 1-, 2- and 5-year cumulative recurrent incidences were 3.9%(95%CIs: 2.3%-5.5%), 6.9%(95%CIs: 4.9%-8.9%) and 13.5%(95%CIs: 10.2%-16.8%) respectively. Patients with uncomplicated PE (HR: 3.52, 95%CI: 1.81-6.84), concurrent deep venous thrombosis(DVT) (HR 5.39, 95%CI: 1.83-15.84) or varicose vein of lower limbs(HR 4.286, 95%CI: 2.210-8.313) had higher risk in recurrence. Conversely, patients with longer duration of anticoagulation(HR 0.971, 95%CI: 0.952-0.991) suffered less.

Conclusions: VTE recurrence is relatively common. Unprovoked PE, concurrent...
DVT and history of varicose vein of lower limbs seem to increase the risk of recurrence. Longer duration of anticoagulation seems to protect patients from recurrent VTE.

**P1503**

Circulating endothelial cell levels decrease after vasodilator therapy and are a biomarker of clinical worsening in refractory pulmonary hypertension in children

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**Background:** Pulmonary vasodilators in general and prostacyclin therapy in particular have improved the outcome of patients with pulmonary arterial hypertension (PAH). Endothelial dysfunction is a key feature of PAH and we previously described that circulating endothelial cells (CECs) could be used as a biomarker of endothelial dysfunction in PAH. We now hypothesized that PAH-specific vasodilator therapy might decrease CEC numbers.

**Methods:** CECs were quantified by immunomagnetic separation with antiCD146 coated beads in peripheral blood from children with idiopathic PAH (iPAH, n = 30) or PAH secondary to congenital heart disease (PAH-CHD, n = 30): before, after treatment and during follow up.

**Results:** Oral treatment with endothelin antagonists and/or PDE5 inhibitors significantly reduced CEC counts in children. In 10 children with refractory PAH despite oral combination therapy, subcutaneous (SC) treprostinil was added and we observed a significant decrease in CEC counts during the first month of such treatment. CECs were quantified during a 6 to 36 month follow-up after initiation of SC treprostinil and we found that CEC counts changed over time, with rising counts always preceding clinical deterioration.

**Conclusions:** CECs might be useful as a biomarker during follow-up of PAH treatment in pediatric iPAH and PAH-CHD, to assess response to treatment and to anticipate clinical worsening.

**P1505**

Atrial flutter and fibrillation in patients with chronic pulmonary hypertension

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**Background:** Atrial flutter and atrial fibrillation are frequently observed in patients with pulmonary hypertension but their clinical implications remain unclear.

**Objectives:** Aim of the study was to determine the prevalence and clinical impact of supraventricular tachyarrhythmias (SVTs) in patients with pulmonary hypertension.

**Methods:** In a 5-year, prospective study, we assessed the incidence of new-onset SVTs as well as risk factors, clinical consequences, management, and impact on survival in patients with pulmonary arterial hypertension (PAH, n=157) or inoperable chronic thromboembolic pulmonary hypertension (CTEPH, n=82).

**Results:** New onset SVTs were detected in 48/239 (20%) patients with a cumulative 5-year incidence of new-onset SVTs of 25.1% (95% confidence interval, 13.8-35.4%). Atrial flutter and atrial fibrillation were equally frequent. Stable sinus rhythm was re-established in 21/24 (88%) of patients initially presenting with atrial flutter and in 16/24 (67%) of patients with atrial fibrillation. Development of SVTs was associated with more severe hemodynamic impairment. New-onset SVTs were an independent risk factor of death (p=0.04, simple Cox regression analysis) with a significantly higher mortality in patients with persistent atrial fibrillation compared to patients in whom sinus rhythm was restored (estimated survival at 1, 2 and 3 years 64%, 55%, and 27% versus 97%, 80%, and 57%, respectively; p=0.01, log-rank analysis).

**Conclusions:** SVTs develop in a considerable number of patients with PAH or inoperable CTEPH and often cause clinical deterioration and right heart failure. Mortality is high when sinus rhythm cannot be restored.
P1508
Prognostic risk factors of disease worsening in patients with functional class II pulmonary arterial hypertension

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Introduction: The open-label extension (OLE) phase of the EARLY trial provides a unique opportunity to analyse long-term data from WHO functional class II pulmonary arterial hypertension (PAH) patients. Here we investigated prognostic factors associated with PAH worsening.

Methods: PAH worsening was defined as initiation of parenteral prostanoids, atrial septostomy, lung transplantation or death. Data on these 4 parameters, collected annually until study end regardless of OLE participation or treatment discontinuation, for all 185 patients originally randomized to placebo or bosentan were included in this analysis. OLE continued until at least 50% of patients had the opportunity to be treated with bosentan for at least 5 years. Cox regression analysis, univariate (significance set at P<0.1 cut-off) and multivariate (backward selection set at P<0.1 cut-off, including all variables having a P-value <0.1 in the univariate analysis), were employed to determine prognostic factors of PAH worsening.

Results: In the univariate analysis, significant prognostic factors for a low risk of PAH worsening were time since PAH diagnosis >16 months, 6-minute walk distance >437.0 m and mixed venous oxygen saturation >68%. High values in NT-proBNP and PAH associated with connective tissue disease versus idiopathic, heritable or HIV-associated PAH were significant risk factors for PAH worsening. Apart from time since diagnosis, these factors were confirmed as significant in the multivariate analysis.

Conclusions: This analysis provides firm evidence of risk factors significantly associated with PAH worsening in patients at a functionally early stage of the disease.

P1510
Potential pharmacological interactions between oral pulmonary arterial hypertension (PAH) therapies and new oral anticoagulants

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Background: Anticoagulation with vitamin-K antagonists is currently recommended in PAH. We aimed to search for potential pharmacological interactions between new oral anticoagulants (NOA) and oral PAH therapies.

Methods: We reviewed the potential pharmacokinetic and pharmacodynamics drug-drug interactions (DDI), in particularly regarding metabolism and drug transport, port, with bosentan (B), ambrisentan (A), sildenafil (S), tadalafil (T) and NOA (rivaroxaban, apixaban, dabigatran).

Results: B is metabolized mainly by hepatic cytochrome P450 (CYP) 3A4, A by uridine 5’-diphosphate glucuronitransferase and to a lesser extent, by CYP3A4 and CYP2C19. The organic anion transport proteins for B and P-glycoprotein for are both probably involved in the transports of these drugs. B, but not A, induces CYP3A4, which is involved in the metabolism of anti-Xa NOA rivaroxaban (30%) and apixaban (50%). Concomitant use of B may reduce their biological efficacy. S and T are also mainly metabolized by CYP3A4, but act as slight CYP3A4 inhibitors. The risk for clinically significant DDI seems low between S or T and anti-Xa NOA. However, in case of PAH-combination therapy, the risk for a decreased concentration might be amplified for anti-Xa NOA. Conversely, an increased risk of myocardial infarction recently evoked with dabigatran, an anti-IIa drug not metabolised by CYP, should preclude its use in PAH.

Conclusion: DDI may occur in PAH patients receiving NOA and PAH therapies, and potentially amplified in case of combination therapy. In the absence of robust clinical and pharmacological data, NOA are not recommended in PAH.
To study pulmonary hemodynamics and the prevalence of porto pulmonary hypertension (POPH) in cirrhotic patients

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Background: Pulmonary hypertension (PH) (mean pulmonary artery (MPA) pressure \(\geq 25\) mm Hg at rest) associated with cirrhosis have variable etiologies and prognostic implications.

Aim: To study pulmonary hemodynamics and determine the prevalence of porto pulmonary hypertension (POPH) in cirrhotic patients.

Method: Retrospective study comprised 1492 patients with cirrhosis seen at a tertiary teaching hospital from July 2001 to March 2011 undergoing invasive haemodynamic measurements during hepatic venous pressure gradient (HVPG) study. The data on etiology of cirrhosis, medical history and Child-Pugh classification of liver disease also collected.

Result: 1492 patients (M:F, 1177:315, Child A:B:C, 378:360:754) mean age 45.4 ± 13.2 37 (2.48%) had confirmed PH and 7 (0.47%) patients satisfied the criteria of POPH. Out of 37 PH patients, precapillary PH was present in 7 (POPH group) while postcapillary PH was present in 30 (2.0%) and was passive in 27 patients. Cardiac dysfunction (n=17), spirometric evidence of COPD (n=10 including 4 overlap with cardiac disease), unknown (n=4) and serological evidence of connective tissue disorders (n=3) were also present in postcapillary PH patients. Only 3 out of 30 patients had reactive postcapillary PH (Transpulmonary gradient (TPG) >12mm Hg). Higher MPA and TPG significantly associated with POPH.

Conclusion: The prevalence of POPH in cirrhosis was 0.47%. Presence of PH in cirrhotic should alert the physician to search for more common causes other than POPH, may be more amenable to treatment, making them eligible and also reducing the risk associated with untreated PH, especially in patients being considered for liver transplantation.
202. Early detection of lung cancer

1636

Interval lung cancers not detected on screening chest x-rays: How are they different?
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Background: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial provides us an opportunity to describe interval lung cancers not detected by screening chest x-ray (cXr) compared to screen-detected cancers. Methods: Participants were randomized to cXr at baseline and annually for two (never smokers) or three (ever smokers) more years. Putative interval cancers were those with a negative cXr screen but with a diagnosis of lung cancer within 12 months. Screen-detected cancers were those with a positive cXr and diagnosis within 12 months. Potential interval cancers were reviewed to determine whether lung cancer was missed and probably present during the initial interpretation or whether the lesion was a “true interval” cancer. Results: 7745 participants were randomized to the intervention arm with 70,633 screened. Of 5,227 positive screens from any screening round, 298 resulted in screen-detected lung cancers; 152 had potential interval cancers with 128 cXr available for re-review. Cancer was probably present in 45/128 (35.2%) at time of screening; 83 (64.8%) were “true interval” cancers. Compared to screen-detected cancers, true interval cancers were more common among males, persons with <12 years education and those with a history of smoking. True interval lung cancers were more often adenocarcinoma (57% vs. 16.7%), more often small cell (27.7% vs. 7.4%), and less often adenocarcinoma, 25.3% vs. 56.4% (p<0.0001), and less likely to be in the right upper lobe, 16.9% vs. 36.2% (p<0.001). Conclusion: True interval lung cancers differ from cXr-screen-detected cancers with regard to demographic variables, stage, cell type and location.

1637

The effect of route of presentation on lung cancer outcome
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Background: Lung cancer is the commonest cause of cancer death in the UK, with one year survival lagging behind the rest of Europe. Early lung cancer diagnosis is imperative in achieving the highest chance of curative therapy. Recent Public Health Campaigns have highlighted importance of early lung cancer detection and early presentation to primary care, allowing onward referral. The Laton and Dunstable Hospital is situated north of london, covering a population of 320,000. Observations show when patients present as an emergency, instead of through outpatient referral, disease is at a later stage and limited treatment, if any, available. Aims: To compare stage of lung cancer, treatment intent and survival, between patients referred from primary care and emergency inpatient presentations. Methods: 2010 lucada data from Laton and Dunstable NHS Trust were analysed, including 144 patients. 63 primary care referrals, and 81 inpatient presentations. Performance status, stage, survival and treatment were compared using the chi-squared contingency test. Results: Patients referred through outpatients had a significantly better performance score (p<0.001) and an earlier stage disease (p=0.0085) compared to those diagnosed following emergency admission. Survival data (at time of analysis), revealed a greater likelihood of death within the inpatient population (p<0.001). A trend existed for more active treatment in outpatient referrals, although this failed to reach statistical significance. Conclusions: Our data shows outpatient diagnosis is associated with better performance scores, earlier cancer stage and prolonged survival. Early symptom recognition, with early referral is vital in improving life expectancy from lung cancer.

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The results of the prevalence screen in Lung SEARCH: A UK based screening trial for lung cancer based on sputum cytology and cytometry, by the Lung SEARCH screening group
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Lung SEARCH is a screening trial in 9 UK centres of 1658 subjects with a ≥20 pack-year smoking history, mild or moderate chronic obstructive pulmonary disease (COPD). Randomisation was to a control group who had no active intervention, but an exit chest x-ray (cXr) at the end of 5 years; or a surveillance group who provide sputum samples annually for 5 years, for cytological and cytometrical analysis, and if normal for the duration of the study, an exit cXr. Samples showing abnormalities would undergo annual low-dose computed tomography (CT) and autofluorescent fiberoptic bronchoscopy (AFB) for the remaining years of the five. Our aim is to identify more early stage cancers in the surveillance arm (<50%) than the control (<10%) and literature on COPD suggested we would need 37 cancers in each study group. We entered 785 subjects into the surveillance, and 783 in the control arms. The two groups were well matched with 52% of men in both groups, 56% and 44% in each group were current or ex-smokers, and their mean ages were 63 years. 75% in each group had moderate COPD and 25% were mild.

Results: Of the 785 subjects in the surveillance arm, 92% provided a sputum sample. Of these only 132 of 742 were inadequate for analysis. 352 (37%) were normal, 128 (17%) were abnormal: 16 were high grade and 112 low grade.

Background: National Lung Screening Trial (NSLT) reported screening with low-dose CT could reduce mortality from lung cancer. Breath analysis such as biomarker discovery could detect volatile organic compounds (VOC).

Objectives: To detect specific VOC peaks in lung cancer then compare lung cancer and healthy subjects.

Methods: IMS coupled to a multi-capillary column (MCC/IMS) (BioScout: B&S Analytik, Dortmund, Germany) with a 95MBq β-radiation source was used to detect VOC peaks. For the Japanese market, regulations restrict 63Ni β-radiation sources to under 100MBq. Exhaled breath samples were collected at quiet breathing in 30 patients with lung cancer and 13 healthy volunteers. Peaks were characterized using Visual Now 2.2 software (B&S Analytik, Dortmund, Germany).

Results: Patients included 17 adenocarcinoma, 3 squamous cell carcinoma, 6 small cell carcinoma and 4 unclassified carcinoma. Forty-seven VOC peaks were detected and 10 VOC peaks showed significant differences between lung cancer and healthy volunteers (p<0.05).

Conclusions: IMS using 95MBq β-radiation source is a feasible screening test in the detection of lung cancer. In the future, IMS may detect histological types of lung cancer and molecular mutation.
Cancer-associated oncogenic BARD1 isoforms: From biomarker expression studies to development of a blood test for early detection of lung cancer

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We have reported that exhaled volatile organic compound (eVOC) profile of lung cancer (LC) subjects differed from healthy ever smokers (HS).

Aim: To find if eVOC profile of LC subgroups (1) peripheral tumours and (2) early stage disease differ from HS.

Method: LC (n=53) and HS (n=177) subjects provided a breath sample after tidal breathing through an inspiratory port filter for 5 mins. It was analysed with a 32 sensor Cyranose 320 (Smiths Detection). Tumours were staged (7th ed TNM system), and defined as peripheral if located in the outer 1/3 of lung fields on axial CT images. LC subgroups were: Stages I/II (n=27), III/IV (n=25), central (n=32) and peripheral tumours (n=21).

Results: The eVOC profile distinguished between LC and HS with a cross validation (CVV) accuracy of 79%, (p<0.0001). eVOC profile CVV accuracy was 77% when analysing central, peripheral and HS cases. A principal component vector was significantly different between early (I/II) stage LC and HS (p=0.035).

Conclusions: These data indicate the ability of exhaled breath VOC profiles to distinguish early stage and peripheral lung cancer cases from healthy ever smokers, and therefore support its potential as a non-invasive screening tool for early detection of lung cancer.

Supported by The Prince Charles Hospital Foundation and Private Practice Trust Fund.

Hyaluronan: A novel sputum marker for the screening and diagnosis of lung cancer patients

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Introduction: Hyaluronic Acid (HA) is elevated in several cancers, but there is no data regarding its concentration in the sputum of lung cancer patients. In this study, we examined the HA concentrations in the sputum and its impact on the screening and diagnosis of lung cancer patients.

Methods: HA was examined in sputum samples of 90 lung cancer patients, 25 COPD patients and 15 healthy controls. All the patients and healthy controls selected underwent a sputum induction. Sputum samples were incubated with area at 60°C and afterwards incubated with a proteolytic enzyme. The levels of HA were measured by a noncompetitive ELISA-like fluorometric assay.

Results: A significant difference in concentration pattern of HA in the sputum was found among lung cancer, COPD and healthy individuals (p<0.001; Fig. 1A). ROC curve between lung cancer and healthy volunteers furnished an area of 0.821 (0.727–0.915). Assuming a cut off value of 31.44ng/mg, the specificity was 100% and the sensitivity was 51% (Fig. 1B). ROC curve to distinguish COPD patients from lung cancer patients showed an area of 0.698 (0.600–0.797) and the cut off

An electronic nose in the discrimination of patients with lung cancer and controls

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Background: Lung cancer is a leading cause of death in men suffering from oncological diseases. Exhaled breath contains hundreds of volatile organic compounds (VOCs) that could serve as biomarkers of lung disease. Electronic nose can distinguish VOC patterns by mixture pattern recognition.

Objective: We hypothesized that an electronic nose can discriminate exhaled air of patients with lung cancer from healthy controls.

Methods: 25 patients with clinically and histologically verified lung cancer and 45 controls were included in a study with sampling of exhaled breath. Subjects inspired VOC-filtered air by tidal breathing for 5 minutes, and a single expiratory sample was collected into polyethylene terephthalate bag that was sampled by electronic nose (Cyranose 320) within 5 minutes. Smellprints were analyzed by multilayer feedforward neural network analysis (MLRA). Optimal detector parameter combination for diagnosis of lung cancer was calculated by MLRA backward stepwise method. Sensitivity, specificity, PPV and NPV of the method were calculated.

Results: Optimal detector parameters for discrimination of lung cancer were maximum of detectors number 6, 13. and 23. and area under curve of detectors 2, 6, 24 and 29. 22 out of 25 or 88.0% of lung cancer cases were predicted correctly by MLRA. Sensitivity of the method was 88.0%, specificity 91.1%, PPV 84.6% and NPV 93.2%.

Conclusions: The electronic nose appears to be able to discriminate exhaled breath from subjects with lung cancer and healthy controls. Analysis of exhaled breath could be used as the lung cancer screening method in the future.

Acknowledgements
Study was sponsored by ERAF activity Nb. 2.1.1.1.0. Project Nb. 2010/0303/2DYP/2.1.1.1.0/10/APEVIA043.
The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend a combined assessment for measuring the impact of COPD which considers current symptoms and future exacerbation risk (A: low risk, less symptoms; B: low risk, more symptoms; C: high risk, less symptoms; D: high risk, more symptoms). Two symptom cut-points are proposed: COPD Assessment Test (CAT) score ≥10 and modified Medical Research Council Dyspnoea (mMRC) score ≥2.

This analysis examined health status scores split by these cut-points, using CAT and mMRC data together with SGRQ and SF-12 Physical Function (PF) scores, in a primary care population from the Health Related Quality of Life in European COPD Study.

Data from 1817 patients (mean [SD] FEV1 1.6 [0.6] L; age 64.9 [9.6] years; males 67.6%) were included. COPD Study.

Conclusions: The mMRC cut-point of ≥2 classified a high proportion of these patients as having low symptoms, despite having moderately high SGRQ scores and poor SF-12 PC scores. The distribution of the individuals according to the two stratification systems differs considerably. With regard to prediction of exacerbations, the A-D GOLD 2011 classification performs well.

Conclusions: The results presented suggest a promising role of HA quantification in the sputum as a novel screening and diagnostic marker for differentiating normal and other type of fibrotic pulmonary problems from lung cancer patients.
followed by spirometry and exacerbation history to determine exacerbation risk (Fig 1). We examined this guidance in the London COPD cohort. 106 patients completed daily symptom diary cards for ≥1 year and the CAT at least once when stable. All exacerbations received additional systemic and/or inhaled therapy. Mean age was 72.6 years (SD 8.3), FEV1 1.1L (0.5), and FEV1 predicted 48.5% (16.4).

Using CAT and GOLD grade to assess exacerbation risk yielded significantly more high risk patients (category C&D) than when exacerbation history was used (56.6% vs. 33.0%, p=0.001). After combined assessment using both GOLD grade and exacerbation history, few patients were included in the high risk, less symptoms category C: 8.5% (9/106) using CAT and 10.4% (11/106) using mMRC. In a specialist outpatient setting, few patients fulfill criteria for inclusion in the high risk, less symptoms category C. Furthermore, the method chosen to assess exacerbation risk had a large influence on risk stratification. Additional work is required to examine the utility of this aspect of GOLD guidance in primary care to screen for exacerbation risk.

1648 Combined assessment according to the new GOLD guidelines and its relation to outcome in COPD

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Background: The new GOLD guidelines recommend pharmacological and non-pharmacological management of COPD to be individualized based on the assessment of symptoms and exacerbation risk (A=low risk, less symptoms; B=low risk, more symptoms; C=high risk, less symptoms; D=high risk, more symptoms). We hypothesize that functional parameters and the risk of future events differ among patients categorized by the combined assessment according to the guidelines.

Methods: We prospectively evaluated 638 patients with stable COPD for exacerbation and death from any cause. Median observation time was 24 weeks, >10 PY and GOLD II-IV seeking care in pulmonary tertiary hospitals in 8 European countries and included in the PROMISE cohort. The outcome variables were exacerbation and death from any cause. Median observation time was 24 months.

Results: There were 1152 exacerbations, 225 severe exacerbations and 63 deaths among 586 patients classified as A=50 (7.6%), B=184 (28.8%), C=27 (4.2%), and D=325 (50.9%). Health-related QoL, as assessed by all domains of the SGRQ (p<0.0001) and most but not all domains of the SF-36, circulating pro-dromalmeulin (p=0.0287), 6 MWD (p=0.0001), exacerbations rate (p<0.0001), severe exacerbation rate (p<0.0001) and mortality (p<0.0001) differ significantly among the 4 groups. Mortality was highest in the group D (12%) followed by groups A (10%), B (6%). Remarkably, mortality was lowest in group C (0%).

Conclusion: The combined assessment according to the new GOLD guidelines is only partially associated with quality of life and the risk of future events in COPD.

1649 Differences in the recommended initial therapy of COPD according to GOLD guidelines 2006 and 2011

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Background: The last GOLD Guideline revision was released in late 2011. We hypothesized that newer GOLD guidelines would frequently lead to a different initial treatment choice. Aims and objectives: To demonstrate the magnitude of difference in recommended initial treatments in COPD patients based on past and recent GOLD revisions. Methods: We retrospectively analyzed 52 patients with first diagnosed stable COPD. Spirometry, COPD Assessment Test and evaluation of exacerbations were done. Patients were allocated to the most appropriate treatment according to GOLD 2006 and 2011 management scheme. Results: According to GOLD 2006 criteria 32 (61.5%), 18 (34.6%) and 2 (3.8%) patients were stage II, III and IV, respectively. Forty (76.9%) patients should be prescribed monotherapy with LABA or ICS/LABA therapy. According to GOLD 2011 6 (11.5%), 19 (36.5%), 2 (3.8%) and 25 (48.1%) patients were Group A, B, C and D, respectively. Thus, 6 (11.5%) patients would not be prescribed long-acting bronchodilators (BD) as initial therapy, 20 (38.5%) patients required monotherapy with long-acting BD and 26 (50.0%) required therapy with ICS/LABA. In accordance with GOLD 2011 treatment scheme, initial therapy was required to be changed in 21 (40.4%) patients (13 (40.6%) stage II and 8 (40.0%) stage III/IV). In 6 (11.5%) cases we had to administer more "light" therapy (with short-acting BD instead of long-acting BD), and 14 (26.9%) patient required more intensive treatment, usually LABA/ICS instead of monotherapy. Conclusions: In significant proportion of COPD patients GOLD 2011 treatment scheme leads to another, generally more intensive, initial treatment.

1650 GOLD assessment of COPD patients: Impact of symptoms assessment choice

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Background: The 2011 GOLD guidelines recommend combined COPD assessment using symptoms (modified Medical Research Council Dyspnoea [mMRC] ≥2 or COPD Assessment Test [CAT] ≥10) combined with a history of exacerbations in the past 12mo (0.1) vs ≥2 and spirometric classification GOLD III vs IIIV. Four groups are identified: A: low symptoms + low risk; B: high symptoms + low risk; C: low symptoms + high risk; D: high symptoms + high risk.

Objectives: Characterize the 4 groups using the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort.

Methods: 2028 COPD patients. FEV1<80%, pred, baseline mMRC, SGRQ and previous 12mo history of exacerbations. SGRQ score ≥25 was used to replace the CAT ≥10, using a validated conversion (Jones: BMCPulmMed 2011).

Results: The 4 groups were comparable on age and gender, but had different characteristics. Size of patient groups classified by mMRC were A: 23%, B: 14%, C: 3%, D: 60%. Compared to the SGRQ, patients classified as "low symptoms" (GOLD A & C) using mMRC had worse health status, more fatigue and lower exercise capacity (6MDW). Categories mMRC ≥2 produced groups of similar size to those classified by GOLD A: 9%, B: 28%, C: 4%, D: 59%. The kappa of agreement for group membership defined by SGRQ and mMRC increased from 0.2 (mMRC ≤1 vs ≥2) to 0.5 (mMRC 0 vs ≥1).

Conclusions: The new assessment permits classification of COPD patients beyond airflow obstruction. GOLD recommends either CAT ≥10 or mMRC ≥2 as the symptomatic cut-point, but this analysis suggests that mMRC ≥1 will classify patients more closely to using the CAT. Clinicaltrials.gov NCT00292552; GSK study SC0104960.
The small differences in classification of patients using CAT or MRC similar health status to those classified by CAT but are not directly equivalent. In influence treatment in only a very small proportion of patients.

Data suggest that CS instillation favors gas diffusion by increasing alveolar surface area, despite a large inhomogeneity in alveolar distension, likely reflecting local differences in surfactant distribution and/or alveolar compliance.

<table>
<thead>
<tr>
<th>Patients</th>
<th>DORQ N (%)</th>
<th>SI-12-PC meanSD</th>
<th>Patients</th>
<th>DORQ N (%)</th>
<th>SI-12-PC meanSD</th>
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<tr>
<td>A40 (20)</td>
<td>36.0±0.9</td>
<td>41.7±0.4</td>
<td>B22 (11)</td>
<td>36.0±0.9</td>
<td>39.7±0.4</td>
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<tr>
<td>B22 (11)</td>
<td>36.0±0.9</td>
<td>39.7±0.4</td>
<td>C12 (5)</td>
<td>41.7±0.4</td>
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<td>C12 (5)</td>
<td>41.7±0.4</td>
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<td>D12 (5)</td>
<td>41.7±0.4</td>
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The mMRC cut-point of identifies a group of low symptom patients who have similar health status to those classified by CAT but are not directly equivalent. The small differences in classification of patients using CAT or MRC ≥1 may influence treatment in only a very small proportion of patients.

204. Modern clinical physiology: imaging structure and evaluating function

1652 In-vivo microscopy of the effect of surfactant on alveolar morphology

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Changes in alveolar morphology induced by intra-tracheal delivery of CUROSurf (CS, Chiesi) were evaluated after opening a pleural window allowing in-vivo microscopic imaging (x300) of sub-pleural alveoli (fig 1a) revealing in physiological, non surfactant deprived conditions, a remarkable degree of geometrical inhomogeneity. Data were collected in 7 male anesthetized, tracheotomized and mechanically ventilated brown Norway rats (fig 1c, closed symbols). No changes in alveolar geometry were observed in animals not receiving CS (open circles).

Surfactant instillation, on average, caused an increase in alveolar area (fig 1b, closed circles), peaking at about 10% after 10 minutes and returning towards baseline after 20 minutes. The large standard deviation reflects the variability in caliper following CS instillation as shown for individual alveoli in one representative animal (fig 1c, closed symbols). No changes in alveolar geometry were observed in animals not receiving CS (open circles).

Conclusions: This is the first comparison of S3v with direct measurements of ventilation heterogeneity confirming the contribution of this parameter to the increase in S3v during bronchoconstriction.

1653 Comparison of changes in the expiratory capnogram waveform and regional ventilation distribution measured by synchrotron imaging during acute bronchoconstriction in brown Norway rat

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Rationale: Although the increase in the phase III slope of the volumetric expiratory capnogram (S3v) is attributed to ventilation heterogeneity in patients, the relation between S3v and direct measurements of ventilation distribution has not been studied.

Methods: Rats divided into 2 groups: ovalbumin-sensitized (OVA) and exposed to air or to NO2, 10 ppm, 6h/d, 5d/wk for 4 weeks underwent K-edge subtraction synchrotron imaging, to measure regional ventilation (sV*), the area of well-ventilation regions (VAA) and ventilation heterogeneity (CV of sV*) at baseline and during intravenous infusion of methacholine (MCH, 15 μg/kg/min (γ)). S3v was computed using a rapid CO2 analyzer.

Results: S3v and CV of sV* increased during MCH infusion and the 2 parameters were correlated (R=0.78, p<0.001).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OVA</th>
<th>MCH/15γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CV of sV* (%)</td>
<td>15.3±5.2</td>
<td>42.6±25.0*</td>
</tr>
<tr>
<td>Baseline VAA (%)</td>
<td>93.8±2.5</td>
<td>66.7±22.1*</td>
</tr>
<tr>
<td>Baseline S3v (mmHg/ml)</td>
<td>2.45±0.07</td>
<td>3.32±0.46</td>
</tr>
<tr>
<td>Baseline MCH15γ</td>
<td>18.2±8.0</td>
<td>49.3±42.4*</td>
</tr>
<tr>
<td>Baseline MCH15γ</td>
<td>90.8±7.7</td>
<td>72.3±25.1*</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline, within a group; # p<0.05 vs. An-OVA, within a condition, by ANOVA.

Conclusions: The increase in the phase III slope of the expiratory capnogram waveform and regional ventilation distribution measured by synchrotron imaging during acute bronchoconstriction in brown Norway rat.
tions can cause the interruption of femoral venous flow (Qfv). The purpose of this study was to determine the values of Pab, airflow, volume and time at which Qfv ceases and restarts within the respiratory cycle time (Ttot).

In 4 healthy subjects (age 45±2.1 yr) lying in semirecumbent position airflow was measured during quiet breathing (QB) by a pneumotachograph. Pab by gastric pressure measurements using catheter-balloon-transducer system and Qfv by an echo-Doppler probe. Qfv contour was extracted from the images recorded by the echo-Doppler. The values of Pab, airflow, volume above FRC (ΔV) and times t1 and t2 at which Qfv stopped and restarted (where femoral venous velocity could no longer be detected and became measurable again) within Ttot were calculated (see figure for a representative case).

t1 and t2 occurred respectively during inspiration and expiration when airflow averaged 0.4±0.04 and -0.39±0.10 L/sec. No significant difference between Pab at t1 (3±1.2±2.3 cmH2O) and t2 (2.8±2.0 cmH2O) was found. ΔV was 0.3±0.6±0.09 at t1 and 0.4±0.1±0.0 L at t2 (p<0.05). The fraction of Ttot in which Qfv was negligible, defined as (t2−t1)/Ttot averaged 0.3±0.07.

These data suggest that diaphragm and Pab variations produced by diaphragm contraction have a profound modulatory within-breadth effect on venous return from the lower limb and this modulation is dependent on Pab dynamics.

1656
Pulmonary edema is frequently triggered by marathon running

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Despite the mounting evidence that pulmonary edema can be triggered by strenuous exercise, (Acta Physiol 2007, 189: 305-17) it is still widely debated (J Appl Physiol 2010, 109: 1276-80). The purpose of this study was therefore to determine if pulmonary edema is triggered by marathon running and, if so, to examine its incidence and severity. Twenty-seven runners completed the 2011 Steamtown Marathon, in Scranton, PA, United States, beginning at an elevation of 452 meters above sea level (8° C, 90% RH) and ending with a net elevation drop of 291 meters at the finish (21°C, 51% RH). All runners finished between 142 and 289 minutes. Posteroanterior (PA) and lateral (LA) radiographs were taken one day before the race, then at 19 (SD 8), 55 (13), and 98 (15) min post-marathon finish, the delay ensuring that any post-exercise increase in capillary blood volume would return to normal. Two experienced chest image readers (EM, MP) independently interpreted the images. They were blinded as to the times at which the images were taken. The PA/LA radiographs were viewed together as a set at each time-point and were scored on eight different radiological characteristics.

When summed together, the scores could range from 0 (no edema) to 32 (severe interstitial edema). Mean edema scores from all subjects increased from 1.5 units pre-exercise to 4.1, 3.7, and 2.8 units at 19, 55, and 98 minutes post-exercise, respectively (p<0.01). Nine runners (33%) had an average increase in the edema score (average of the 19 min post-score minus the average of the pre-score) >7.1 units (5-fold increase), which still remained high at 55 min post-exercise. In conclusion, pulmonary edema is triggered in 33% of marathon finishers.

1657
Regional hyperinflation in COPD patients: Correlation between lobar hyperinflation and internal flow redistribution

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Background: Diagnosis of COPD patients is mainly based on lung function tests. Severe COPD patients often develop dynamic and static hyperinflation. However, few studies have addressed the association of hyperinflation and internal flow redistribution. This study describes the relation between regional hyperinflation and flow distribution in COPD patients.

Methods: Lobar volume levels in COPD patients (n=39). (FEV1)= 42.1±2.1 (n=141) (pried) were determined using functional imaging based on CT data (De Backer J. et al, Radiology 2010; 257(3):854-862). Lobar flow distribution was obtained by calculating the relative difference in the TLC and FRC volumes on the lobar level. The flow distribution towards the different lobes was compared to the imaged based volumes of the corresponding lobes.

Results: Statistically significant correlations (R²= 0.4, p< 0.04) were observed between lobar flow distribution and lobar volume-hyperinflation with more flow going to more hyperinflated areas.

Conclusion: Internal flow is redistributed towards the hyperinflated zones which means that also inhaled medication would mainly go to the hyperinflated areas leaving other areas flow partially untreated and this may further enhance the observed flow redistribution.

1658
Residual lung volume is associated with increased left ventricular mass

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Increased left ventricular (LV) mass and chronic obstructive pulmonary disease (COPD) predict cardiovascular (CV) events, but their relationship is poorly understood. We hypothesized that residual volume would be associated with increased LV mass.

We recruited participants ages 50-79 years with ≥10 pack-year smoking history that were free of clinically apparent CV disease. LV mass was estimated by cardiac magnetic resonance. Body plethysmography and pre- and post-bronchodilator spirometry were performed according to ATS/ERS guidelines. Percent emphysema-like lung was estimated on full-lung CT. Anthropometry, medication use, blood pressure (BP), fasting glucose and lipid levels were measured in a standardized fashion. COPD was defined according to GOLD criteria. Multiple linear regression was used to adjust for age, sex, race/ethnicity, height, weight, body surface area term, smoking status, pack-yers, systolic BP, BP meds, fasting glucose, diabetes meds, low density lipoprotein, lipid lowering meds, and percent emphysema. Of 419 participants completing all study components, 65% had COPD (24% mild, 29% moderate, and 12% severe/very severe). Mean LV mass was 122±34 grams.
Residual lung volume was independently associated with increased LV mass in the fully adjusted model (p < 0.001). The magnitude of association for residual volume was similar on a SD basis to that of systolic BP (8.7 gm/95%CI 4.5–13 gm per 714 ml increase in residual volume versus 6.9 gm/95%CI 3.5–10 gm per 16 mmHg increase in systolic BP, respectively).

Residual volume is associated with increased LV mass. Further understanding of this relationship may improve cardiovascular risk assessment and represent a novel therapeutic target.

1659

Evidence of impaired spontaneous baroreceptor sensitivity in patients with COPD as a potential link to cardiovascular morbidity and mortality

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Objectives: Recent studies suggest reduced cardiac filling pressures in patients with COPD due to hyperinflation. A reduction in cardiac preload may result in unloading of baroreceptors. We thus investigated spontaneous baroreceptor sensitivity, an independent predictor of cardiovascular morbidity and mortality, in patients with COPD and controls.

Methods: 33 patients with severe airflow obstruction but free from clinical cardiovascular disease (age 64±7 yrs, BMI 23±4 kg/m², FEV1 27±7%, TLC 140±19%) and 12 age, gender, and body-weight matched controls without airflow obstruction were studied. Spontaneous baroreceptor activity was measured using the sequence method during resting conditions. The baroreceptor effectiveness index was calculated from the total number of baroreceptor sequences divided by the total number of systolic blood pressure ramps.

Results: The mean slope of spontaneous baroreceptor sequences (7±±4±7 msec/mmHg vs. 13±±5±6 msec/mmHg, p < 0.01) and the baroreceptor effectiveness index (71±±54±9 vs. 103±±34±4, p < 0.05) were significantly lower in patients with COPD than controls. There was a significant inverse relationship between the slope of baroreceptor sensitivity (r = -0.302, p < 0.05) and baroreceptor effectiveness index (r = -0.391, p < 0.01) with RV/TLC ratio. There were no such associations with airflow obstruction.

Conclusions: Our findings indicate a link between hyperinflation and baroreceptor function in patients with COPD.

205. “Snoring and scoring”: subjective and objective measures of sleep-disordered breathing

1660

The Epworth sleepiness score should not be used to screen out patients with suspected sleep-breathing disorders

Sara Neale, Adrian H. Kendrick. Department of Respiratory Medicine, University Hospitals, Bristol, United Kingdom

The Epworth Sleepiness Score (ESS) is used to assess the level of daytime sleepiness as perceived by the patient. In some centres and in primary care, the ESS is used to reduce the number of referrals for suspected sleep-breathing disorders (SBD), where an ESS is within normal range (ESS 0–10), to be a reliable subjective measure of symptom improvement. However, there was poor correlation between ESS & hypersomnolence.

Reference:

1662

Sleep-breathing disorders (SBD) – Sleepiness, fatigue, quality of life (QoL) and depression

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Patients with SBD may present with sleepiness, fatigue, and often cannot separate them. SBD affects QoL and depression may occur.

Aim: To determine sleepiness, fatigue, depression and QoL in relation to the severity of SBD.

Methods: 150 consecutively referred patients had 2 nights of home oximetry (Minolta 300i). Oximetry data was analysed by experienced Physiologists (Down-load 2001, Stowood Scientific,UK) for 4% dips/hr and an Δindex cut-off of ≥0.6. Data is given as median (range). The highest dips/hr and Δindex was used in the analysis from either night.

Results: 130 patients had usable data; 39F and 91M, aged 50 yrs (19-79), ESS - 11.5 (1–23), MFI-20 - 4.8 (0.3-119) and 6.2 (0.1-118), and Δindex - 0.57 (0.2-5.6) and 0.63 (0.2-10.9) on the 2 nights respectively. There was no correlation between ESS and oximetry indices.

Distribution of patients based on Epopwth score:

<table>
<thead>
<tr>
<th>ESS</th>
<th>≤10</th>
<th>11–15</th>
<th>&gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5% 4% dips/hr</td>
<td>25</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>5–18% 4% dips/hr</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>15–30% 4% dips/hr</td>
<td>11</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>&gt;30% 4% dips/hr</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Δindex ≥0.6</td>
<td>20</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Δindex &lt;0.6</td>
<td>34</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

25/130 (19%) had a normal 4% dips/hr and 20/130 (15%) had a normal Δindex in with a normal ESS of ≤10. 27/130 (21%) had a normal 4% dips/hr with an ESS >10.

Conclusion: The ESS, within limitations, is a guide as to whether daytime sleepiness is present. It should not be used to reduce referrals for assessment of suspected SBD, as part of a screening assessment using oximetry and a good clinical history. The reasons why patients have a high ESS in the absence of a significant SBD requires further investigation.

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Clinical audit of the Quebec Sleep Questionnaire in a routine sleep apnoea service

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Introduction: We reviewed 2 years of our obstructive sleep apnoea & hypopnoea syndrome (OSASH) service. The Quebec Sleep Questionnaire (QSQ) was used as a subjective measure of improvement with CPAP. We aimed to see if QSQ reflected symptomatic improvement in treated patients.

Methods: Referrals underwent history & baseline overnight oximetry (Pulsox 300e, Minolta, Japan). If positive for OSASH, they underwent an auto-titration and, if beneficial, a trial of CPAP. Of 783 patients, only 155 completed QSQ before & after the CPAP trial. QSQ includes 5 areas; Q1: hypersomnolence, Q2: diurnal symptoms, Q3: nocturnal symptoms, Q4: emotions, Q5: social interactions. An increased score indicated improved symptoms. We compared objective & subjective improvements with CPAP.

Results: Patients exhibited witnessed apnoeas (68%), snoring (90%), excessive daytime sleepiness (76%) with 56% showing all 3 symptoms. Differences in SpO2 dip rate, Epworth Score (ESS) & QSO pre- & post-CPAP trial are shown in Table 1. Surprisingly, there was poor correlation between hypersomnolence (Q1) & ESS.

QSQ scores (Q1-Q5), Diprate and ESS pre- & post-two week CPAP trial

Q1 Q2 Q3 Q4 Q5 ESS

Diprate >4% EDS SpO2/hr

Baseline 23.9 (10.4) 35.4 (15.1) 24.8 (9.8) 21.1 (7.5) 16.8 (6.7) 31.4 (27.5) 13.1 (5.0)

QSO Pre 10.5 p < 0.05 0.05 p < 0.05 0.05 p < 0.05 0.05 p < 0.05 0.05 p < 0.05

P < 0.05 p < 0.05 p < 0.05 p < 0.05 p < 0.05 p < 0.05

Data is presented as mean (SD) with T-Test comparisons of Baseline to End of Trial.

Conclusion: QSQ correlates with subjective improvements in OSASH & appears to be a reliable subjective measure of symptom improvement. However, there was poor correlation between ESS & hypersomnolence.

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MONDAY, SEPTEMBER 3RD 2012
Conclusions: We observed high levels of fatigue and sleepiness and poor QoL. Patients with mild SBD had high levels of fatigue, depression and sleepiness, whereas patients with moderate SBD had a lower percentage of patients. It is essential to account for fatigue and QoL and to investigate negative studies further.

Screening for obstructive sleep apnoea (OSA) in patients attending a respiratory function laboratory

Aims: Some sleep laboratories use two SpO2 channels to better detect artefact. This study aimed to examine the agreement between two SpO2 monitors used concurrently on the same polysomnography (PSG).

Methods: 117 PSGs were audited for this study. The PSGs included channels from an integrated SpO2 monitor (Nonin) and an external device from another manufacturer (Masimo). The mean SpO2 and the desaturation index (DI) for both oximeters were compared. Comparisons were made using Bland Altman analysis, with limits of agreement (LOA) of 1.96 standard deviations, and confidence intervals (CI) of 95%.

Results: Bland Altman analysis indicated a bias of +1.7% (CI +1.4%, +2.0%), showing a systematic offset towards Masimo. The LOA were -1.2% (CI -1.7%, 0.7%) to 4.5% (CI 4.0%, 5.0%), indicating a variation of ±2.8%. Bland Altman analysis of the DI indicates a -38.5% (CI: -28.0%, -49.1%) smaller DI for the integrated sensor as compared to the external sensor.

Conclusions: When used to assess mean SpO2 there is a variation of ±2.9%, this may not be clinically acceptable. Additionally the external sensors produced systematically higher readings than integrated sensor. Therefore the outcome of an assessment of hypoxia is device dependent, if only one of these devices is used. There is poor agreement between devices with regards to the desaturation index. The integrated sensor detected 38.5% less desaturations compared with the external sensor. This systematic bias suggests that an assessment of sleep disordered breathing is device dependant.

Screening for obstructive sleep apnoea (OSA) in patients attending a hypertension clinic with features of the metabolic syndrome

Aim: To see if OSA is a common finding in patients with Metabolic Syndrome.

Background: Metabolic Syndrome has been described as a constellation of risk factors for cardiovascular disease (CVD). The WHO places the incidence at 21% of the population. OSA syndrome occurs in 2-4% of males and females. Both conditions represent a significant burden to the health service in terms of diagnosis, treatment and management. Volunteers agreed to undergo a home cardiopulmonary sleep study and interview with questionnaires including the Epworth score. Studies were manually scored to determine the Apnoea Hypopnoea Index.

Results: 35 volunteers were recruited. This yielded 32 studies (10 female) that were analysed. Mean age: 50 yrs (Range 26 – 73), mean BMI: 37.5 (±5.8). Significance of OSA (AHI>5) was found in 7 females (80%) and 20 male (88%) subjects, 86% overall.

Summary findings

<table>
<thead>
<tr>
<th>AHI</th>
<th>No. Subjects</th>
<th>Mean AHl (±sd)</th>
<th>Mean Epworth (±sd)</th>
<th>Mean BMI (±sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;5)</td>
<td>6</td>
<td>2.1 (1)</td>
<td>15.6 (6)</td>
<td>40.4 (4)</td>
</tr>
<tr>
<td>Mild (5 to ≤15)</td>
<td>13</td>
<td>10 (3)</td>
<td>4 (3)</td>
<td>35 (5)</td>
</tr>
<tr>
<td>Moderate (15 to ≤30)</td>
<td>5</td>
<td>22.6 (4)</td>
<td>7 (4)</td>
<td>36.7 (6)</td>
</tr>
<tr>
<td>Severe (&gt;30)</td>
<td>8</td>
<td>55 (27)</td>
<td>15 (4)</td>
<td>40 (6)</td>
</tr>
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</table>

Conclusion: OSA is prevalent in this group of patients and was not the primary reason for attendance. Epworth Score alone was a poor predictor of sleep breathing disorder in those with mild to moderate AHI. OSA is a risk factor for CVD and so we suggest that there should be routine screening for OSA in this particular patient group.

Pulse oximetry to assess sleep disordered breathing (SDB)

Aim: To determine the use of pulse oximetry in the assessment of SDB using 4 indices and the value of using 2 nights of assessment

Methods: 50 consecutively referred patients had 2 nights of oximetry at home (Minolta 300i). Data was analysed (Download 2001; Stowood Scientific, UK), by experienced Physiologists and artefact removed. The 4% and 3% dip/hr, cumulative %time at SpO2 < 90% (CT%, Olson et al, J Sleep Res 1999;8:51-55) and Aindex<0.6 (Levy et al, Chest 1996:109;395-99) were obtained for each night.

Results: 132 patients gave usable data, 39F and 93M, aged 50 yrs (19–79).

The median (range) differences between the two nights (N1 – N2) for the group were: 4% dip/hr: -0.78 (-29.5 to 19.9), 3% dip/hr: -1.2 (-15.6 to 20.2), CT%: -0.12 (-21.9 to 29.7) and Aindex: -0.04 (-10.4 to 1.2). Using a combination of these indices, 26/132 (20%) were negative for all 4, 66 (50%) positive for all 4, 10 for any 3, 12 for any 2 and 18 for any one.

Conclusions: To use pulse oximetry

1) requires analysis by experienced practitioners to ensure accuracy of data; 2) requires two nights, resulting in a > 25% increase in a positive diagnosis from the second night; 3) with a combination of the 4 indices, all of which have good sensitivity and specificity for SDB, gives an indication of the likelihood of SDB being present. Using a combination of any 3 or all 4 accounts for 77% of the patients assessed.

Forensic oximetry: Is it possible to confirm that the same patient has worn an oximeter on 2 nights?

Introduction: We suspected a patient had performed home oximetry on their partner as they did not wish to receive treatment or be stopped from driving due to their obstructive sleep apnoea syndrome (OSAHS). We wanted to see if it was possible to recognise a pulse rate “fingerprint” in patients who had performed consecutive sleep studies. We wanted to determine the normal variation in pulse rate (PR) on 2 nights in the same subject. The mean PR or the SD of the PR should be close enough to tell that the same patient is using the device.

Method: We reviewed mean and standard deviation (SD) of the pulse rates recorded during routine overnight oximetry and a multi-channel study in 37 patients [17F:20M Mean (SD); Age 50.8 (13.9) yrs] with suspected OSAHS. 16.4 (8.4) >4 dips per hour 37% of patients had confirmed OSAHS.

Results: The results (Table 1) show that mean difference in heart rate was 3.5 bpm (±1.7) and that statistically there was no little difference between the 2 nights. However, analysis by Bland & Altman (Fig 1) shows that the variation in pulse rate was 9-12%.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Night 1</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>Mean PR</td>
</tr>
<tr>
<td>SD PR</td>
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<td>COV % PR</td>
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</table>

*Values shown as Mean (SD). No significant difference were found between Nights 1 & 2.

Discussion: The variation in pulse rate between any two oximetry studies is on average 10% or between ±7 bpm difference in the mean PR. However, 3 out of 37 patients had greater variation than this.

Conclusion: It is not possible on an individual basis to confirm if the same patient has performed an oximetry study. We have shown the expected normal range in PR for the same patient.

Cheest wall mechanics during induction of anesthesia

Background: It has been reported that anesthesia may be associated to variation in chest wall (CW) mechanics. We have developed a CW scanning system (CWS) based on self-mixing laser interferometers that allows the measurement of relative displacement. If this approach is combined with Forced Oscillation Technique (FOT) it allows to infer CW mechanics.

Methods: Five patients were studied during anesthesia induction at different stages, while they were submitted to a sinusoidal pressure forcing at the mouth with components at 5, 11 and 19 Hz. At each step FRC (GE, Engstrom CareStation) and CW mechanics (phase displacement among these points and the pressure stimulus) were estimated by spectral technique.

Results: Figure 1 shows results at 11 Hz. At all steps rib cage and abdomen the pressure stimulus travels faster in the rib cage than in the abdomen, likely because of the high inert of the latter. FRC presents a minimum during sedation, then it increased during pressure support and it reaches physiological values after the inhalation of sevoflurane.

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in the vastus lateralis of seventeen COPD patients, ten with low fat free mass index (FFMI, COPD1) (FEV1, 33±4.3%pred, FFMI 15±0.2 kg m⁻²), seven with preserved FFMI (COPD2) (FEV1, 47±7.3%pred, FFMI 19±0.6 kg m⁻²) and compared with nine age and gender-matched healthy sedentary subjects (C) (FEV1, 96±4.0%pred, FFMI 20±0.9 kg m⁻²). Mitochondrial density was reduced in COPD1 in comparison to COPD2 (1.8±2.0±0.5% and 2.7±2.4±0.4% respectively, p<0.05). In comparison to C, only COPD1 showed a reduction in mitochondrial mean linear diameter (0.15±0.0μm and 0.13±0.0 μm respectively, p<0.05) reflecting a reduction in mitochondrial size.

Mitochondrial density correlated with parameters of lung function, muscle function, exercise capacity and exacerbation frequency. Only exacerbations frequency remained independently related to mitochondrial density in a multiple regression analysis.

We conclude that peripheral muscle of COPD1 patients have a reduced mitochondrial density that is likely to contribute to a decreased oxidative capacity of the muscle.

Supported by Chief Scientist Office (CSO) Scotland 06/110/05 and The British Lung Foundation (Trevor Clay, Te0709). SG was supported by an ERS long term research fellowship.

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Blunted muscle angiogenic response after exercise training in COPD patients

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In chronic obstructive pulmonary disease (COPD) patients, the skeletal muscle impairment reduces the exercise capacity. Systemic factors (i.e. oxidative stress, low grade inflammation ...) have been incriminated. Then, as for the muscle oxidative fibers, the muscle angiogenic-adaptive response to training could also be blunted in COPD, like in other chronic conditions. Therefore, we aim to characterise the muscle functional response, myofiber remodeling and angi-adaptations to training in COPD patients and sedentary healthy subjects (SHS). 21 COPD patients and 23 SHS completed a 6-week rehabilitation program based on individualized moderate-intensity endurance and resistance training. Histomorphological muscle analysis and measurements of pro-angiogenic vascular endothelial factor-A (VEGF-A) and antiangiogenic thrombospondin-1 (TSP-1) were conducted before and after training.

Both COPD patients and SHS improved their peak oxygen consumption (respectively, +0.96±2.4 and +2.9±2.6 ml/kg/min, p<0.001) and muscle endurance (respectively, +6.5% and +10.8%, p<0.001), although improvements were lower in COPD patients (group-time interaction: p<0.05 and p=0.06 respectively). Whereas the capillary-to-fiber ratio (C/F) and the angiogenic-adaptive VEGF-A/TSP-1 ratio increased in COPD patients and SHS (C/F: p<0.01, VEGF-A/TSP-1: p<0.05), the improvement in C/F was significantly reduced in COPD patients vs. SHS (p<0.05), and no fiber type switch occurred in patients. Absolute changes in C/F and in VO_2max were correlated (r=0.51, p<0.05). The angiogenic response may have driven the functional improvements. In addition to a lack of fiber switch, the angiogenic response to training was blunted in COPD patients.

1671
Effects of a 3-week inpatient pulmonary rehabilitation (PR) on muscle remodelling in patients with emphysema

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Rationale: Exercise training of at least 10 weeks duration induces significant changes in myofiber size, capillarization and distribution in patients with emphysema. Up to date it is unknown which changes in muscle structure can be achieved by a German inpatient PR with a standard duration of 3 weeks.

Methods: Ten patients with emphysema (age: 57±5y; BMI: 24±3kg/m²; FEV1: 31±9%pred.) were included in this prospective trial. All patients performed an incremental cycle test to determine the peak work rate (PWR). The PR included daily supervised exercise training sessions (strength- and endurance training). Pre and post PR, biopsies from vastus lateralis muscle were taken.

Results: PWR improved significantly during PR (+17%M [95% CI, 6.3 to 22.7]% p<0.01). We observed a significant increase in the capillary to fibre ratio in fibre types I and IIa respectively (+0.5% [95% CI, 0.1 to 1.0]% p=0.03; +1.0% [95% CI, 0.6 to 1.4]% p<0.01) in skeletal muscle. We found a significant negative correlation between FEV1 pred. and the change in capillary to fibre I ratio (r=-0.633, p<0.05).
A non-significant but notable increase in the quantity of fibre type I (+6.5%), IIa (+2.2%) and IIx (+2.6%) was detected. Hybrid fibres decreased during PR (type IIa: -1.3% [95% CI. -2.21 to -0.39] p<0.01, type IIx: -5.2%, p<0.09).

**Conclusions:** These preliminary data show that an inpatient 3-week PR is able to exert relevant adaptations in peripheral muscle of COPD patients. This includes an increase in capillarization and an augmented type I myofiber distribution. To confirm these first results, further patients will be investigated.

### 1672 Changes in fatigue index during an 8 week quadriceps resistance training programme for patients with COPD & healthy controls

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**Introduction:** Fatigue index (FI) measures the reduction in muscle force during muscle testing/training & can be altered by resistance training (RT). FI is seldom reported in patients with COPD. In isokinetic testing 2 variables are of interest: peak torque (PT) & total work (TWor).

**Aims:** To evaluate changes in FI for PT & TWor during 3-weeks of RT in patients & healthy controls.

**Methods:** 70 patients (mean ± SD age 68.6 [9.1]yr, FEV₁:44.8[15.2%] pt, 42 men & 22 controls [age 66.6 [5.1]yr, FEV₁:103.4[15.9%] pt, 12 men] completed quadriceps RT for 8weeks. RT was 5x30 knee extensions; 3times/week on a cybex dynamometer (speed=180°/sec). PT (Newton-metres:Nm) & TWor (Joules:J) were recorded for each set & FI was calculated as: set5/set1x100 for the right leg (weekly average). A high FI:less fatigue.

**Results:** There were no significant differences between/within-groups for PT FI over 8 weeks (FI approx 90% in both groups for all weeks). TWor FI in the COPD group did not significantly change over 8weeks. Control subjects displayed improvements in TWor FI & the difference in FI at week8 was significant compared to baseline & week4. However there were no significant differences between the 2 groups for TWor FI (Fig. 1).

**Figure 1**

**Conclusions:** Healthy controls experienced less fatigue in TWor as RT progressed. This did not occur in the COPD group & may be related to muscle dysfunction. TWor seems a more sensitive measure than PT.

### 1673 Effects of home-based pulmonary rehabilitation on the time spent in active- and passive-walking in elderly patients with COPD

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**Purpose:** The objective of this study was to evaluate the effect of home-based pulmonary rehabilitation (PR) including a chair-walking exercise and lower muscle training on daily active- and passive-walking time in elderly patients with COPD.

**Methods:** We assessed walking time according to the walking speed using a newly developed triaxial accelerometer (A-MES activity monitor, Kumamoto, Japan), which could measure the time spent in walking, standing, sitting and lying separately and also could discriminate active walking (>2 km/hour) from passive walking (<2 km/hour). Twenty elderly patients with COPD (Age:76±7 years; FEV₁:56±18.7% pred) were evaluated using this activity monitor for 3 consecutive days before and after PR. The home-based PR program included a chair-walking exercise, lower muscle training, stretching of body trunk, respiratory muscle training and education of self management. Pulmonary function, exercise capacity (6-min walking distance; 6MWD), quadriceps muscle force (QF), and health-related QOL (CRQ) were evaluated before and after PR.

**Results:** Active-walking time increased (pre PR: 27±23 vs. post PR: 52±31 min/day) and lying time decreased (pre PR: 53±18 vs. post PR: 36±18 min/day) significantly after PR. Frequency of standing increased (pre PR: 8±42 vs post PR: 117±63 times/day) significantly after PR. The degree of improvement of active-walking time after PR correlated with 6MWD and QF.

**Conclusions:** These data suggested that home-based PR consisting of a chair-walking exercise and lower muscle training was effective in improving active-walking time in elderly patients with COPD.

### 1674 The effect of post operative physical training on activity after curative surgery for non small cell lung cancer (NSCLC) – RCT

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**Background:** In England and Wales the incidence of lung cancer is around 0.05%, with surgery the preferred curative intent. Strategies addressing quality of life (QoL) and activity post op are lacking.

**Aims and objectives:** To evaluate the effect of in-patient, cycle training, provided post op for NSCLC on physical activity at 4 weeks post op.

**Methods:** This RCT recruited patients undergoing curative lung resection. The control group received usual care. The active group additionally received daily cycle training a home walking programme with diary. Outcomes, measured pre, 5 days and 4 weeks post op, activity monitor data, muscle strength, exercise tolerance and QoL, (SF36). ANCOVA was used to test for differences between groups.

**Results:** 131 patients (72 female), mean age 67.5 (SD: 10.97) years, FEV₁ 2.4 (1.13) l, median ISWT to 290 [IQR: 190-440] were randomised. 63 (48%) had evidence of spirometric obstruction (OB). Physical activity was not significantly different between groups nor in those with OB. There were no significant differences in any secondary outcomes for the groups as a whole. However, in those with OB, physical and mental component scores for the SF36 were 11.7 (p = 0.04) and 19.6 (p=0.01) higher in the active group compared to controls at 4 weeks post op and muscle strength was significantly different between groups in favour of active (p = 0.04).

**Conclusions:** Compared with a control group, a cycle and home walking programme prevented decline in QoL and quadriceps muscle strength seen at 4 weeks post op in people with OB. These data support the need for further exercise interventions aimed at patients with OB undergoing surgery for NSCLC.

### 1675 Atherosclerosis in subjects with COPD is independently determined by the degree of airflow limitation

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**Background:** Subjects with COPD have an increased cardiovascular risk that may be related to shared risk factors. To date, it is not clear whether this is a consequence of the severity of COPD itself.

**Objective:** We aimed to determine independent predictors of the presence of atherosclerosis in patients with COPD and establish whether and to what extent the degree of airflow obstruction is independently predictive for the degree of atherosclerosis in a model including all traditional cardiovascular risk factors.

**Method:** Pulmonary function, blood gases, packyears, body composition (BMI, FMFM), lipids, glucose, hsCRP, renal function (eGFR) and blood pressure were determined in 197 patients (mean±SD: age: 64±7 year, 60% male, FEV₁:51±17% pred., BMI: 26.2±5.2 kg/m²) with stable COPD prior to pulmonary rehabilitation. Carotid-wall intima-media thickness (c-IMT) was assessed in all patients (mean±SD: 0.93±0.18 mm) as an ultrasonographic surrogate measure of atherosclerosis. Independent predictors of an increased c-IMT were assessed using multivariate backward linear regression.

**Results:**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>0.450</td>
<td>6.830</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.237</td>
<td>3.886</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>-0.174</td>
<td>-2.865</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>0.142</td>
<td>2.330</td>
<td>0.021</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.143</td>
<td>2.262</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Other variables included in the model: Gender, BMI, packyears, c-IMT, age, FEV₁, eGFR.
207. COPD: risk factors, biomarkers and diagnosis

1676 
Respiratory health at the extremes of the ageing population: Initial results of the UK Newcastle 85+ study
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People aged 85+ years are demographically the fastest growing age group worldwide, increasing the burden on healthcare resources. In the Newcastle 85+ study subjects born in 1921, recruited from the Newcastle area, underwent domiciliary health assessment, including respiratory history, symptoms, spirometry and review of general practitioner (GP) records for pre-existing disease. 319 (Male: 52%, Female: 48%) took part, regardless of current health status.

Significant occupational exposure to heavy industry was reported by 42% men and 11% women. 31% men and 52% women were current or ex-regular smokers. Review of GP records showed 18% men and 16% women had a diagnosis of Chronic Obstructive Pulmonary Disease (COPD); 7% men and 13% women a diagnosis of Asthma; and 10% men and 7% women had other primary respiratory diagnoses. 92% performed reproducible spirometry. 28% males had normal spirometry, 13% restrictive and 59% obstructive spirometry (Mild 36%; Moderate 46%; Severe 15% and very severe 3%). In the females, 33% had normal spirometry, 16% restrictive and 51% obstructive spirometry (Mild 44%; Moderate 43%; Severe 11% and very severe 2%). The MRC Dyspnoea score was ≥2 in 38% men and 40% women. This study presents data on a large population of very elderly people. It shows a high prevalence of diagnosed airways diseases with 25% men and 29% women having asthma or COPD. Obstructive spirometry was reported in 59% men and 50% women with significant disability shown by MRC-dyspnoea score. These initial results suggest that respiratory compromise could have a significant impact on health care services in the coming years.

1677 
Passive smoking and COPD – More dangerous than believed
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Background: Passive smoking has been identified as a risk factor for cardiovascular diseases, asthma, lung cancer and with detrimental effects on lung function, but the relationship between passive smoking and COPD is not fully established.

Aim: To study environmental tobacco smoke (ETS) as a risk factor for COPD in never-smokers.

Methods: Data from three cross-sectional studies from the Swedish OLIN database were pooled. Only never-smokers were included in the analyses, and 2118 never-smokers had completed structured interviews and lung function tests of acceptable quality. COPD was defined according to the GOLD criteria. Risk analysis was performed by using multiple logistic regression analysis.

Results: Exposure to ETS at home was associated with COPD (OR 1.5, 95% CI 1.0-2.2). ETS at current or past workplace was also associated with COPD. The relationship was more pronounced in subjects who reported exposure to ETS at both past and current workplace (OR 2.4, 95% CI 1.5-4.0). Current exposure to ETS at home in combination with ETS at both current and previous workplace was strongly related to COPD (OR 3.6, 95% CI 1.6-8.5). There was a strong relationship between increasing amount of exposure to ETS in various settings and the prevalence of COPD, especially among women. Interestingly, of the 14 women aged ≥65 years who had reported current exposure to ETS at home and at both previous and current workplace, 7 had COPD.

Conclusion: ETS was found to be an independent risk factor for COPD. This relationship was stronger in women and the association was stronger with increasing degree of exposure.

Rationale: Smoking is the strongest COPD risk factor, however it has been recognised that a substantial proportion of COPD cases arises in non-smokers. Many studies suggest that obesity is more prevalent in patients with COPD, but it has not been elucidated whether this is also true for never-smokers. Aim of the current study was to assess the effect of change in BMI on incidence and persistence of COPD in never smoking women.

Methods: The current study used pooled data from the population based SAPAL-Dina and SALIA cohorts. Weight status was defined based on BMI at baseline and change in BMI. Pre-bronchodilator ratio of forced expiratory volume in one second over forced vital capacity (FEVI/FVC) was measured in both studies at baseline and follow-up. COPD was diagnosed according to the GOLD criteria or having FEVI/FVC<70% of normal limit of normal and percent predicted FEVI<80%.

Mixed regression models with random intercept for study area were used to assess the association between BMI change and COPD prevalence and incidence in non smoking women after adjustment for selected confounders.

Results: Lung function data and information on potential confounders were available in 962 women. The majority of women were never smokers (62.5%). The average BMI between baseline and follow-up ranged between 15.48-5.38 kg/m². The incidence of COPD according to the GOLD criteria stage 1 was 3.2% and the incidence in the combined stage 2 and higher was 2.52%. The odds of developing COPD in stage 2 increased by a factor of 1.1 for each unit increment in BMI. Menopausal status did not influence this association.

Conclusion: The results of our analysis suggest that a change in BMI influences the development of COPD in never-smoking women.

1679 
COPD – Prevalence and risk study from rural north India
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Background: The increasing impact of Chronic Obstructive Pulmonary Disease (COPD) on health care resources is now being recognised as a major public health problem and is projected to be the third leading cause of death worldwide by 2020.

Aims and objectives: To estimate the prevalence and assess the risk factors for COPD in adults using spirometry (GOLD criteria).

Methods: A community-based, cross-sectional, multiphasic survey was conducted on 2112 adults, age ≥35 years. COPD was diagnosed using fixed ratio post bronchodilator FEV1/FVC<70% on spirometric evaluation conducted on participants who screened positive using clinical (by validated respiratory questionnaire) or PEF criteria.

Results: The overall prevalence of COPD was 8% (10.8% in males and 5.1% in females). The prevalence of COPD was 15.3% in the ever smokers and were at 3.54 times higher risk (95% CI 2.6-4.9) compared to non smokers. The exposure to high risk occupation showed an increased risk for development of COPD [OR 3.983, 95% CI 2.8-5.5] than the non exposed individuals. Among females, the prevalence was highest for the heavy kitchen smoke exposure (8.2%). On logistic regression the factors related with COPD were age >65 years [OR 1.079-95% CI 0.641-1.095], exposure to high risk occupation [OR 2.395 95% CI 1.485-3.861] and smoking [OR 2.263 95% CI 1.467-3.492]. Other factors as exposure to passive tobacco smoke, education, socio-economic status did play a role independently, however no significant higher risk was observed using multivariate statistical model.

Conclusion: Ageing, smoking, occupation and biomass smoke exposure certainly explain the web of causation on the background of other risk factors as passive smoking, education and socioeconomic status.

1680 
Association between serum levels of clara cell secretory protein and lung function in adults from ECRHS
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The 16-kD Clara cell secretory protein (CC16) has anti-inflammatory properties and protective effects from oxidative stress on the respiratory tract and has been

Conclusion: In addition to traditional cardiovascular risk factors, such as obesity, older age, higher blood pressure and higher fasting triglycerides, atherosclerosis (c-IMT) is independently predicted by increasing airflow limitation in patients with COPD.
proposed as a biological marker of pulmonary health. Whether CC16 is associated with lung function and airflow limitation in the general population remains proposed as a biological marker of pulmonary health. Whether CC16 is associated with lung function and airflow limitation in the general population remains unclear.

We used data from the population-based Austrian BOLD study. Parameters (FEV1% and FVC% predicted and FEV1/FVC), airflow limitation (AL) defined by GOLD criteria (FEV1/FVC <0.70) were considered. All the analyses were adjusted for center, sex, age, smoking, pack-years, body mass index (BMI), and height. Mean CC16 level was 5.8 (sd=2.9), ranging from 0.4 to 19 g/l. CC16 <5 g/l was associated with lower lung function and moderate/severe airflow limitation in the general population.

This association was stronger in asthmatics (2.6% increase (95% CI 0.6-4.5) in FEV1/FVC) as compared to non-asthmatics (0.6% CI 0.1-1.0) (p for interaction 0.01). CC16 levels were lower in subjects with moderate/severe AL (4.1 μg/l) compared to multifactorial multivariate regression=0.04), but not in those with mild AL (5.7 μg/l, p=0.3) compared to subjects with no AL (5.9 μg/l). This study shows that reduced CC16 levels are associated with lower lung function and moderate/severe airflow limitation in the general population.

Funded by Spanish FIS ISCIII PS09/01354 and ERS fellowship 123-2011.

**1681 Screening of citizens with suspicion of COPD in eight municipalities in Denmark**

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**Background:** Around 430,000 Danes suffer from chronic obstructive pulmonary disease (COPD) with one-third diagnosed today. Danish National Board of Health (NBH) recommends early detection of COPD, focusing on smokers/ex-smokers (or high-risk occupation) above 35 years with ≥ 1 respiratory symptom. Municipalities have been suggested to be responsible for early detection. A pilot study found early detection in municipalities to be feasible and reliable in terms of citizens ending up with the final diagnosis of COPD at their GP.

**Aim and objective:** To investigate the success of screening for COPD in eight Danish municipalities.

**Methods:** Eight municipalities (430,000 inhabitants) offered spirometry to citizens (self-referral) with no previous COPD diagnosis fulfilling the NBH criteria. Citizens with airway obstruction (fixed ratio: FEV1/FVC <0.70) were requested to visit their GP for diagnosis. Data, including spirometry and smoking habits, were recorded in a secure database.

**Results:** 950 citizens in the risk group of COPD were included (55% females, 58 years, 45% smokers, 30 pack-years, 1-2 lung symptoms, MRC 1.6). Of the sample 34% (323) (22-44% in different municipalities) had indication of airway obstruction. Screening spirometry suggested 86% had mild to moderate COPD. With evidence from the pilot study: 85% detected by municipality screening end up diagnosed with COPD at their GP. This suggests that 29% (275) of the patients in the present sample were COPD patients. After screening 65% of smokers were interested in quitting smoking.

**Conclusions:** Early detection of COPD at the municipality level seems to be worthwhile and successful. Together with the GP-level this might identify undiagnosed COPD patients.

**1682 Is spirometry properly used to diagnose COPD? Results from the population-based BOLD study in Salzburg, Austria**

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**Background & objective:** Current guidelines recommend post-bronchodilator spirometry to confirm a diagnosis of COPD. We investigated whether a self-reported diagnosis of COPD was associated with prior spirometry and, whether a correct diagnosis of COPD was made reliably when spirometry was reported.

**Methods:** We used data from the population-based Austrian BOLD study. Participants were aged >40 years, and completed the BOLD questionnaire and post-bronchodilator spirometry.

Reported COPD diagnosis and reported prior lung function test were based on the BOLD questionnaire. Non-reversible airways obstruction (AO) was defined as post-bronchodilator FEV1/FVC <0.7. A correct diagnosis of COPD was defined, when subjects reported a prior COPD diagnosis and demonstrated non-reversible airways obstruction on post-bronchodilator spirometry.

**Results:** 68 (5.4%) of 1258 participants reported a prior physician’s diagnosis of COPD. Among those only 25.0% (1768) reported a lung function test within the past 12 months, and 67.6% (46/68) at any time in the past. The likelihood for a correct COPD GOLD stage I+ diagnosis was similar among subjects reporting (likelihood ratio 2.07 [95% CI, 0.89 – 5.00 CI]) and subjects not reporting (likelihood ratio 2.78 [95% CI, 1.58 – 4.87]) a lung function during the last 12 months. Similar likelihood ratios were seen when GOLD stage II+ was investigated and, when lung function was reported at any time in the past.

**Conclusion:** One third of subjects with a reported diagnosis of COPD never had a lung function test. When spirometry was reported, this did not increase the likelihood for a correct COPD diagnosis.

**1683 Inhaled corticosteroids and the risk of pneumonia in Medicare patients with COPD**

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**Background:** A growing number of studies have found a positive association between the use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) and the risk of pneumonia.

**Objective:** To determine the relationship between ICS use and risk of pneumonia among Medicare patients with COPD.

**Methods:** We performed a nested case control analysis to study the relationship between ICS use and risk of pneumonia in a cohort of Medicare Advantage members with COPD. We designated a case to be a member’s first inpatient or outpatient episode of pneumonia. Cases were matched to controls of the same age and sex who entered the COPD cohort at the same time but had not yet contracted pneumonia by the case’s event date. We estimated the association between ICS use and pneumonia using logistic regression analysis. Adjusted models controlled for age, sex, race, use of other COPD medication classes, markers of COPD severity, receipt of the pneumococcal vaccine, and comorbidities.

**Results:** Out of a COPD cohort of 83,455 members, we identified 13,778 episodes of pneumonia, which were matched to 36,767 controls. Adjusting for covariates, we found that having used any ICS during the past year is associated with an increased risk of a pneumonia episode (OR 1.16, 95% CI: 1.14-1.18). In alternative specifications, we found the risk of pneumonia is highest for current ICS users (OR 1.26, 95% CI: 1.16-1.36) and current high-dose users (OR 1.55, 95% CI: 1.25-1.92), compared to non-users.

**Conclusion:** Our study confirms the finding of previous studies that ICS use – especially current use and high-dose use – is associated with increased risk of pneumonia.

**208. Novelties in clinical management of thoracic diseases: from diaphragm paralysis to pleura**

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Diaphragm paralysis may cause symptomatic respiratory disturbances, and often occurs as a result of iatrogenic or traumatic phrenic nerve injury. Treatment options have been limited to placement of the diaphragm, however it is likely that most patients receive no therapeutic intervention regardless of the severity of symptoms. Although nerve transplantation is efficacious for various peripheral nerve injuries, it has only begun to be established for analogous conditions involving the phrenic nerve. Thirty consecutive patients presenting with chronic, symptomatic phrenic nerve injuries following surgery, traumatic manipulation, trauma or anesthetic blocks were screened for eligibility. Interventional evaluation, including radiographic and electrophysiologic assessments. Inclusion criteria consisted of patients who failed to improve.
during six months of conservative management, in whom a clear etiology for phrenic nerve injury could be elicited and confirmed with pre-operative evaluation. Measures of post-operative improvement included: pulmonary function testing, chest fluoroscopy, and a standardized quality-of-life survey.

Reversal of diaphragm paralysis was clearly demonstrated in 77% of patients (2/3) following nerve transplantation. In four patients (13%) there was no clinical or radiographic evidence of diaphragm function after 18 months, whereas in the remaining three patients (10%) it was too early to determine if surgical intervention was successful. There were no pulmonary or cardiac complications.

Nerve transplantation may reverse phrenic nerve injury and should be considered as an effective treatment option in the management of symmetric diaphragm paralysis.

Conclusion: The data suggest that NF eliminated significant acid liquid reflux. An abnormal airway pH with a mean Ryan score of 175.28 (range 17.5-573.46) of 3.47 (range 0.5-11.7), normal of 15 (68%) of these patients had an abnormal airway pH study with a mean upright normal of 39 (range 25-66), normal of 14.72. Out of the 7 with normal DeMeester 5 had substituted the study population. All of these patients continued to have troublesome cough in impaction of gaseous reflux in the pharynx and upper airways rather than acid reflux.

Proadrenomedullin improves the prognostic property of the BODE index. We prospectively evaluated 638 patients with stable COPD for improvement in COPD. We hypothesize that systemic biomarkers might additionally improve categorization and outcome prediction in COPD. There were 63 deaths among the 638 patients (9.9%). 32 (51%) of the deaths were attributed mainly to COPD. Patients with higher proadrenomedullin (p < 0.0001 both) were significantly associated with 2 year survival. The C-index for the prediction of mortality in COPD was 0.72 (0.68-0.76, p = 0.001). The addition of proadrenomedullin to the BODE index improved its performance significantly (C-index 0.743, p = 0.00020). In combination with proadrenomedullin, the BMI (B), the degree of airflow obstruction (O) and dyspnea (D) domains by itself (e.g. without exercise capacity) performed similarly to the BODE index (C-index 0.772).

Conclusion: Proadrenomedullin improves the performance of the BODE index at predicting the risk of death from any cause among patients with COPD.

1687 Is the bacterium T. whipplei cause of the disease in a subgroup of patients with presumed sarcoidosis?

Aim: To assess pharyngeal gaseous pH in patients who failed to respond to NF, a recognised treatment option for patients who fail medical treatment. Unfortunately some patients continue to be symptomatic even after NF.

Methods: Retrospective case review of 22 patients who remained symptomatic post NF at Castle Hill Hospital, UK. All subjects had pre-NF oesophageal manometry, a 24 hour ambulatory PH monitoring and a post-NF airway pH measurement, using Restech DP-H pH measurement system. Some of these patients continued to have troublesome cough evidenced by a high pH Cough Hypersensitivity Score with a mean score of 28 (range 25-46), normal < 12.

Results: Total of 22 patients (18 female) with a mean age of 44±18.72 years, underwent a subtotal paraesophageal hysterection and a normal Ryan score of 145 (range 17.2-573.46), normal < 9.41. All of the 7 patients who had 24 hour oesophageal pH monitoring had a normal DeMeester score with a mean of 3.47 (range 0.5-11.7). Out of the 7 patients with a normal DeMeester score 5 had an abnormal airway pH with a mean Ryan score of 175.28s (range 17.5-573.46).

Conclusion: The data suggest that NF eliminated significant acid liquid reflux. A significant proportion of patients continued to have airway gaseous reflux as evidenced by a positive Ryan score. This implies that the aetiology of chronic cough lies in impaction of gaseous reflux in the pharynx and upper airways rather than acid reflux detected on conventional testing.

1688 Sarcoidosis relapses in corticosteroid treated patients

Assessing the frequency of relapses and the disease characteristics associated with relapses in corticosteroid treated sarcoidosis patients.

Aim: Assessing the frequency of relapses and the disease characteristics associated with relapses in corticosteroid treated sarcoidosis patients. Sarcoid relapses were defined as 125 patients with biopsy-proven sarcoidosis treated with corticosteroids for 6-18 months after diagnosis were evaluated. Number and type of relapses were noted during the follow-up period. The clinical and laboratory parameters were compared in patients with a relapse of the disease versus (vs) patients without relapses.

Results: 38 patients (30%) had a sarcoid relapse, 2-4 months after the treatment stop (mean interval 11±6.13 months). The manifestations were clinical in 36 patients (similar symptoms as at diagnosis), radiological in 34 and functional in 26 (decreased diffusion capacity in 22 patients, pulmonary volumes in 13 and flows in 15). The relapses were seen in 7 patients with complete remission after the first treatment, 30 with partial remission and 1 with stationary evolution. The patients with relapses had more frequent interstitial lung disease at diagnosis compared to patients without relapses (88 vs 59%, p = 0.007), more frequent duration <1 year of the first treatment (42 vs 10%, p = 0.007), more severe diffusion capacity impairment (26 vs 10%, p = 0.044) or absence of complete remission after the first treatment (81 vs 45%, p = 0.003). No other significant differences were seen in clinical or laboratory parameters.

Conclusions: Almost one third of the sarcoidosis patients in which corticosteroid treatment was necessary at diagnosis had a disease relapse during the follow-up period. Disease severity at diagnosis or at the end of the first corticosteroid treatment and the short duration of the treatment were associated with the occurrence of a relapse.
1689
Occurrence of hypersensitivity to beryllium among patients with diagnosed sarcoidosis. Initial results
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Introduction: Sarcoidosis is a form of interstitial lung disease of unknown cause. In this disease the formations of granulomas are diagnosed also among individuals with berylliosis – an occupational disease clinically similar to sarcoidosis, but associated with hypersensitivity to beryllium.

Aim of study: Our objective is to determine the frequency of hypersensitivity to beryllium in individuals with diagnosed sarcoidosis and to attempt to work out diagnostic methods of berylliosis.

Methodology: Individuals selected for the research were diagnosed with sarcoidosis. All individuals were screened using a modified beryllium lymphocyte proliferation test (BeLPT). The method involved isolating blood lymphocytes, staining them with fluorescent marker (CFSE) and exposing them to beryllium sulfate (of various concentration) or mitogen (positive control). The number of dividing cells (CFSE dilution) was marked after 5 days of incubation with flow cytometry. Individuals suspected of positive proliferation test result and those suspected of the risk for beryllium compounds exposure will be examined by patch tests with beryllium sulfate.

Results: 30 individuals with sarcoidosis have been tested. 5 of them (14.3%) exhibited increased lymphocyte proliferation index.

Conclusions: The study attempts to present a new diagnostic method of identifying hypersensitivity to beryllium. Presently, neither reliable in vitro tests for berylliosis have been standardised nor routinely carried out. Our method requires validation against patients with berylliosis, testing the method in control group and comparison of BeLPT-CFSE methods with a standard thymidine test.

1690
Pentraxin-3: A novel biomarker for the differentiation of parapneumonic effusion and malignant pleural effusion
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Pentraxin-3 (PTX-3) is a new marker of inflammation. Pentraxins like C-reactive protein are key components of the innate immune system. Diagnostic value of PTX-3 in parapneumonic pleural effusion (PPPE) and malignant pleural effusion (MPE) has not been examined before.

The concentrations of pleural fluid PTX-3 were measured in a total of 61 patients: 20 with PPPE and 41 with MPE. A diagnosis PPPE was based upon the presence of an effusion in patients with clinical and radiological evidence of acute pneumonia. A malignant pleural effusion (PE) was defined by pleural biopsy or the presence of malignant cells on PE cytology. The area under the curve (AUC) quantified the overall diagnostic accuracy of the tests.

The study demonstrated that PTX-3 concentration was higher in pleural fluid of PPPE patients compared with MPE patients (31.8 ng/mL vs 6.9 ng/mL, respectively, p<0.001). Pleural effusion PTX-3 for PPPE at the cut-off concentration of 8.5 ng/mL was 80% and 64%, respectively.

Measuring PTX-3 concentrations in pleural fluid may be helpful in distinguishing pleural effusion due to a PPPE or MPE aetiology.

209. Pulmonary circulation and functional lung imaging

P1692
Simultaneous imaging of lung structure and function with triple nuclear MRI
J. M. Wild1, Helen Marshall2, Graham Norquay1, Peggy Xu1, Juan Parra-Robles3, 1Academic Radiology, University of Sheffield, United Kingdom

Rationale: In this work, we re-engineer a standard clinical MRI scanner to allow spatially registered human lung imaging from three different nuclei simultaneously with 1H anatomical images and hyperpolarized 3He and 129Xe lung ventilation images.

Methods: This is achieved by the use of geometrically nested, decoupled radio-frequency (RF) coil hardware resonating at the respective resonant frequencies. Multi-nuclear RF transmission and reception is achieved by rapid switching (<10 ms) between the signals from the respective nuclei. The technique is demonstrated with simultaneous imaging of 3He, 129Xe and 1H in the lungs of healthy normal’s following an inhalation of a 1 litre bag of gas containing 300 ml of 3He and 400 ml of 1H.

Main results: See Fig. 1. Images of 1H, 3He (red), and 129Xe (blue) acquired from a healthy volunteer in the same breath containing 300 ml of 129Xe and 300 ml of 3He; the anatomical 1H image shows excellent spatial registration with the 3He and 129Xe ventilation images as demonstrated by the overlaid fused image (purple).

Figure 1

Conclusions: The precise temporal and spatial registration of these images is impossible to achieve in separate breath-hold scans. This new system opens up the possibility of simultaneous capture of regional lung function by exploiting the different properties of 3He and 129Xe gases (eg different diffusivities) with lung structure and anatomy from the 1H MRI without reliance on ionizing radiation.
P1693
PET imaging with [11C]PBR28 and [18F]FDG distinguishes macrophage from neutrophil lung inflammation
Delphine Chen1, Eugene Agapow2, Kiran Solingaparam1, Jacqueline Engle1, Elizabeth Griffin1, Steven Brody2, Jason Woods2, Robert Mach1, Richard Pierce2, Michael Holtzman1, 1Multinuclear Institute of Radiology, Washington University School of Medicine, St. Louis, MO, United States; 2Internal Medicine/Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, United States.

Introduction: Noninvasive methods for quantifying macrophage and neutrophil activation and recruitment in chronic obstructive pulmonary disease (COPD) would be highly useful in assessing the efficacy of anti-inflammatory therapies.

Objective: To test whether positron emission tomography (PET) imaging with [11C]PBR28 and [18F]fluorodeoxyglucose ([18F]FDG) could distinguish macrophage-dominant from neutrophilic inflammation in a mouse model of COPD.

Methods: C57BL/6J mice inoculated with PBS or Sendai virus were imaged by microPET (Inveon or Focus 220, Siemens/CTI) with both [11C]PBR28 and [18F]FDG at Days 3 and 84 post-inoculation (p.i.). Regions of interest placed over the lungs determined the % injected dose per cc (%ID/cc) at 60 min. Lung sections were stained for TSPO ([11C]PBR28 ligand), Ly6G (neutrophil marker) and CD68 (macrophage marker).

Results: Only [18F]FDG uptake increased significantly during acute illness at p.i. Day 3. Both [11C]PBR28 and [18F]FDG uptake increased significantly during chronic disease at p.i. Day 84. The [11C]PBR28/[18F]FDG ratio, calculated for each mouse, was different between infected (1.9 ± 0.5) and uninfected mice (2.0 ± 0.9) at Day 3. This ratio increased significantly at p.i. Day 84 (3.1 ± 0.9) in infected mice compared to controls (1.7 ± 0.5). Lung sections showed macrophages with intense TSPO staining at p.i. Day 84.

Conclusion: PET imaging with [11C]PBR28 and [18F]FDG quantitatively distinguishes macrophage-dominant from neutrophilic inflammation in a mouse model of COPD. This approach may be useful for monitoring the pulmonary macrophage burden in humans with COPD, thereby guiding emerging targeted anti-inflammatory therapies.

P1694
3He MRI in young adults with congenital diaphragmatic hernia: Alveolar size differences between lungs
Maaike Snel1, Helen Marshall1, Hanneke Jissevijn1, Juan Parra-Robles2, Piet Wielopolska1, Elis van der Wiel1, Andrew Swift2, Shmita Rajaram2, Dick Tibboel1, Harm Tiddens2, Jim Wild1.

Methods and Measurements
3He MRI was used to image regional ventilation and to compute apparent diffusion coefficients (ADC) for ipsilateral (left) and contralateral lung separately. Volumes were gated CINE MR and phase contrast imaging sequences were acquired in all patients. During follow-up of 42 months, 16 patients died. Cardiac volumes and function and survival in patients with pulmonary hypertension due to COPD were assessed using univariate and multivariate regression or Kaplan-Meier analysis.

Results: Low SV measured by phase contrast MRI predicted mortality independently of demographic, haemodynamic, lung function and embolus severity data (p=0.029). LVEF predicted mortality from univariate analysis (p=0.017), but did not reach significance at multivariate analysis (p=0.573). According to Kaplan-Meier survival curves, outcome was less favourable for patients with an inframedian SV index < 40 mL/m² (log rank: p=0.007), and worse outcome was associated with a LVEF <61%.

Right ventricular end-diastolic and systolic volume and left ventricular end-diastolic and end-systolic did not significantly predict mortality at Cox proportional hazards regression or Kaplan-Meier analysis.
Conclusions: Low SV is a strong predictor of adverse outcome in patients with PH-COPD. Static ventricular volumes did not aid the prediction of adverse outcome.

P1607
Quantitative estimation of lung perfusion scintigraphy in patients with chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension
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Aim: To estimate lung perfusion in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and idiopathic pulmonary arterial hypertension (IPAH) by perfusion scintigraphy with technetium-99m macroaggregated albumin.

Methods: The study included 54 pts with pulmonary arterial hypertension: 21pts (12 f/9m) with CTEPH and 33 pts with IPAH. Patients were comparable on age (45.7±12.5/37.5±10.5), WHO FC, systolic pulmonary artery pressure and distance in the 6 minute walking test. A 111-MBq dose of 99mTc-labeled macroaggregated albumin (99mTc-MAA) was injected into a cubital vein with the patient in a horizontal position. Just after, lung scanning was performed using a gamma-camera system Philips SKY LIGHT. Calculated including 99mTc-MAA in the upper, mean, lower zones of each lung and relation of the upper share to the lower was considered (U/L). Results:

<table>
<thead>
<tr>
<th>Zone</th>
<th>CTEPH</th>
<th>IPAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone V esta No. 1, %</td>
<td>41.3±6.8</td>
<td>40±3.2</td>
</tr>
<tr>
<td>Left Lung</td>
<td>36.2±5.0</td>
<td>37.5±5.0</td>
</tr>
<tr>
<td>Right Lung</td>
<td>7.0±3.2</td>
<td>6.5±3.2</td>
</tr>
</tbody>
</table>

Conclusions: Decrease of perfusion in the upper zone and decrease of U/L was revealed only in patients with IPAH. On the contrary CTEPH was characterized by increased in U/L. This finding may be helpful for differential diagnostics of pulmonary hypertension.

P1608
New insights into functional consequences of pulmonary embolism by cardiac MRI
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Introduction: The objective of the present study was to evaluate a magnetic resonance imaging (MRI) algorithm which facilitates morphological diagnosis of pulmonary embolism (PE), right ventricular function and pulmonary perfusion (PP) in same examination.

Methods: 12 patients with documented PE on multidetector computed tomography (MDCT) and 14 healthy probands served in controls underwent multicomponent cardiovascular MRI. Diagnosis of PE was based on embolus visualization in MDCT. First, cine MRI was done employing multiple standard views. Second, high resolution, contrast-enhanced dynamic imaging of PP was performed. Third, a three-dimensional MRI angiography was acquired. Quantitative analysis of PP was derived from the signal intensity curve.

Results: In patients with PE compared to controls, RV ejection fraction was significantly lower (47±1±10.4% vs. 57±2±2.9%, p=0.002). Diagnosis of PE on a patient basis was 100% concordant between MDCT and MRI. PP in MRI of areas affected by PE compared to normal lung areas showed a lower relative peak enhancement (17±1±157% vs. 54±2±13%, p<0.001), maximum peak enhancement (31±1±198% vs. 691±264%, p<0.001), wash-in rate (58±2±72a.u. vs. 184±77a.u., p<0.001), AUC (32±1±2269 vs. 7215±3199, p<0.001) and a longer time-to-peak enhancement (17.5±1±6.9s vs. 9.5±1±3s, p<0.001).

Conclusions: Multicomponent cardiovascular MRI facilitated characterization of pulmonary arterial supply, RV function and PP during a single session examination and may serve as a profound basis for rapid clinical decision and for determination of therapeutic options in patients suspected of pulmonary embolism.

P1609
Cardiac magnetic resonance imaging versus echocardiography for assessment of cardiac involvement in pulmonary sarcoidosis
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Study objectives: Data on the prevalence of cardiac involvement in sarcoidosis patients vary depending on the patient population and diagnostic modality studied. We aimed to compare cardiac involvement diagnosed by cardiac magnetic resonance imaging (CMR) with standard echocardiography and speckle tracking echocardiography for detection of cardiac sarcoidosis in patients with pulmonary sarcoidosis.

Methods: 41 patients (mean 47 years) with biopsy-proven pulmonary sarcoidosis underwent echocardiography and CMR imaging. Cardiac involvement was diagnosed if a positive late gadolinium enhancement (LE) pattern not typical for coronary artery disease on CMR was found. LE was compared to regional wall motion abnormalities on standard echocardiography and to global longitudinal peak systolic strain (GLPSS) on speckle tracking echocardiography. NT-proBNP was evaluated.

Results: (p<0.001) 40 (97.6%) patients showed a positive LE on CMR (14 (34%) patients showed a positive LE on CMR (p<0.001). Four (10,5%) patients with positive LE showed a reduced GLPSS compared to 3 (7,9%) patients without LE (p=0.245). Mean NT-proBNP was higher in patients with positive LE (127 pg/ml), when compared to subjects without LE (87 pg/ml).

Conclusion: Cardiac involvement in pulmonary sarcoidosis patients was detected in more cases by CMR than by standard echocardiography. Speckle tracking echocardiography was also more sensitive than standard echocardiography. However, cardiac involvement in a caucasian population was rare compared to previously published data based on a predominantly afro-american population.

P1700
Comparison of dynamic contrast-enhanced MRI tracer-kinetic modeling in the lungs of smokers vs non-smokers
David Luke, Penny Hubbard, Geoff Parker, Josephine Naish. Imaging Science and Biomedical Imaging, The University of Manchester, United Kingdom

Previous analysis [1] of dynamic contrast-enhanced (DCE) MRI data in smokers vs non-smokers using the extended Kety model revealed increased K trans in smokers. By fitting the indicator dilution theory (IDT) and adiabatic approximation to the tissue homogeneity (AATH) models we hypothesise that we can decouple the contribution from perfusion and permeability to K trans to yield enhanced information on lung function and changes due to smoking. Figure 1 summarises the results obtained from the three models used in the smoker study.

Conclusions: LV is a strong predictor of adverse outcome in patients with PH-COPD. Static ventricular volumes did not aid the prediction of adverse outcome.
K$_{trans}$ showed a significant difference between smokers and non-smokers from both the extended Kety (p=0.032) and AATH (p=0.038) models. The AATH model implies that the increase in K$_{trans}$ is due to an increase in the permeability of the capillaries (p=0.030), rather than an increase in blood flow. Both the extended Kety (p=0.026) and AATH (p=0.025) models show a significant increase in the extracellular/extravascular space (EES) in smokers compared to non-smokers. In conclusion, the use of all three tracer-kinetic models indicate a coherent picture, supporting the hypothesis that increases in K$_{trans}$ observed in smokers compared to non-smokers are related to increased capillary permeability rather than increased blood flow.

Reference:

### P1701

**Simultaneous imaging of lung structure and function with triple nuclear MRI**

Jim Wild, Helen Marshall, Xuxin Xu, Graham Norquay, Juan Parra-Robles

Academic Radiology, University of Sheffield, United Kingdom

Hybrid medical imaging scanners (e.g. PET-CT) allow imaging with different detection modalities at the same time, providing complementary anatomical and functional information within the same physiological time course. Here, we re-engineer a standard clinical MRI scanner for the simultaneous acquisition of lung MR images from three different nuclei (1H, 3He and 129Xe) in a single breath-hold. The temporal and spatial registration of these images is impossible to achieve in separate breath-hold scans. This new system opens up the possibility of simultaneous capture of regional lung function from the 3He and 129Xe gases and lung structure from the 1H MRI without reliance on ionising radiation.

Figure 1 shows images of 3He, 1H and 129Xe acquired from a healthy volunteer in the same breath-hold; the anatomical 1H images show excellent spatial registration with the 3He and 129Xe ventilation images.

The method has multiple potential applications, allowing side-by-side quantitative analysis of early signs of impaired lung function from the 3He and 129Xe images and anatomical signs of disease from 1H MRI. For a variety of lung diseases, registration of ventilation MRI to anatomical 1H MRI would allow subsequent image registration to the radiological gold standard for anatomy, CT, which serves as the clinical gold standard in diseases such as emphysema.

### P1702

**Physiological modelling of dynamic contrast-enhanced MRI in COPD**

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We present the results of a dynamic contrast-enhanced (DCE-)MRI study in subjects with COPD and age-matched healthy subjects. The pharmacokinetic model applied allows for extravasation of the contrast agent and can therefore be used to probe pulmonary capillary permeability.

Significant differences were not observed between healthy and moderate COPD groups in any of the DCE-MRI parameters. Significantly lower v$_p$ and K$_{trans}$ were observed in severe COPD compared with healthy and in v$_p$ compared with moderate COPD (Fig. 1). v$_p$ (extra-vascular/extra-cellular space) can be related to inflammation and shows an non-significant increase in moderate COPD.

<table>
<thead>
<tr>
<th>Group mean and standard deviation of physiological DCE-MRI parameters</th>
<th>Healthy</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>K$_{trans}$ (ml/ml tissue/ min)</td>
<td>0.31±0.16</td>
<td>0.29±0.13</td>
<td>0.21±0.05</td>
</tr>
<tr>
<td>v$_p$ (ml/ml tissue)</td>
<td>0.22±0.11</td>
<td>0.22±0.09</td>
<td>0.14±0.04</td>
</tr>
<tr>
<td>v$_p$ (ml/ml tissue)</td>
<td>0.27±0.07</td>
<td>0.32±0.09</td>
<td>0.25±0.05</td>
</tr>
</tbody>
</table>

K$_{trans}$ is related to perfusion and/or capillary permeability and decreases significantly in severe COPD. v$_p$ (vascular space) also decreases with disease severity and, when considered in combination with decreased K$_{trans}$, is suggestive of reduced perfusion in the region analysed. This sensitivity to disease severity shows that DCE-MRI may provide a novel window on the progression of COPD.

Reference:

### P1703

**Regional measures of 3D lung mechanics using magnetic resonance imaging**

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Lung disease, such as emphysema and fibrosis, can result in changes in pulmonary mechanical properties that are not easily identified on a regional level using current methods. A recently reported method, using 2D structural proton MRI in conjunction with post-processing and image registration, to provide measures of local lung motion and relative regional tissue compliance demonstrated differences between healthy and diseased lungs. This technique has been extended to 3D, to overcome the limitations of the 2D method.

Multi-slice structural lung MR images were acquired in 2 healthy volunteers during breath-hold at end-expiration and end-inspiration. 3D lung volumes were segmented, and an automatic mesh-based image registration used to identify correspondence points in the lung between the two respiratory extremes. Vector field maps of local lung motion show an increasing magnitude of motion from apex to diaphragm, as expected in healthy lungs, with motion in the anterior-posterior as well as in the foot-head direction (Figure 1). These methods provide potentially useful information on local lung mechanics in diagnosis of disease, and may be used to calculate regional lung compliance.

Reference:
P1704 Modelling of hyperpolarized gas diffusion in lungs of COPD patients and healthy volunteers using a fractional dynamics approach

Juan Parra-Robles, Helen Marshall, Jim M. Wild

Aim: To study the ventilation-perfusion ratio (V/Q), apex-base gradient of ventilation (UL-V/L) and perfusion (UL/Q) and alveolar-capillary permeability (ACP) in bronchial asthma (BA) patients on the basis of scintigraphy data.

Materials and methods: 30 people aged 18-60 took part in the study: patients diagnosed with moderate BA. The study was performed with 20 healthy non-smokers (SH). Three scintigraphic studies were performed by means of Omega 500 gamma camera (Technicare, USA-Germany). The subject of the research was an examination of ACP in the right (RL) and left (LL) lungs in the process of radiopharmaceutical derivation, static conditions, during the 1st, 10th and 30th minute after 99mTc-DTPA inhalation.

Results: BA patients: V/Q in both RL and LL was not higher than 1.0 and amounted to 0.96 (0.92-1.04) in the RL and 0.98 (0.95-1.01) in the LL. These parameters did not differ from those of healthy volunteers (p=0.72 and p=0.65). UL-V/L amounted to 0.55 (0.33-0.77) in the RL and 0.57 (0.45-0.69) in the LL. It was lower than that of healthy people (p=0.03 and 0.04). UL/Q amounted to 0.82 (0.68-0.98) in the RL and 1.1 (0.84-1.36) in the LL. This parameter was higher than that of healthy people (p=0.004, p=0.02). ACP in the RL amounted to 10.19% (6.49-14.19%) and 27.21% (22.99-31.41%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.001). ACP in the LL amounted to 9.68% (8.49-10.87%) and 27.87 (24.26-31.48%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.002).

Conclusions: The study findings may serve as additional scintigraphic criteria for bronchial asthma diagnostics.

P1705 Quantitative CT-estimation of total and regional lung inflation in patients with bronchial asthma (BA)

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Background: Functional abnormalities are often the first and the only symptoms in BA. Spirometry do not allow lung inflation estimation.

Aim: To estimate the potential of CT in identification of total and regional lung hyperinflation in BA patients.

Methods: 70 BA patients were examined compared with 20 healthy persons. The method of two stage multispiral CT by Actisum 16 ( Toshiba ) with the further 3D-reconstruction and volumetry (850 HU and lower) was used. The quantitative densitometric estimation at axial scanning in fixed upper, middle and lower lung zones was also done. Bronchodilatation test with salbutamol inhalation was used. Results: The lung dysfunction was registered in 66 patients. By 3D-volumetry, lung inflation at maximal expiration against inspiration in mild BA was 3.8±2.46% (in healthy people - 3.0±0.55%, p<0.001), in moderate BA - 16.2±5.27% (p<0.05 to mild BA) and in severe BA - 30±6.47% (p=0.05 to moderate BA). By densitometry the mean inspiration to expiration ratio of density in mild BA was 80±13.14% (in healthy people - 76.74±5.37%, p<0.01), in moderate BA - 85±5.48% (p=0.05 to mild BA), in severe BA - 91.5±4.19% (p=0.05 to moderate BA) and 103±5.06% of total inflation patients with mild BA had a decrease of "air traps" volume: before the test the expiration to inspiration ratio of lung

P1706 Synchrontron imaging of regional ventilation/perfusion-ratio after methylcholine provocation in rabbit

Lisa Perlla1, Mathieu Guylart1, Sara Strengell2, Pelka Suorti2

Aim: To assess the feasibility of quasi-simultaneous KES imaging of V and VB during inhalation and regional volume (VB) distributions during isoflurane infusion. In this study we assessed the feasibility of quasi-simultaneous KES imaging of V and VB.

Methods: Experiments were performed in anaesthetized and ventilated New Zealand rabbits (n=5). Images of V and VB were obtained at baseline and after infused MCh (125 mg/ml). Heterogeneity of both parameters was estimated as the coefficient of variation (CV) between pixels.

Results: Images of V, VB and their ratio (V/ VB) are shown in one rabbit at baseline and after MCh challenge (Figure). MCh inhalation produced clustered areas of poor ventilation; mean V decreased to 75.7±24.2 % and VB to 69.4±12.7% of baseline. The CV of V increased to 334±186%, CV of VB to 140±216%, and CV of V/ VB ratio to 193±50% of baseline. Values are m±SD, *significant change vs. baseline (p<0.05, Students paired t-test).

P1707 Scintigraphic parameters in bronchial asthma patients

Tatyana Ageeva1, Nikolay Kevzakov2, Anna Dubrdolav1, 1 Propedeutics of Internal Diseases Department, Siberian State Medical University, Tomsk, Russian Federation; 2 Radionuclide Diagnostics Laboratory, Cardiology Research Institute of Siberian Department of Russian Academy of Medical Sciences, Tomsk, Russian Federation

Aim: Study the ventilation-perfusion ratio (V/Q), apex-base gradient of ventilation (UL-V/L) and perfusion (UL/Q) and alveolar-capillary permeability (ACP) in bronchial asthma (BA) patients on the basis of scintigraphy data.

Methods and materials: 30 people aged 18-60 took part in the study: patients diagnosed with moderate BA. The study was performed with 20 healthy non-smokers (SH). Three scintigraphic studies were performed by means of Omega 500 gamma camera (Technicare, USA-Germany). The subject of the research was an examination of ACP in the right (RL) and left (LL) lungs in the process of radiopharmaceutical derivation, static conditions, during the 1st, 10th and 30th minute after 99mTc-DTPA inhalation.

Results: BA patients: V/Q in both RL and LL was not higher than 1.0 and amounted to 0.96 (0.92-1.04) in the RL and 0.98 (0.95-1.01) in the LL. These parameters did not differ from those of healthy volunteers (p=0.72 and p=0.65). UL-V/L amounted to 0.55 (0.33-0.77) in the RL and 0.57 (0.45-0.69) in the LL. It was lower than that of healthy people (p=0.03 and 0.04). UL/Q amounted to 0.82 (0.68-0.98) in the RL and 1.1 (0.84-1.36) in the LL. This parameter was higher than that of healthy people (p=0.004, p=0.02). ACP in the RL amounted to 10.19% (6.49-14.19%) and 27.21% (22.99-31.41%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.001). ACP in the LL amounted to 9.68% (8.49-10.87%) and 27.87 (24.26-31.48%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.002).

Conclusions: The study findings may serve as additional scintigraphic criteria for bronchial asthma diagnostics.

P1708 Modelling of hyperpolarized gas diffusion in lungs of COPD patients and healthy volunteers using a fractional dynamics approach

Juan Parra-Robles, Helen Marshall, Jim M. Wild

Aim: To investigate the ventilation-perfusion ratio (V/Q), apex-base gradient of ventilation (UL-V/L) and perfusion (UL/Q) and alveolar-capillary permeability (ACP) in bronchial asthma (BA) patients on the basis of scintigraphy data.

Materials and methods: 30 people aged 18-60 took part in the study: patients diagnosed with moderate BA. The study was performed with 20 healthy non-smokers (SH). Three scintigraphic studies were performed by means of Omega 500 gamma camera (Technicare, USA-Germany). The subject of the research was an examination of ACP in the right (RL) and left (LL) lungs in the process of radiopharmaceutical derivation, static conditions, during the 1st, 10th and 30th minute after 99mTc-DTPA inhalation.

Results: BA patients: V/Q in both RL and LL was not higher than 1.0 and amounted to 0.96 (0.92-1.04) in the RL and 0.98 (0.95-1.01) in the LL. These parameters did not differ from those of healthy volunteers (p=0.72 and p=0.65). UL-V/L amounted to 0.55 (0.33-0.77) in the RL and 0.57 (0.45-0.69) in the LL. It was lower than that of healthy people (p=0.03 and 0.04). UL/Q amounted to 0.82 (0.68-0.98) in the RL and 1.1 (0.84-1.36) in the LL. This parameter was higher than that of healthy people (p=0.004, p=0.02). ACP in the RL amounted to 10.19% (6.49-14.19%) and 27.21% (22.99-31.41%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.001). ACP in the LL amounted to 9.68% (8.49-10.87%) and 27.87 (24.26-31.48%) during the 10th and 30th minutes of the study, respectively; it was increased during the 30th minute of the study (p=0.002).

Conclusions: The study findings may serve as additional scintigraphic criteria for bronchial asthma diagnostics.
inflation was 7.3%, after the test - 2.3%; the quantity of voxels before the test was 3727 at inspiration, 276 at expiration (after the test - 4772 and 110, respectively). Conclusion: By 3D-volume and densitometric analysis the conclusions about the lung inflation abnormality and the volume of “air traps” in BA patients can be drawn, which considerably supplements the spirometry.

P1709 MRI-informed electrical impedance tomography from phantom to thorax
Rose Line1, John Davidson2, Josephine Nash1, Paul Wrigley2, Alexandra Morgan1, Ron Kikinis1, Hugh McCann2, Geoff Parker1
1 Imaging Science, University of Manchester, United Kingdom; 2 School of Electrical and Electronic Engineering, University of Manchester, United Kingdom; Surgical Planning Laboratory, Brigham and Women’s Hospital, Boston, MA, United States

Electrical impedance tomography (EIT) has the potential to provide non-invasive, high temporal resolution, long term lung function monitoring. We present an instrument capable of volumetric data acquisition applied to a male torso, show an MRI-informed reconstruction, and correspondence of EIT measurements with high resolution MRI.

EIT data were acquired using two planes of 16 electrodes on the Manchester EIT system, a BS EN 60601-1:2006 compliant system, followed by MRI acquired using a fast field echo on a 1.5 T Philips Achieva. The data were coalignaged using the open source medical image platform 3D-Slicer. Figure 1(a)-(c) shows an MRI axial slice of the torso, coalignaged with EIT, and EIT alone.

The system acquired volume data using 32 electrodes in two planes. The EIT was reconstructed using a torso boundary-only model derived from the MRI. This should produce a more faithful reconstruction than a generic model, allowing investigation of sensitivity of EIT measurements using increasingly precise models. At 100 fps, the EIT provides excellent temporal resolution. For example, it shows different temporal sequences of lung ventilation (dorsal versus ventral) within the breathing cycle for an upright subject as compared with supine. Current analyses of EIT data for lung function monitoring use sub-cycle statistics and time difference (minimum) 3-fold increase in frame rate provided by EIT will improve these methods substantially.

210. Current trends in home mechanical ventilation

P1710 Home mechanical ventilation and respiratory rehabilitation: Influence in respiratory functional test and exercise capacity
Eduardo Marquez-Martín, Pilar Cepajo, Jose Luis Lopez-Campos, Ana Rodriguez, Borja Valencia, Emilia Barrot, Francisco Ortega.
Medical-Surgical Unit of Respiratory Diseases, Virgen del Rocío University Hospital, Seville, Spain

Our aim is to assess the impact on respiratory function and exercise capacity of a respiratory rehabilitation program (RR) compared with a program of home mechanical ventilation (HMV) and the summation of both interventions.

Methods: 45 COPD patients with severe functional impairment and in situations of hypercapnic respiratory failure were prospectively randomized to 3 groups: RR (12 weeks in 40-minute sessions that included strength training and resistance), HMV (12 weeks BiPAP mode) and RR-HMV (combination of the two interventions). The patients underwent different components of BODE index, quality of live (CRDQ) and IP. C Reactive Protein (CRP), Tumor Necrosis Factor α (TNF-α), Interleukin-6 (IL-6), IL-8 and Surfactan D Protein (SDP).

Results: HMV group improved BODE index significantly by decreasing median 2 points (p = 0.003). Also get statistically significant improvement in quality of life index CRDQ (in total and its four components) IP improved significantly by decreasing TNF-α and IL-8. RR group obtained the same results in BODE index, and CRDQ. IP significantly improved by lowering CRP IL-8, SDP and C3. RR-HMV group improves BODE index significantly when going from 3 to 5.3 (p = 0.001). CRDQ in total and components of hypoxemia, fatigue, fear, and social control. Significantly improved IP by lowering CRP. TND-α, SDP and prealbumin.

Conclusions: HMV and the RR produced improvement in the BODE index and quality of life as well as when the two interventions are given together without finding differences when applied independently. The combination of both intervention control more IP than each other separately.

P1712 Home non-invasive ventilation (HNV) improves survival in hypercapnic patients with cystic fibrosis
Sergey Adevse, Gulnara Baimakanova, Stanislav Krasovsky, Victor Samoilenko, Elena Amelina, Alexander Chuchalin.
Clinical Department, Pulmonology Research Institute, Moscow, Russian Federation

Background: The clinical benefits of home non-invasive positive pressure ventilation (HNV) have not been well established in adult patients with cystic fibrosis (CT).

Objective: The purpose of this matched case-control study was to compare the effects of HNV and long-term oxygen therapy (LTOT) on survival of adult CF patients with chronic hypercapnic respiratory failure (CHRF).

Methods: Twelve patients receiving HNV were matched with 12 patients receiving LTOT regarding age, FEV1, PaCO2 and BMI.

Results: There were no differences between groups of patients in demographic, clinical and functional characteristics (HNV patients: 24.9 ± 4.8 years, BMI 16.1 ± 3.3 kg/m2, FEV1 15.3 ± 3.4%, PaCO2 59.8 ± 7.7 mmHg; and LTOT patients: 23.9 ± 4.0 years, BMI 15.8 ± 4.2 kg/m2, FEV1 16.1 ± 4.4%, PaCO2 61.4 ± 7.9 mm Hg). HNV settings were: ST mode, IPAP 20.1 ± 4.2 cm H2O, EPAP 4.6 ± 0.7 cm H2O (nasal mask – 4, oronasal mask – 8). Compared with LTOT, HNV significantly reduced breathing rate (p = 0.036), PaCO2 (p = 0.038) and number of exacerbations (p = 0.028). Survival was significantly better in HNV group in comparison with LTOT group (survival time 12.5 [95%CI 0.6-16.4] months vs 6.0 [95%CI 0.7-7.3] months; log-rank test, p = 0.024).

Conclusions: The survival of adult CF patients receiving HNV was better than that of patients treated with LTOT alone. We suggest HNV is a first-line treatment for adult patients with CHRF.

P1713 Meta-analysis on nocturnal non-invasive positive pressure ventilation for stable COPD: an update
Fransien Struijk1, Yves Lacasse2, Huib Kerstjens1, Peter Wijkstra1,3
1 Department of Pulmonary Diseases/Home Mechanical Ventilation, University of Groningen, University Medical Center Groningen, Netherlands; 2 Centre de Pneumologie, Institute Universitaire de Cardiologie et de Pneumologie de Quebec (Hospital Laval), Quebec, Canada; 3 GRIAC Research institute, University of Groningen, University Medical Center Groningen, Netherlands

Introduction: Nocturnal non-invasive positive pressure ventilation (NIPPV) might be beneficial in stable hypercapnic patients with COPD. However, evidence remains conflicting.

Aim: To determine the effect of NIPPV in patients with stable hypercapnic COPD. Methods: This meta-analysis gathered individual patient data from randomized controlled trials (RCTs) comparing NIPPV plus standard therapy with standard therapy alone. The current analyses are limited to gas exchange parameters.

Results: Our older Cochrane review and 3 new studies were identified, totaling
in PaCO2 and increase in PaO2 in stable hypercapnic COPD patients after 3 months with the newer studies, this update now finds a significant decrease (n=118; CI=0.24; 3.45 mmHg) but no significant changes after 12 months of NIPPV (mean difference= -3.56 (95% CI=-4.93;-2.18 mmHg)) and PaO2 (1.84 (95% 5 short-term and 2 long-term RCTs. After 3 months (n=162; age 66 yrs; FEV1 decreased from 88% to 51% of all patients treated in favor of pulmonary diseases and hypoventilation syndromes (from 3 to 12%). The change in BODE index is correlated with Oxygen Desaturation during sleep. Conclusion: NIV is largely used to treat patients with obesity-associated hypventilation treated with long-term non-invasive ventilation. Methods: A Cohort of OH patients initiated on NIV between March 2003 and July 2008. Anthropometry, diurnal and nocturnal respiratory parameters, comorbidities, medications, conditions of NIV initiation and NIV compliance were used as co-variates. Survival curves were estimated by the Kaplan-Meier method. Univariate and multivariate Cox models allowed estimating predictive factors of mortality. Conclusion: In 107 patients (56% women, mean follow-up of 43±14 months) NIV was initiated in acute conditions in 36%. The 1, 2, 3-year survival rates were 99, 85, 82% respectively. In univariate analysis, death was associated with older age (>63 yrs), low FEV1 (<60% pred value), male gender, concomitant COPD, obesity, diabetes and neuromuscular disease. In multivariate analysis, combination of cardiovascular agents was the only factor associated with a higher risk of death (HR=5.3; 95% CI: 1.18; 23.9). In contrast, female gender was associated with a lower risk. Conclusion: Cardiovascular comorbidities represent the main factor predicting mortality in NIV-treated OH patients. In this population, NIV should be used among a combination of treatment modalities allowing a reduction in cardiovascular risk.

P1716
Co-morbidities and cardiovascular medications are the best predictors of mortality in patients with obesity-associated hypventilation treated with long-term non-invasive ventilation.

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Rationale: NIV is largely used to treat patients with obesity-associated hypventilation (OH). The impact of comorbidities, their medications and NIV compliance on survival of these patients remain unexplored.

Methods: We included 214 patients (55.6% women, mean age 63.8 years ± 13.3). 50% required hospital readmission and the median time to readmission was 170 weeks (144.1 to 195.8). Readmission was not related to the presence of comorbidities neither the initial results of HMV and appear related to poor quality of life. Predictors of readmission were also worse PaO2 control and PaCO2 control, greater number of previous admissions and poorer lung function. The multivariate model identified as independent predictors of readmission: Poor quality of life (HR 2.3-3.3, p<0.017), previous admissions, previous respiratory failure and a poor quality of life. Predictors of readmission were also worse PaO2 control and PaCO2 control, greater number of previous admissions and poorer lung function. The multivariate model identified as independent predictors of readmission: Poor adherence to NIV (OR 1.7; CI 95% 1.1 - 2.6), PaCO2 control (OR: 1.03, 95% CI I to 1.06) and the level of dyspnea at follow up (OR:2.3,95%CI:1.5-3.3).

Conclusions: 1. In our experience, a high percentage of patients on HMV required hospital readmission. 2. - Readmissions does not appear to be directly related to comorbidities neither the initial results of HMV and appear related to poor treatment adherence and severity of respiratory failure.

P1717
Predictors of readmission in patients on home mechanical ventilation (HMV)


Objectives: There are few studies that examine which factors determine the readmission of patients on HMV. Our objective was to study the variables related to this fact to determine which aspects should be monitored more closely.

Methods: Prospective observational study over a period of 10 years. We collected clinical variables during hospitalization and data related to treatment adherence and the date of hospital readmission. Bivariate analysis and a Cox multivariate model were performed

Results: We included 214 patients (55.6% women, mean age 63.8 years ± 13.3). 50% required hospital readmission and the median time to readmission was 170 weeks (144.1 to 195.8). Readmission was not related to the presence of comorbidities, morbidity, situation at the start of ventilation (chronic respiratory vs. acute respiratory failure) or main diagnosis that led to the start of HMV. During follow-up readmission was associated with poor adherence to HMV (46.7% vs 29.9%, p = 0.017), previous admissions, previous respiratory failure and a poor quality of life. Predictors of readmission were also worse PaO2 control and PaCO2 control, greater number of previous admissions and poorer lung function. The multivariate model identified as independent predictors of readmission: Poor adherence to HMV (OR 1.7; CI 95% 1.1 - 2.6), PaCO2 control (OR: 1.03, 95% CI I to 1.06) and the level of dyspnea at follow up (OR:2.3,95%CI:1.5-3.3).

Conclusions: 1- In our experience, a high percentage of patients on HMV required hospital readmission. 2- - Readmissions does not appear to be directly related to comorbidities neither the initial results of HMV and appear related to poor treatment adherence and severity of respiratory failure.

P1715
NIV (non invasive ventilation) improves Bode index in stable COPD with CHRF (chronic hypercapnic respiratory failure)

Andriani Zikiri, Chando Pastaka, Vasso Toulaki, Andrew Dimoulis, Konstantinos Georgioulanis, Maria Patent, George Sestanides. Pulmonary Department, University Hospital of Thessaly, Larissa, Greece

Introduction: The BODE index, a simple multidimensional grading system, is used to predict the risk of death from any cause and from respiratory causes among patients with COPD. The use of NIV in exacerbation of COPD is suggested. On the other hand there are not any guidelines for the use of NIV in patients with stable COPD.

Purpose: To investigate any improvement in patients with COPD and CHRF using NIV at home, in relation with BOE index and the factors that predict the improvement.

Material and methods: Patients with COPD and CHRF (in stable condition) with LTOT were included. Patients underwent a polysomnography study to exclude OSA (AHI<10). The patients used NIV at home for a year. BODE index and its components (FEV1, MRC, BMI, 6MW) were estimated at baseline (0 month) and 6 and 12 months after use. In addition, BODE index change on the 6th month was correlated with initial parameters (AHI, OD, min saturation, mean saturation at sleep, PO2, PCO2, BODE index (lnmonth), FVC, FEV1/FVC, age).

Results: There is a statistically significant change of BODE index after 6 months and after 12 months of using NIV. There is a correlation between BODE index change and oxygen desaturation (OD) (polysomnography study).

Conclusion: NIV improves BODE index in stable COPD and CHRF. The change in BODE index is correlated with Oxygen Desaturation during sleep.

P1714
The evolution of home mechanical ventilation in Poland between 2000 – 2010

Jacek Nasłonowski1, Marian Wachulska1, Wojciech Trzniadel1, Wendi Andrzejewski1, Marek Migdal1, Beata Drazuga1, Andrzej Pytel1, Robert Suchanke1, Małgorzata Czajkowska-Malinowska3, Tomasz Mączyński2, Ryszard Chazan1, 1Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Poland; 2Home Mechanical Ventilation Center, Pulmmed, Bydgoszcz, Poland; 3Home Mechanical Ventilation Center, Ventamed, Zielona Gora, Poland; 4Home Mechanical Ventilation Center, Hospice for Children and Adults, Łódź, Poland; 5Home Mechanical Ventilation Center, The Children's Memorial Health Institute, Warsaw, Poland; 6Home Mechanical Ventilation Center, Beta-Med, Katowice, Poland; 7Home Mechanical Ventilation Center, HELP, Poznan, Poland; 8Home Mechanical Ventilation Center, Kujawsko-Pomorskie Pulmonology Centre, Bydgoszcz, Poland; 9Home Mechanical Ventilation Center, St. Vincent Medical Center, Warsaw, Poland

In the last decades the methods and indications for home mechanical ventilation (HMV) have changed significantly mainly due to technological development and an increasing number of patients with chronic pulmonary disorders. Data about HMV comes from developed countries. However, the shift was not as marked as in more developed countries. Prevalence of ICU is the principal location where HMV was initiated. However, its role diminished from 6 to 23% and the date of hospital readmission. Bivariate analysis and a Cox multivariate model were performed to comorbidities neither the initial results of HMV and appear related to poor quality of life. Predictors of readmission were also worse PaO2 control and PaCO2 control, greater number of previous admissions and poorer lung function. The multivariate model identified as independent predictors of readmission: Poor quality of life (HR 2.3-3.3, p<0.017), previous admissions, previous respiratory failure and a poor quality of life. Predictors of readmission were also worse PaO2 control and PaCO2 control, greater number of previous admissions and poorer lung function. The multivariate model identified as independent predictors of readmission: Poor adherence to NIV (OR 1.7; CI 95% 1.1 - 2.6), PaCO2 control (OR: 1.03, 95% CI I to 1.06) and the level of dyspnea at follow up (OR:2.3,95%CI:1.5-3.3).

Conclusions: 1- In our experience, a high percentage of patients on HMV required hospital readmission. 2- - Readmissions does not appear to be directly related to comorbidities neither the initial results of HMV and appear related to poor treatment adherence and severity of respiratory failure.
P1718
Effect of an automatic triggering and cycling system on patient-ventilator synchrony during noninvasive ventilation in a mechanical lung model

Lídia Melo, Renata Vasconcelos, Raquel Sales, Carla Magalhães, Mirzana Almeida, Juliana Silveira, Marcelo Holanda. Laboratório da Respiração - Respbak, Universidade Federal do Ceará, Fortaleza, CE, Brazil; Pós Graduação em Ciências Médicas, Universidade Federal do Ceará, Fortaleza, CE, Brazil.

Evaluate the effect of an automatic triggering and cycling system on patient-ventilator synchrony during NIV in a mechanical lung model. Bench study, one ICU ventilator (Esprit®) and one NIV ventilator (Trilogy®) were tested. The lung simulator ASL 5000 (Ingmar) was set with obstructive model: compliance 60 mL/cmH2O, resistance 20 cmH2O/L/s, and restrictive: compliance 30 mL/cmH2O and resistance 8 cmH2O/L/s, both with respiratory rate 15 bpm and ventilatory demand of 60 L/min. A facial mask was adapted to a head manikin, with an air leak of 10 L/min. The Esprit® was adjusted in the NIV mode and the Trilogy® in the S/T mode; PAP 10 cmH2O and EPAP 4 cmH2O, triggering and cycling were set automatically (AutoTrak®) or flow triggering (3 L/min) with expiratory cycling 25% (conventional) in both ventilators. Inspiratory and expiratory delay, inspiratory work and patient-ventilator asynchrony were analyzed. Auto-triggering was observed in the restrictive model in the Esprit® with conventional adjustments, but the phenomenon was abolished with the automatic settings. Little difference was observed between the systems, suggesting that both methods were equivalent with respect to inspiratory and expiratory delay and work.

Table 1. Inspiratory and expiratory delay and work in the mechanical lung models

<table>
<thead>
<tr>
<th></th>
<th>Obstructive</th>
<th>Restrictive</th>
</tr>
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<tbody>
<tr>
<td>AT = AutoTrak®, CV = conventional; *persistent asynchrony.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspiratory delay (ms)</td>
<td>37/31</td>
<td>28/80</td>
</tr>
<tr>
<td>Expiratory delay (ms)</td>
<td>18/28</td>
<td>14/42</td>
</tr>
<tr>
<td>Inspiratory work (J/L)</td>
<td>1.40/1.38</td>
<td>1.36/1.39</td>
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P1719
The acute effects of postural change and non-invasive ventilation breathing on the regional distribution of lung ventilation: A electrical impedance tomography study

Nathalia Parente de Sousa1, Liliana Silveira Marinho1, Luana Torres Monteiro1, Aline Menezes Sampaio1, Vasco Pinheiro Diógenes Bastos1, Andréa da Nóbrega Alcântara Holanda1. Laboratory Respiration, Department of Medicine, Federal University of Ceará, Fortaleza, Brazil; 2Laboratory of Medical Investigation, University of São Paulo, Brazil.

Introduction: The combined effects of postural changes and the use of noninvasive positive pressure ventilation (NIV) on the regional distribution of lung ventilation (RLDV) is still underexplored. The electrical impedance tomography (EIT) has emerged as a consistent technique for the dynamic evaluation of RLDV. Objectives: To evaluate the RLDV in healthy subjects during spontaneous respiration (SR) and during NIV breathing in different body positions. Methodology: The RLDV was assessed by EIT (32 electrodes) in 10 healthy subjects (5 men), during 10 minutes of SR, or with CPAP of 10 cmH2O and with BiPAP of 15 cmH2O in four body positions (dorsal (D), ventral (V), right lateral (RL) and left lateral (LL)). Results: The figure below shows the % of RLDV in the four quadrants of the lungs.

During SR, the RLDV was higher in the gravity dependent quadrants, mainly in the lateral decubitus, except for the V position. NIV breathing (CPAP and BiPAP) did not alter the pattern of RLDV as compared to SR.

Conclusions: EIT can clearly demonstrate that, with the exception of prone positioning, the dependent regions of the lungs are better ventilated both during SR or CPAP and BiPAP breathing.
of physical impairment and respiratory failure. PPV may accelerate the delayed gastric emptying, possibly by esophago-gastric air inflation.

P1722 Unplanned respiratory crises requiring ventilation in Duchenne muscular dystrophy (DMD) patients can be reduced by timely respiratory review and care co-ordination at the age of transition

Emily Ballard1, Natalie Grey1, Heinz Jungbluth2, Elizabeth Wraige2, Stam Kapetanakis1, Craig Davidson1, Nicholas Hart1,4, 1The Lane Fox

The introduction of home mechanical ventilation (HMV) in DMD is associated with increased life expectancy. In 2009, we introduced a transitional care co-ordinator role with the hypothesis that we would reduce the number of unplanned respiratory crises with early intervention. We have prospectively gathered data for all 75 patients with DMD under review in 2009.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of DMD patients receiving HMV</td>
<td>34</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>New elective HMV initiations</td>
<td>2</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mean age of initiation NIV (yrs)</td>
<td>19.3 (16-23)</td>
<td>20.3 (16-25)</td>
<td>20.1 (16-25)</td>
</tr>
<tr>
<td>Mean length of set up – elective days</td>
<td>5.3 (3-10)</td>
<td>4.14 (2.9)</td>
<td>3.28 (2-4)</td>
</tr>
<tr>
<td>Mean length of set up – emergency days</td>
<td>67</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>No. of new patients requiring invasive ventilatory support with emergency set up</td>
<td>1</td>
<td>1</td>
<td>1*</td>
</tr>
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*This patient did not require long term NIV; data expressed as absolute values.

Analysis of these data was focused on the primary respiratory crisis admission requiring ventilatory support. Within 3 years we identified 19 patients who required initiation of HMV, all known to the respiratory team prior to initiation and only (15.8%) were as a result of an emergency admission. Of the 19 patients initiated on HMV, 16 were elective with a mean length of stay of 4.7 days (2-9) days. 1 patient was admitted directly from clinic as an emergency, requiring invasive ventilation but without tracheostomy formation. Of the two patients who required tracheostomy formation, one did not require NIV post discharge from hospital. The data supports that with timely intervention and coordination you can reduce the need for emergency intituation of ventilation through respiratory crisis.

P1723 Introduction of domiciliary mechanical insufflation-exsufflation can reduce the incidence of crisis admissions in patients with Duchenne muscular dystrophy (DMD)

Emily Ballard1, Natalie Grey1, Heinz Jungbluth2, Elizabeth Wraige2, Stam Kapetanakis1, Craig Davidson1, Nicholas Hart1,4, 1The Lane Fox

Although trials are ongoing, there is limited evidence to support the use of mechanical insufflations-exsufflation as a method of secretion clearance to prevent chest infections in patients with DMD. However our local unit practice is to provide a machine to DMD patients that are established on non-invasive ventilation with a peak expiratory cough flow < than 160 litres per min despite maximal physiotherapy adjuncts with either: (1) > 2 episodes of chest sepsis per year requiring antibiotics and hospital admission (2) 1 episode of severe chest sepsis requiring invasive ventilation. The aim of the use of the cough assist machine is to reduce the frequency of hospital admissions and length of stay (LOS). We reviewed the prospective data from our DMD patient cohort over a 7 year period in which 32 patients had been initiated with a machine. We reviewed the data for 12 months pre and post base in order to establish the effect on admission frequency and LOS.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Pre home issue</th>
<th>Post home issue</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean frequency of respiratory admissions in a 12 month period</td>
<td>3 (1-6)</td>
<td>0.3 (0.1)</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td>Mean LOS of respiratory admissions in a 12 month period</td>
<td>12.9 (2067)</td>
<td>11.4 (0.51)</td>
<td>p&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as absolute value (range). *Significant using Wilcoxon signed ranks test.

These data have showed a significant reduction in both hospital admission frequency and LOS for those patients using a domiciliary cough assist machine. These are the first data to add support to the use of domiciliary cough assist machines in DMD patients with an ineffective cough and previous episodes of chest sepsis already established on NIV.

P1724 Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: A meta-analysis

Justine Aaronson1, Wynne Kylstra1, Winni Hofmann2, Ben Schmud2, 1Research & Development, Helsemure, Wijk aan Zee, Netherlands; 2Psychology, University of Amsterdam, Netherlands

Introduction: The generally held clinical view is that treatment with continuous positive airway pressure (CPAP) substantially improves cognition in patients with obstructive sleep apnea (OSA). The cognitive domains in which recovery is found as well as the extent of recovery differs widely between studies, however.

Objective: A meta-analysis was conducted to quantify the magnitude of the overall effect of CPAP treatment in OSA on neuropsychological functioning

Methods: A comprehensive literature search of clinical trials published from January 1990 to June 2011 was performed. The inclusion criteria were: randomized controlled trial, diagnosis OSA by polysomnography, apnea-hypopnea index, duration and compliance of CPAP treatment, one or more standardized neuropsychological tests. Mean-weighted effect sizes of CPAP treatment for 7 cognitive domains were calculated.

Results: 12 studies encompassing 516 OSA patients were included. A small significant effect on attention was observed in favour of CPAP treatment (d=0.2). For the other cognitive domains the effect sizes did not reach significance. Improvement on measures of sleepiness was modest (d=0.30-0.40) and comparable to a prior meta-analysis.

Conclusion: This meta-analysis shows that effect of CPAP treatment on cognition is small and limited to the attention domain. These findings indicate that, contrary to the general assumption, only slight improvement of cognitive functioning after CPAP treatment can be expected.

P1725 Inaccuracy of built-in ventilator softwares (BIVS) in monitoring apnea-hypopnea index (AHI) in patients treated by home non invasive ventilation (NIV)

Julie Teule1, Frédéric Damagnes2, Ha Tran1, 1Pediatric Sleep Center, Center for Reference of CCHS, Robert Debré Hospital, Paris, France; 2ADEP Assistance, Suresnes, France; 3Univ Paris Diderot, Paris, France

Home ventilators are often equipped with BIVS able of recording various parameters over many months. AHI is one of the parameter most frequently used by clinicians to monitor efficiency of ventilation applied to patients with Obstructive Sleep Apneas (OSA). However, the reliability of algorithms used by BIVS to detect apnea (A) or hypopnea (H) has yet to be determined.

Patients & methods: We studied 55 patients with severe OSA (4M, 1F, 10.5 years, range 2.5-15 years) and treated by NIV (4 CPAP, 1 BiPAP). An overnight respiratory polygraphy (RP) was performed while the patient was on NIV at home. All RP were analyzed as usually recommended by one of us (J.T.) blinded to BIVS data. We compared A and H detected by BIVS versus those detected by RP.

Results: BIVS detected 169 A-H that were related to movements in 56% and no visible event using RP in 25% of cases.

Table 1

<table>
<thead>
<tr>
<th>Nb of events (%)</th>
<th>Movements-RP</th>
<th>No event-RP</th>
<th>A-RP</th>
<th>H-RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-VS</td>
<td>28 (100%)</td>
<td>21 (75%)</td>
<td>4 (14%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>H-VS</td>
<td>141 (100%)</td>
<td>74 (52%)</td>
<td>39 (28%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>A-H-VS</td>
<td>149 (100%)</td>
<td>95 (66%)</td>
<td>43 (25%)</td>
<td>31 (18%)</td>
</tr>
</tbody>
</table>

Among the 88 A-H detected by RP, only 35% were recognized by BIVS.

Table 2

<table>
<thead>
<tr>
<th>Nb of events (%)</th>
<th>No event-VS</th>
<th>A-VS</th>
<th>H-VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-RP</td>
<td>19 (100%)</td>
<td>8 (42%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>H-RP</td>
<td>69 (100%)</td>
<td>49 (71%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>A-H-RP</td>
<td>88 (100%)</td>
<td>57 (65%)</td>
<td>31 (35%)</td>
</tr>
</tbody>
</table>

Conclusion: The majority of A-H detected by BIVS was related to patient movements, whereas BIVS was unable to detect A-H seen in RP. These preliminary data support that AHI provided by BIVS is largely inaccurate in patients during NIV and should not be used to adjust NIV. Polysomnographies are required to monitor efficiency of NIV.
P1726
The inter-observer reliability of using a new non-invasive technique to identify patient ventilator asynchrony (PVA) during non-invasive ventilation (NIV) for respiratory muscle unloading resulting in patient discomfort and reduced adherence. We hypothesised that non-invasive measurements with pre-defined PVA criteria would be reliably correlated between 2 independent observers.

Methods: 5 patients initiated on NIV were assessed for PVA using respiratory inductance plethysmography (RIP), 2nd intercostal space parasternal electromyo-gramy (EMGpara) and mask pressures (Pmasks). Two independent observers each recorded PVA from the overnight traces examining each breath from a 2 minute period for each 10 minute epoch over an hour.

Results: A total of 1347 breaths were analysed by each observer. Correlation between two independent observers

<table>
<thead>
<tr>
<th>Type of Asynchrony</th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Intraclass correlation coefficient (ICC), 95% CI</th>
<th>Bland-Altman correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineffective efforts</td>
<td>255 (19%)</td>
<td>219 (16%)</td>
<td>0.90, 0.39-0.99</td>
<td>7.2 (-45.3, 59.7)</td>
</tr>
<tr>
<td>Premature cycling</td>
<td>63 (5%)</td>
<td>49 (4%)</td>
<td>0.75, -0.19-0.97</td>
<td>2.8 (-49.9, 25.5)</td>
</tr>
<tr>
<td>Extended cycling</td>
<td>4 (1%)</td>
<td>10 (1%)</td>
<td>0.36, -0.58-0.00</td>
<td>-1.2 (-6.5, 4.1)</td>
</tr>
<tr>
<td>Auto-triggering</td>
<td>103 (8%)</td>
<td>22 (2%)</td>
<td>0.08, -0.29-0.76</td>
<td>16.2 (-151, 47.5)</td>
</tr>
<tr>
<td>All asynchronies</td>
<td>429 (32%)</td>
<td>312 (23%)</td>
<td>0.87, 0.75-0.94</td>
<td>2.6 (-33.5, 40.7)</td>
</tr>
</tbody>
</table>

Conclusion: PVA can be reliably identified using the above technique. The predominant PVA was ineffective effort. This analysis could be automated to provide a simple approach to assessing PVA.

P1727
How well do questionnaires capture symptomatic relief and well-being over time with NIV in motor neuron disease?

Hikari Ando1, Biswajit Chakrabarti2, Carolyn Young3, Rosanna Cousins4, Everard Thornton5, Robert Angus5, 1Health Sciences, Liverpool Hope University, Liverpool, United Kingdom; 2Chest Centre, Aintree University Hospitals NHS Foundation Trust, Liverpool, United Kingdom; 3Neurology and Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom; 4School of Psychology, University of Liverpool, United Kingdom

Benefits of non-invasive ventilation (NIV) in motor neuron disease (MND/ALS) have been explored using quantitative health measurements with little examination of subjective experience. This study explored whether current quantitative tools commonly used in MND adequately capture the effects of NIV. 6 patients (all male, mean age 67) from an original cohort of 35 were available for the present study having survived a year on NIV. Both questionnaires and semi-structured interviews were completed at 3 occasions: pre-NIV (Point A), 4-months (Point B) and 10-months post-NIV (Point C). The scales used were ALSFRS-R (physical functioning), ALSAQ-40 (ALS specific health status), MNDRS (dyspnoea), BDI (depression), BHS (hopelessness), HADS (depression and anxiety) and ESS (sleepiness). During the interviews, experience of NIV, physical changes and their impact on daily life were explored. All interviews were assessed using thematic analysis. Quantitative scores were compared using analysis of variance. Changes were seen from points A to C in ALSFRS-R 33 ± 27 (p=0.021), ALSAQ subscale for communication 46 ± 29 (p=0.018), BHS 3.67 ± 1.80 (p=0.03) and ESS 9.50 ± 2.8 (p=0.046). The scores of ALSFRS-R denote worsening functional status, while the other scales indicate improvement. Qualitatively, 4 symptoms were discriminated as problematic and were improved by NIV: energy level, quality of night sleep, daytime sleepiness and breathlessness. The results show the multidimensional range of symptoms that relate to hypoventilation in MND and how the routinely employed scales may fail to capture significant symptomatology or the impact of NIV on such symptoms.

P1728
Chronic pulmonary diseases and the epidemiology of invasive pneumococcal infection

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Chronic pulmonary disease is an established risk factor for acquiring invasive pneumococcal disease (IPD), but estimates have in most cases been based on studies with aggregated denominators data on comorbidities and have not been large enough to allow detailed analyses on less prevalent pulmonary diseases. There have also been conflicting results whether or not an underlying pulmonary disease increases the risk of death from IPD. We examined the association between COPD, asthma, pulmonary fibrosis, sarcoidosis and pneumoconiosis and IPD, and the impact of these diseases on mortality from IPD.

IPD cases ≥ 18 years of age, 1990-2007, were identified via computerized databases. The associations between IPD and prior pulmonary diseases were assessed using conditional logistic regression, comparing IPD cases to 10 control subjects randomly selected from the general population (matched for sex, year of birth and county of residence). Adjustments were made for other chronic diseases, educational level and socio-economic position. Information on these was obtained through record linkage with other national databases.

4,085 cases of IPD were identified. COPD was associated with increased risk of IPD, (adjusted OR [aOR]: 4.7 [95% CI 4.0-5.6], as well as asthma (aOR: 2.2 [95% CI 1.6-2.8]) and pulmonary fibrosis (aOR: 5.3 [95% CI 2.8-10.0]), whereas sarcoidosis and pneumoconiosis were not independently associated with increased risk of IPD. In hospital mortality and 28-days mortality was not increased for patients suffering from the pulmonary diseases studied. Several but not all pulmonary diseases increase the risk of IPD although this seems not to be a risk factor for increased case-fatality rate.

P1729
Comparison of clinical characteristics between healthcare-associated pneumonia and community-acquired pneumonia in patients admitted into secondary hospitals

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Background: To evaluate the clinical characteristics of HCAP patients admitted into secondary hospitals in Korea.

Methods: This study was retrospectively conducted between March 2009 and January 2011.

Results: Among 303 patients, 31.7% had HCAP. 42 (43.7%) resided in a long-term care facility, 36 (37.5%) were hospitalized in an acute care hospital for ≥ 2 days within 90 days. The rates of patients with CURB-65 ≥ 3 (22.9% vs. 9.1%) and PSI IV or more (82.2% vs. 34.7%) were higher in the HCAP group. Drug resistant pathogens were more frequently detected in the HCAP group (23.9% vs. 0.4%; p<0.001). Despite lower overall survival rate (p<0.001), multivariable analyses failed to show that HCAP was a prognostic factor for mortality.
Institute, Herston, QLD, Australia; 3Respiratory Medicine, Royal Children's Hospital, Queensland Children's Medical Research Institute, Brisbane, Australia; 4Institute of Medical Microbiology, University of Wuerzburg, Bochum, Germany; Dipartimento di Medicina Clinica e Prevenzione, Università di Milano-Bicocca, San Gerardo Hospital, Monza, Milan, Italy; Pneumology, Hospital La Fe de Valencia, Spain Infectious Disease, Hospital Clinic, IDIBAPS, Barcelona, Spain; Thoraxzentrum Ruhrgebiet, Klinikum für Pneumologie und Infektiologie, Thoraxzentrum Ruhrgebiet, Klinikum für Pneumologie und Infektiologie, EKV Herne und Augusta-Kranken-Anstalt, Bochum, Germany; Dipartimento di Medicina Clinica e Prevenzione, University of Milan-Bicocca, San Gerardo Hospital, Monza, Milan, Italy; Pneumology, Hospital La Fe de Valencia, Spain Infectious Disease, Hospital Clinic, IDIBAPS, Barcelona, Spain; Respiratory Medicine Section, Departamento Toracico-Pulmonare e Cardiocircolatorio, University of Milan, IRCCS Fondazione Ca' Granda Ospedale Maggiore, Milan, Italy

Background: Community-acquired pneumonia (CAP) is currently undergoing re-evaluation. The aim of the study was to determine the influence of age and comorbidity on microbial patterns in elderly patients with community-acquired pneumonia (CAP).

Methods: In a prospective observational study of adult patients with CAP, excluding those residing in nursing homes, we compared patients aged 65 - 74 years, 75 - 84 years and 85 years or older for potential differences in clinical presentation, comorbidities, severity on admission, microbial investigations, aetiologies, antimicrobial treatment, and outcomes.

Findings: We studied a total of 2149 patients. The number of patients in each age group was as follows: 759 (35.3%) patients aged 65-74 years, 941 (43.7%) aged 75-84 years, and 449 (20.8%) patients aged 85 years or older. At least one comorbidity was present in 1710 (79.6%) patients. Strepococcus pneumoniae was the most frequent pathogen in all age groups, regardless of comorbidity. Pathogens such as S. aureus (including MRSA), enterobacteriaceae, and P. aeruginosa were present in 15% and were found almost exclusively in patients with comorbidities. Increasing CAP severity on admission and mortality by decreasing ICU admission rates and use of mechanical ventilation suggested an increasing frequency of treatment restrictions across age groups.

Interpretation: Age did not significantly affect pathogen patterns. Potential multidrug-resistant (MDR) pathogens were not frequent and were found almost exclusively in patients with comorbidities. Excess mortality in the elderly was not related to aetiology but to age and disability.

P1732

Impact of age and comorbidity on presentation, aetiology and outcome in patients with community-acquired pneumonia

Cata Cilliron1, Eva Polverino, Santiago Ewig, Stefano Alberiti, Albert Gabarras, Ruthi Moreno, Josep Mena, Francesco Blasi, Antoni Torres.

Background: The ATS/IDSA guidelines for community-acquired pneumonia (CAP) were published in 2005. Both the bacteriological incidence and CAP risk factors have been described in recently published studies. Many of these CAP patients had risk factors for CAP and most of them had a comorbid illness. The objective of this study was to determine the influence of age and comorbidity on CAP presentation, aetiology and outcome in elderly people.

Methods: A total of 2149 patients were included in this prospective study: 759 patients aged 65 - 74 years, 941 patients aged 75 - 84 years, and 449 patients aged 85 years or older. A comparison of the main clinical and demographic characteristics was performed using a logistic regression model.

Findings: The main clinical and demographic characteristics were similar among the age subgroups. Only age, presence of comorbidities, and mortality were significantly different between the age groups.

Interpretation: Age and comorbidity are important factors in the presentation, aetiology and outcome of CAP. Further studies are needed to determine the impact of age and comorbidity on the treatment and prevention of CAP in elderly people.
important in addition to potentially drug-resistant pathogens (P. aeruginosa and S. aureus), and oral streptococci were more important than previously reported in patients with HCAP.

P1734

Effect of excluding ICU-admission on clinical outcomes in a randomized control trial addressing the effect of corticosteroids in patients hospitalized with CAP

Background: The effect of corticosteroids in patients hospitalized with CAP has not been thoroughly evaluated. In 2010, Snijders performed a multicenter cohort study and reported a higher rate of late failures in the prednisolone group. The objectives of this study were to evaluate the effect of excluding patients admitted to the ICU in a prospective randomized controlled trial.

Design: Randomized, placebo-controlled, double-blind trial.

Setting: Pulmonary Diseases, Medical Centre Alkmaar, Alkmaar, Netherlands; 
3 Internal Medicine and Pulmonary Diseases and Tuberculosis, University Medical Center, Groningen, Netherlands.

Methods: A prospective multicenter cohort study was performed in 13 hospitals. Severe sepsis was diagnosed using Drensmizov criteria (Chest 2006;129:968-978). 4,137 patients were included: 1,171 (28.3%) without severe sepsis, 1,394 (33.7%) with non severe sepsis and 1,572 (38%) with severe sepsis: 521 (33.1%) of these had early (≥48 hours) and 1,051 (62%) late onset. There were no gender differences in early vs. late onset. Early sepsis was associated to elderly patients (≥65 years: 72.2% vs. 65.2%; p=0.006). Statistical differences in clinical presentation and comorbid conditions are depicted in Table 1. Early/severe sepsis showed higher CURB65 scores than late sepsis (49.6% of patients vs. 41.5% with score 3).

Results: A prospective multicenter cohort study was performed in 13 hospitals. Severe sepsis was diagnosed using Drensmizov criteria (Chest 2006;129:968-978). 4,137 patients were included: 1,171 (28.3%) without severe sepsis, 1,394 (33.7%) with non severe sepsis and 1,572 (38%) with severe sepsis: 521 (33.1%) of these had early (≥48 hours) and 1,051 (62%) late onset. There were no gender differences in early vs. late onset. Early sepsis was associated to elderly patients (≥65 years: 72.2% vs. 65.2%; p=0.006). Statistical differences in clinical presentation and comorbid conditions are depicted in Table 1. Early/severe sepsis showed higher CURB65 scores than late sepsis (49.6% of patients vs. 41.5% with score 3).

Table 1. CAP with severe sepsis characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early onset (≥48h)</th>
<th>Late onset (&gt;48h)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consomorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>121 (23.2%)</td>
<td>184 (17.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>85 (16.3%)</td>
<td>85 (8%)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90 mmHg</td>
<td>161 (30.9%)</td>
<td>235 (22.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tachypnea ≥30</td>
<td>143 (27.1%)</td>
<td>205 (19.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Tachypnea &lt;30</td>
<td>278 (51.7%)</td>
<td>355 (33.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>46 (8.7%)</td>
<td>140 (13.1%)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Conclusions: This study showed that excluding ICU-patients prednisolone did have an impact on LOS and TTCS with an increased rate of late failures.

P1735

Characterization of community acquired pneumonia (CAP) with severe sepsis at diagnosis

Background: Early severe sepsis in CAP presents with greater severity while late onset does with large radiographic involvement. Diabetics, elderly patients and those with cerebrovascular disease are more prone to develop rapid onset severe sepsis in CAP.

Methods: We analyzed the degree of HRF measured as PaO2/FiO2 ≥250 in a group of patients with SCAP (PSI IV-V) who scored the item hypoxemia in PSI score (PaO2 <60 mmHg, >10 ps). Factors that determined a greater degree of HRF and its influence in the outcome (complications and mortality) were analyzed.

Results: From a cohort of 1,314 pneumonias, 364 (27.7%) were hypoxemic SCAP (PSI IV-V and PaO2/FiO2 <250) rated higher in PSI score [123.9 (23.4) vs 116.3 (20.2); p=0.01]. Multivariate analysis showed that PaO2/FiO2 ≤250 group (17.1% vs 4.1%; p=0.01), and a longer hospital stay (13.4 (14.7) vs 10.2 (6.5) days; p=0.014). Mortality was significantly higher in PaO2/FiO2 ≤250 group (17.1% vs 4.1%; p<0.01). The degree of HRF could negatively impact in the outcome (complications and mortality) of CAP.3-Our data suggest that the assessment of hypoxemia in SCAP should be considered as semi-quantitative data due to its prognostic implications.

P1737

Cardiac diseases in patients with community acquired pneumonia (CAP)

Background: Community Acquired Pneumonia (CAP) and cardiac diseases are mutually aggravating conditions. There is a surge of interest in the association of major cardiac diseases and CAP and this study was done to contribute to the world’s literature from the Indian sub-continent.

Materials and methods: In this retrospective analysis of patients admitted with CAP between January 2011 and January 2012 at a tertiary care referral centre we looked for associated cardiac diseases.

300s
Results: Of the total patients included in the analysis (n=73), 34.24% (25) had an associated cardiac disease. There were 45 instances of cardiac problems. 19.17% (14) had pulmonary hypertension, 16.44% (12) had CCF/Acute LVF, 13.69% (10) had ischemic heart disease, 4.1% (3) had Rheumatic heart diseases, 2.76% (2) had arrhythmias and there was 1 instance each of Infective endocarditis, acute pulmonary thromboembolism, congenital heart disease and MI (1.36%). 14.36% (out of 25) patients who had cardiac diseases required ICU care while 9 (18.75%) out of 48 patients who did not have cardiac conditions required ICU care(p=0.001). 6 out of 25 patients had new onset cardiac problems. Two patients in the cardiac disease group and 1 patient in the non cardiac disease group, one patient died.

Conclusions: There is a high degree of correlation between pre existing cardiac disease and CAP as also between CAP and new onset cardiac diseases especially CAD.

P1738

The role of procoagulant activity in patients with community acquired pneumonia

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Pulmonary Department, Meir Medical Center, Kfar Saba, Israel Internal Medicine E Department, Meir Medical Center, Kfar Saba, Israel

Community acquired pneumonia (CAP) is still one of the most important causes of morbidity and mortality. In severe cases, parapneumonic effusions or empyema may develop. In these patients, the increased vascular permeability, mediated by several cytokines, allows migration of inflammatory cells, an increased fluid accumulation and bacterial invasion into pleural space. The activation of the fibrinolytic system produces D-dimer and follow by increased other procoagulant markers like thrombin anti thrombin (TAT), fragment 1.2. Moreover, serum levels of AT-III, D-D and CRP at admission appear to be useful biomarkers for assessing the severity of CAP. Our study included patients with CAP Blood D-dimer, TAT and Fragment 1,2 levels were measured by Enzyme Linked Fluorescent assay 24 and 48 hours after admission. The results were correlated with the clinical, laboratory, and radiologic findings (PORT and ARDS II). A total of 50 patients with pleural effusion were included in the study. Eleven patients (18%) developed pleural effusion. Only D-dimer levels increased 48 hours following admission compared to the 24 hours levels (1939±1234 vs 1812±1192 ng/ml). Fragment 1 and TAT levels decreased after 48 hours. D-dimer at 24 hours was correlated with the age, platelet counts and PORT score. F 1.2 and TAT at 24 hours were correlated with recent of neuprophils. PT at 24 hours was correlated with WBC count. After 48 hours, D-dimer was correlated only with age. F1.2 and TAT had no correlations with clinical parameters after 48 hours. The 24 hours D-dimer predicts severity of CAP. Other coagulation markers and serial monitoring of blood coagulation markers have a limited role in predicting CAP.

P1739

Pancreatic stone protein predicts positive sputum bacteriology in exacerbations of COPD

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Background: Pancreatic Stone Protein(Regenerating protein) (PSP/Reg) is increased in bacterial inflammatory processes. PSP/Reg might therefore be also useful as a predictor of bacterial infection in COPD. Methods: 200 consecutive patients presenting to the emergency department due to acute exacerbation of COPD were prospectively assessed. Patients were evaluated based on clinical, laboratory and lung-functional parameters at admission (exacerbation) and after short term follow-up (14-21 days). PSP/Reg serum values were measured by a new developed enzyme linked immunosorbent assay (ELISA). Results: PSP/Reg levels were elevated in subjects with COPD exacerbation (23.8 ng/ml 95% CI [17.1-32.7]) when compared to those with stable disease (19.1 ng/ml 95% CI [14.1-30.4]) and healthy controls (14.0 ng/ml 95% CI [12.0-19.0], p<0.01). Higher of CAP were observed in exacerbation with positive (26.1 ng/ml 95% CI [19.2-38.1]) as compared to those with negative sputum bacteriology (20.8 ng/ml [15.6-27.2], p<0.01). Multivariate regression analysis revealed PSP/Reg as an independent predictor of positive sputum bacteriology. A combination of PSP/Reg cut-off of ≥ 33.9 ng/ml and presence of discolored sputum had a specificity of 97% to identify patients with pathogen bacteria on sputum culture. In contrast, PSP/Reg levels <18.4 ng/ml and normal sputum color ruled widely out positive bacterial sputum culture (sensitivity 92%). In survival analysis, high PSP/Reg levels at cut-off of 33.9 ng/ml were associated with increased 2-year mortality. Conclusions: PSP/Reg might represent a promising new biomarker to identify bacterial etiology of COPD exacerbation in future.
Results: A total of 110 patients (68 F) had a diagnosis of bronchiectasis with a median(range) age of 62(17-87) years and median(range) age of 65(12%-133%). Investigations carried out are shown in table 1 & underlying etiology in table 2.

<table>
<thead>
<tr>
<th>Investigations carried out</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunglobulins</td>
<td>82%</td>
</tr>
<tr>
<td>CT Chest</td>
<td>73%</td>
</tr>
<tr>
<td>IgE levels</td>
<td>62%</td>
</tr>
<tr>
<td>Specific Antibodies titre</td>
<td>53%</td>
</tr>
<tr>
<td>Asperigillus IgG Levels</td>
<td>49%</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>36%</td>
</tr>
<tr>
<td>Sweat test</td>
<td>27%</td>
</tr>
<tr>
<td>IgG subclass</td>
<td>25%</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin levels</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 2. Underlying Aetiology of Bronchiectasis

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No underlying aetiology identified as yet</td>
<td>54%</td>
</tr>
<tr>
<td>Asthma</td>
<td>16%</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>10%</td>
</tr>
<tr>
<td>Post infective</td>
<td>9%</td>
</tr>
<tr>
<td>Primary Pulmonary Hypertension</td>
<td>6%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>5%</td>
</tr>
</tbody>
</table>

P1743 Bacterial aetiology in the Danish pleural empyema project

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Recent publications identified the aetiology of pleural empyemas with results varying according to antimicrobials given before sampling. Objectives: Our aim was to identify the microbiological aetiology in pleural empyema by standard methods and later evaluate, if DNA-amplification methods may supplement culture results by detecting further clinically relevant microorganisms.

Methods: From 2008-2011 in the Danish Pleural Emphyema Project, the respiratory medical departments from 8 Danish hospitals participated. Cases were prospectively identified clinically and pleural fluid samples were collected for standard microbiological analysis (microscopy and culture). Further samples were collected and kept in storage at minus 80 degrees Celsius for later PCR analyses. Cases judged as non-infectious were excluded. Clinical data were collected regarding symptoms, pre-admission treatment, clinical findings, risk factors, co-morbidity, blood test results, radiology, treatment, and outcome.

Results: A total of 434 episodes of pleural empyema were identified. In 242 cases (56%), the cultured were either negative (n=198) or no pleural samples were successfully taken (n=44). Among the 192 cases with proven aetiology, mixed infections were identified in 47 cases (24%), 34 Streptococcus pneumoniae (18%), 53 non-pneumoniae streptococci (28%), 16 Staphylococcus aureus (8.3%), 15 enterobacteriaceae (7.8%), 15 anaerobes (7.8%), and 5 Enterococcus species (2.6%).

Conclusions: 56% of the cases were culture negative by standard methods. Future studies are planned to implement DNA-methods optimised for mixed infections for identification of the micro-organisms. This may expand the identified spectrum of detected micro-organisms and improve the treatment.

P1744 Predictors of rehospitalization after admission for community-acquired pneumonia

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The aim of our study was to examine variations in rates of rehospitalization, and predictors of rehospitalization, for patients hospitalized with community-acquired pneumonia (CAP) in the United States Department of Veterans Affairs (VA) health care system.

We conducted a retrospective national cohort study over 5 years including patients >65 years of age hospitalized with CAP. Our primary outcome was all-cause rehospitalization within 90-days. Our primary analysis was a multilevel regression model, adjusting for admitting hospital, and included 38 variables encompassing demographics, pneumonia severity, antibiotics received, prior outpatient medications, pre-existing comorbid conditions, and prior outpatient utilization (e.g., emergency department, primary care) the year prior to the pneumonia admission.

We identified 50,119 patients with CAP of which 21.8% required rehospitalization within 90-days. Hospital rates varied from 14.3% to 32.3%. In the regression model, factors significantly associated with increased rehospitalization included alcohol abuse (odds ratio 3.07, 95% confidence interval 1.23-7.61), number of prior outpatient pulmonary medications (1.10, 1.01-1.19), and number of prior emergency department visits (1.1, 1.04-1.14).

A large number of patients required rehospitalization after admission for CAP, and rates varied widely. Only a few factors were significantly associated with rehospitalization and these factors were not related to the pneumonia hospitalization. Additional research is needed to determine which rehospitalizations after pneumonia are preventable and ways to prospectively identify hospitalized CAP patients at risk for rehospitalization.

P1745 Comparison of PSI, A-DROP, CURB-65, CRB-65, and SOAR indices in hospitalized patients with community acquired pneumonia

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We evaluated the relation between PSI, A-DROP, CURB-65, CRB-65, and SOAR indices and investigate the importance of these indices in the follow up of hospitalised patients with community acquired pneumonia(CAP).

Patients hospitalized in Celal Bayar University Chest Disease Clinic between January 2009 and January 2010, due to CAP, were included in the study. Socio-demographic findings, symptoms, comorbidities, habits, history, physical examination findings, laboratory and radiological findings, pneumonia severity groups, treatment result, duration of hospitalization, and cost of disease treatment of patients were obtained from "Pneumonia Data Base" prepared by Turkish Thoracic Society Respiratory Infections Scientific Assembly.Indices above were calculated for each patient.

70 patients were included to study. There were 49 male(70%) and mean age was 63.07±18.08 years. Mean duration of hospitalization was 10.08±5.64 days. 57 patients(81.4%) were totally cured after one month follow up. Indices mentioned above were correlated with each other(Pearson correlation test)(p<0.005). There was no difference between indices according to total cure and development of complication due to pneumonia(p>0.05). Duration of hospitalization of CAP patients was categorized as 0-14 days and more than 14 days. These indices were found significantly different when comparison was done according to this categorization(p<0.05).

PSI, A-DROP, CURB-65, CRB-65, and SOAR indices were found to be correlated with each other.All of the indices mentioned above has low estimation rate for the duration of hospitalization. We identified 50,119 patients with CAP of which 21.8% required rehospitalization within 90-days. Hospital rates varied from 14.3% to 32.3%. In the regression model, factors significantly associated with increased rehospitalization included alcohol abuse (odds ratio 3.07, 95% confidence interval 1.23-7.61), number of prior outpatient pulmonary medications (1.10, 1.01-1.19), and number of prior emergency department visits (1.1, 1.04-1.14).

A large number of patients required rehospitalization after admission for CAP, and rates varied widely. Only a few factors were significantly associated with rehospitalization and these factors were not related to the pneumonia hospitalization. Additional research is needed to determine which rehospitalizations after pneumonia are preventable and ways to prospectively identify hospitalized CAP patients at risk for rehospitalization.

P1746 Selection of suitable housekeeping genes for real-time quantitative PCR in CD4+lymphocytes from asthmatics with or without depression

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Objective: No optimal housekeeping genes (HKGs) have been identified for CD4+ T cells from non-depressive asthmatic and depressive asthmatic adults for normalizing quantitative real-time PCR (qPCR) assays. The aim of present study was to select appropriate HKGs for gene expression analysis in purified CD4+ T cells from these asthmatics.

Methods: Three groups of subjects (Non-depressive asthmatic, NDA, n=10, Depressive asthmatic, DA, n=11, and Healthy control, HC, n=10) respectively were studied. qPCR for 9 potential HKGs, namely RNA, 28S ribosomal 1 (RN28S1), ribosomal protein, large, P0 (RPLP0), actin, beta (ACTB), cyclophilin A (IPPA), glyceraldehydes-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase 1 (PGK1), beta-2-microglobulin (B2M), glucuronidase, beta (GUSB) and ribosomal protein L13a (RPL13A), was performed. Then the data were analyzed with three different applications namely BestKeeper, geNorm, and NormFinder.

Results: The analysis of gene expression data identified B2M and RPLP0 as the most stable reference genes and showed that the level of PPA was significantly different among subjects of three groups when the two best HKGs identified model, adjusting for admitting hospital, and included 38 variables encompassing demographics, pneumonia severity, antibiotics received, prior outpatient medications, pre-existing comorbid conditions, and prior outpatient utilization (e.g., emergency department, primary care) the year prior to the pneumonia admission.

We identified 50,119 patients with CAP of which 21.8% required rehospitalization within 90-days. Hospital rates varied from 14.3% to 32.3%. In the regression model, factors significantly associated with increased rehospitalization included alcohol abuse (odds ratio 3.07, 95% confidence interval 1.23-7.61), number of prior outpatient pulmonary medications (1.10, 1.01-1.19), and number of prior emergency department visits (1.1, 1.04-1.14). A large number of patients required rehospitalization after admission for CAP, and rates varied widely. Only a few factors were significantly associated with rehospitalization and these factors were not related to the pneumonia hospitalization. Additional research is needed to determine which rehospitalizations after pneumonia are preventable and ways to prospectively identify hospitalized CAP patients at risk for rehospitalization.

212. Recent progress in mechanisms and diagnostics of COPD and asthma
were applied. Post hoc analysis by Student-Newman-Keuls correction shows that depressive asthmatics and non-depressive asthmatics exhibited lower expression than other groups, and this group showed significantly lower expression of IL-17A mRNA in the lungs on day 21 in PPE-treated WT mice, which was significantly increased compared to PBS-treated ones (p < 0.05). In contrast, IL-17A–/– mice administered with PPE showed significantly less increase in the CSE lung and Lm (p < 0.05, compared to WT).

Conclusions: These results suggest that IL-17A contributes to the development of elastase-induced neutrophilic inflammation and emphysema in mice.

P1748 Promotor methylation of Bcl-2 in cigarette smoke extract-induced emphysema
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Objective: Abnormal apoptotic events may play an important role in emphysema. We determined whether Bcl-2, a pivotal regulator of apoptosis, participates in emphysema. Furthermore, given the methylation in promoter CpG islands causing gene silencing, and existence of CpG islands in Bcl-2 promoter, we hypothesized that the demethylation in CpG islands of Bcl-2 gene might reduce its expression.

Methods: BAL/Bc mice were divided into four groups (n=10 per group): CSE–, CSE+5-aza-2'-deoxycytidine(AZA, demethylation reagent), AZA, and control (phosphate buffered saline, PBS). CSE group were intratracheally injected with CSE once a week for 3 weeks to build emphysema models. AZA and PBS were also administered weekly as CSE. After 3 weeks of treatment, TUNEL assay was used to assess apoptotic index of pulmonary cells; western blotting or Real-time-RT-PCR were used to detect expression of Bcl-2 and Cyt C in pulmonary tissue; bisulphite sequencing PCR (BSP) was used to observe the methylation status of Bcl-2 promoter.

Results: The apoptotic index of pulmonary cells in CSE group (42.5 ± 2.8%) was significantly higher compared with others (p < 0.05). The CSE induce-emphysema mice presented lower expression of Bcl-2 protein and RNA than other groups, and this group showed significantly lower expression of Bcl-2 protein and RNA than other groups (p < 0.05). (3) The CSE demethylation group showed higher expression of cytoplasmic Cyt C than other groups (p < 0.05). (4) The CSE group showed higher methylation ([19.2±2.6]% ± [3.0±0.8], [4.5±0.6]% ± [0.9±0.5]) in CSE group on day 0. IL-17A mRNA expression in the lungs was assessed with RT-PCR. Lung inflammation was determined by differential cell count in bronchoalveolar lavage fluid. On day 0, IL-17A lung expression by forced oscillation method. Emphysema was assessed by alveolar mean liner intercept (Lm) determined by computer-assisted morphometric analysis.

Conclusions: We established a mouse model of short-term cigarette smoke exposure, which is accompanied by neoplastic transformation in the lungs. The methylation of Bcl-2 gene promoter might be involved in the pathogenesis of cigarette smoke-induced emphysema. These results suggest that the deregulation of Bcl-2 in emphysema might be caused by methylation.

P1747 Interleukin-17A in the pathogenesis of elastase-induced emphysema in mice Nobumitsu Kamishi1, Koichiro Aso1, Takahisa Takahira1, Shizuko Kagawa1, Shuichi Yoshida2, Naoto Minematsu1, Hideotsuyu Nakamura1, Kyuto Tanaka1, Jun Miyata1, Yuseake Suzuki1, Tetsuya Shimizu1, Koshi Fukunaga1, Koichi Sayama1, Seitaro Fujishima1, Yoshiro Iwakura1, Tomoko Betsuyaku1.

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Background: Recent studies show that interleukin (IL) -17A is highly expressed in the lungs of patients with chronic obstructive pulmonary disease (COPD) and in the emphysematous lungs of mice after long-term cigarette smoke exposure. However, the role of IL-17A in the pathogenesis of emphysema is still unknown. In the present study, we examined the role of IL-17A in the development of emphysema.

Methods: Porcine pancreatic elastase (PPE) or phosphate buffered saline (PBS) was administrated intratracheally in B6-D2F1 and wild-type (WT, C57BL/6J) mice on day 0. IL-17A mRNA expression in the lungs was assessed with RT-PCR. Lung inflammation was determined by differential cell count in bronchoalveolar lavage fluid. On day 1, lung expression by forced oscillation method. Emphysema was assessed by alveolar mean liner intercept (Lm) determined by computer-assisted morphometric analysis.

Results: IL-17A mRNA expression was increased in WT mice 6 hours after the administration of PPE. It was accompanied by neutrophilic inflammation in the lungs on day 2– day 14 whereas neutrophil recruitment was significantly reduced in IL-17A–/– mice (p < 0.05). Lung compliance and emphysema (Lm) on day 21 in PPE-treated WT mice was significantly increased than in PBS-treated ones (p < 0.05). In contrast, IL-17A–/– mice administered with PPE showed significantly less increase in the compliance and Lm (p < 0.05, compared to WT).

Conclusions: These results suggest that IL-17A contributes to the development of emphysema.

P1750 Effect of genetic polymorphisms of some cytokines and xenobiotic-metabolizing enzymes on the lung function in patients with COPD
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Background: COPD is a chronic inflammatory lung disease characterized by decreased expiratory flow rate. The decrease of lung function in COPD depends on tissue remodelling due to xenobiotic- and inflammation-induced ROS-mediated tissue damage and impaired proteinase/antiproteinase balance. Since the activity and/or the protein level of cytokines and enzymes involved in inflammation and xenobiotic and antioxidant detoxification are found to be associated with some gene variants, we aim to evaluate the role of gene polymorphisms of three xenobiotic-metabolizing enzymes and three proinflammatory cytokines as factors involved in decline of lung function in COPD. We genotype altogether 164 patients with COPD and 174 non-affected by the disease, control group.

Methods: In the present study, we analyzed six genetic polymorphisms of three enzyme systems: GSTP1+313A, IL-10 –174G/C, TNFA –308G/A, IL1B –511C/T, IL1B +3953C/T and for the null polymorphisms in GSTM1 and GSTTI. Our results displayed that the carriers of A allele of GSTP1+313A-G showed a tendency for higher FEV1%, compared to the carriers of GG genotype (p=0.097). Patients COPD stage III/IV having GSTM1 null genotype demonstrated significantly lower FEV1% values (39.16%) than those with non-null genotype (43.91%, p=0.032). Moreover, patients with C containing genotypes of IL-10 –174G–C SNP had significantly lower FEV1/FVC% (59.7%) compared to the patients with GG genotype (62.7%, p=0.034). The polymorphisms in GSTTI, TNFA and IL1B did not show any significant associations with the lung function.

Results: In conclusion, we suggest that the polymorphisms in the genes of some cytokines and xenobiotic-metabolizing enzymes, such GSTP1, GSTM1 and IL1B are factors that may affect the lung functions in COPD.

P1751 Gender differences in 5- and 12/15-lipoxygenase products in bronchoalveolar lavage fluid from healthy never-smokers, smoker and COPD patients
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Background: Chronic obstructive pulmonary disease (COPD) is a leading disease that is increasing particularly among females. Smoking represents the main risk factor for developing COPD and chronic inflammation persists after smoking cessation.

Aims: We have investigated the effects of smoking, in relation to COPD, on lipid mediators in the inflammatory response in the lower airways.

Methods: Bronchoalveolar lavage fluid (BALF) was collected from healthy never-smokers, non-symptomatic smokers, and COPD patients of GOLD stage I-II (smokers and ex-smokers) of both genders. Different lipid mediators derived from the cytochrome P450, lipoxygenase (LOX) and cyclooxygenase (COX) pathways were analyzed by mass spectrometry.

Results: Products of 12/15-LOX and 5-LOX clustered respectively when analyzed by multivariate analysis and were summed for further comparisons. 12/15-LOX products were selectively increased in females. 5-LOX products exhibited a distinct pattern with increases in smokers, but no gender-specificity. There was no difference in lipoxygenase products between healthy smokers and smoking COPD patients. However, in COPD ex-smokers the levels of 5-LOX products were decreased compared to COPD smokers.
P1752

The role of chaperone α-B-crystallin (HspB8) in COPD pathogenesis

Radoszina Cherneva1, Ognian Georgiev1, Daniela Petrova2, Vesela Ivanova2

Background: α-B-crystallin is a chaperone whose role as a marker of innate immunity activation as well as its therapeutic potential have recently been investigated in several inflammatory diseases – multiple sclerosis, myocardial ischaemia, Guillain Barre syndrome.

Aim: The aim of the study is to determine the role of α-B-crystallin in COPD pathogenesis and immunization.

Materials: Plasma levels of α-B-crystallin were studied in 163 patients – 52 healthy non-COPD smokers; 20 COPD smokers I - II stage GOLD; 43 COPD smokers – III-IV stage (GOLD) and forty-eight patients with acute inflammatory respiratory disease. The plasma levels of α-B-crystallin antibodies were determined by ELISA (human anti α-B-crystallin Abcam), and were confirmed with Western blotting.

Results: The mean levels of anti - α-B-crystallin antibodies were: in non-COPD smokers and control group 0.169 ± 0.130 OD in healthy non-COPD smokers – 0.433 OD. There was a statistically significant difference between COPD smokers and healthy non-COPD smokers (p=0.010). The same could be observed comparing the group of patients with acute inflammation and non-COPD healthy smokers and healthy non-COPD smokers.

Conclusion: α-B-crystallin is increased in patients with inflammatory lung diseases. Further studies could be used in a panel of garkers discriminating COPD smokers from healthy non-COPD smokers. Being a regulator of innate immunity and a therapeutic anti-inflammatory agent its role in COPD pathogenesis and therapy should be further explored.

P1753

The incidence of alpha-1-antitrypsin (A1AT) deficiency alleles in Polish population – Preliminary results from newborn screening

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Background: α-B-crystallin (HspB8) is a chaperone whose role as a marker of innate immunity activation as well as its therapeutic potential have recently been investigated in several inflammatory diseases – multiple sclerosis, myocardial ischaemia, Guillain Barre syndrome.

Aim: The aim of the study is to determine the role of α-B-crystallin in COPD pathogenesis and immunization.

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Conclusion: α-B-crystallin is increased in patients with inflammatory lung diseases. Further studies could be used in a panel of garkers discriminating COPD smokers from healthy non-COPD smokers. Being a regulator of innate immunity and a therapeutic anti-inflammatory agent its role in COPD pathogenesis and therapy should be further explored.

P1754

Aim: The aim of the study is to determine the role of anti-α-β-crystallin (A1AT) deficiency alleles in Polish population.

The frequencies of the A1AT haplotypes of the studied two loci of A1AT (-511C-T and +3935C-T) did not differ significantly between controls and COPD patients (p=0.099). However, the T_C haplotype constructed by alleles found to determine enhanced expression of IL-1β, appeared to be associated with higher risk of COPD (OR 1.25, 0.88-1.79, p=0.231) compared to the most common C_C haplotype and with 1.7-fold higher risk of COPD (95% CI, 1.0-2.64, p=0.018) compared to the T_C haplotype, previously described in COPD patients.

Based on the results of the study the first time we propose that the T_C haplotype of A1AT-511C>T-3935C>T, supposed to determine enhanced expression of IL-1β, is a predisposing factor for COPD in Bulgarian population.

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Results: The proposed method of DNA extraction allowed successful DNA isolation from all analyzed DBS samples. Both quantity and quality of DNA were sufficient for further real-time PCR and genetic sequence analysis of all samples. The 100% concordance between AAT DBS genotypes and serum phenotypes in positive detection of two major deficiency alleles was achieved. Both assays, DBS AAT genotyping by real-time PCR and AAT phenotyping by IEF, positively identified AAT and PPZ AAT deficiency variants by real-time PCR. The results of AAT genotyping were validated by IEF phenotyping and concentration measurement of AAT protein in sera from the same patients. The diagnosis of rare/unknown AAT variants was established by direct sequencing.

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**P1757** Effect of cigarette smoking on sputum proteome profiles in patients with asthma and healthy volunteers

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**Background:** Smokers with asthma have more severe symptoms and impaired short-term recovery compared to non-smokers, but the mechanisms accounting for these adverse effects are poorly understood. We hypothesise that the differences in sputum protein profiles provide insight into the pathophysiological effects of smoking in asthma.

**Methods:** High resolution label-free shotgun proteomics was employed to investigate sputum protein profiles in 43 asthmatic non-smokers, 50 asthmatic smokers, 10 healthy non-smokers and 10 healthy non-smokers. Protein expression was normalised to sputum albumin level.

**Results:** A total of 596 and 335 proteins were confidently detected (FDR < 1%), Mascot) in asthmatic patients and healthy volunteers, respectively. Among them, 73 and 68 proteins were found differentially expressed between smokers and non-smokers for asthmatic patients and healthy volunteers, respectively (p < 0.05, Benjamini corrected). Majority of differences observed were up-regulation in smokers. Functional enrichment analysis showed that peptidase inhibitor activity and acute inflammatory/defence response were over-representative in healthy smokers compared to healthy non-smokers (p < 0.05, Benjamini corrected). In asthmatic smokers, there was an over-expression of oxidoreductase activity, thorodoxen fold (glutathione S-transferase), response to extracellular stimuli and lysosome related peptidase activity.

**Conclusions:** These results suggest that asthmatic patients may be hyper-responsive to cigarette smoke and that their airways may be susceptible to potential damage from lysosome related peptidase activity.

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**P1758** Polymorphisms of MDR1, ADRB2 and IL13 genes are markers of therapy-resistant bronchial asthma (BA) in Russian patients

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**Background:** BA is a multifactorial disease caused by the interaction of genes and environment. Genetic polymorphisms influence BA development, progression and severity as well as response to BA therapy.

**Aim:** To assess severity of BA and effectiveness of BA pharmacotherapy in patients with BA with different genetic background.

**Methods:** Genomic DNA was extracted from peripheral leukocytes. We investigated 4 SNPs by PCR-RFLP in 122 BA patients and in 103 healthy controls.

**Results:** Distribution of genotypes was similar to other European populations, except MDR1 gene. We revealed numerous associations of genetic variants with increased risk (IR): 3435CC with IR of BA (OR=3.92, 95%CI 1.74-8.79); 3435CC increased risk (IR): 3435CC with IR of therapy-resistant BA (OR=6.12, 95%CI 2.42-15.48); 1602yy with IR of respiratory failure (OR=17.31, 95%CI 2.01-149.28); 27Glu with IR of therapy-resistant BA (OR=3.5, 95%CI 1.16-9.66); 130Gln with IR of therapy-resistant BA (OR=2.09, 95%CI 1.01-4.30).

**Conclusions:** Analysis of MDR1, ADRB2 and IL13 polymorphisms is useful for both preventive care (revealing subjects with increased predisposition to BA) and pharmacotherapy optimization due to prediction of BA severity and risk of therapy-resistant BA.

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**P1759** Genome wide association study of lung function in asthmatics

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**Objective:** To investigate genes that may be important in determining lung function in subjects with asthma.

**Methods:** A genome-wide association study has been performed in subjects with asthma from the COMPASS study (Bleecker et al, Lancet 370: 2118-25, 2007). To reduce population stratification, homogenous populations were identified based on geographic region, self-reported race, and genetic ancestry using HapMap reference data. Standard quality control measures were applied to the resulting genotype data. Genome-wide association studies (GWAS) for percent predicted FEV1 and FEV1/FVC was performed on the genetically homogenous population from Eastern Europe using PLINK.

**Results:** To date, GWAS has been performed on 587,020 SNPs in Eastern Europeans (n = 885). For percent predicted FEV1, the top three SNP were in or near SLITRK5 (SLIT and NTRK-like family, member 5) on chromosome 13 (p=1.2-2.3x10-08). Additional genes of interest for percent predicted FEV1 include ADAM7 (A Disintegrin And Metalloprotease 7) (p=9.1x10-08) and ARAID (alpha-1d-adrenergic receptor) (p=1.1x10-09). For FEV1/FVC ratio, the top three genes are FGFI (fibroblast growth factor 1) (p=2.2x10-08), EPHA5 (ephrin type-A receptor 5) (p=2.8x10-09) and WNT3A (wingless-type MMTV integration site family, member 5A) (p=6.3x10-09).

**Conclusions:** Evidence was found to support the hypothesis that genes involved in regulation of cellular growth (ARAD1 and FGFI) and asthma susceptibility (EPHA5) are associated with lung function in subjects with asthma.

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**P1760** Assessment of allergic status of severe asthma with a new component resolved method using micro-array technique

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**Objective:** To investigate the concomitant allergen specific IgE status in severe asthmatics and evaluate the IgE reactivity of severe asthmatics.

**Methods:** We have used this test to screen a group of severe asthmatics. ISAC was performed in 21 consecutive patients with severe asthma (American Thoracic Society criteria). Lung function, exhaled nitric oxide (NO), blood eosinophilia, serum total IgE and skin prick tests for predominant allergens were systematically collected.

**Results:** Included 11 women and 10 men (mean age 52±6), median FEV1 76% predicted normal, mean NO 66±47 ppm. Seventy-eight (81%) patients had a negative ISAC and 4 (19%) had sIgE for at least one molecular allergen of the test. None of the 4 positive patients had sIgE toward several allergic sources (mice, pollens, animal dander). One patient was exclusively sensitized for Fel d1 (cat major allergen). Skin prick tests and ISAC were concordant in all patients. The other parameters, clinical, lung function and biology were not different in patients with positive ISAC compared to patients negative for the test. ISAC is useful to confirm the non atopic status of a subgroup of severe asthmatics and to identify precisely the sensitization profile of severe allergic asthmatics.

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**P1761** The roles of PCDH1 on epithelial barrier function in the airway

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**Background:** PCDH1 is recently identified as a susceptibility gene of bronchial hypersensitivity (BHR). Although PCDH1 seems to be involved in the differentiation of the airway, the roles of PCDH1 on epithelial barrier functions have not been determined.

**Methods:** A human airway epithelial cell line, 16HBE, cells were cultured on Transwell chamber for 5days. Barrier function was evaluated by Trans Elec- tric Resistance and dextran permeability. Expression of inflammatory cytokine and chemokine were determined by RT-PCR. Morphology of cell junctions was analysed by immunostaining using anti-PCDH1, anti-ZO-1, anti-Occludin and an anti-e-cadherin antibody.

**Results:** The paracellular barrier function of 16HBE cell monolayer increased over time in culture. Similarly, the expression of PCDH1 increased for the period. The knockdown of PCDH1 significantly inhibited the paracellular barrier function. In addition, it inhibited the dsRNA-induced inflammatory cytokines expressions. Immunocytostaining revealed that CTDH1 might coexist with E-cadherin at the cell-cell contact sites.

**Conclusion:** Our results indicated that a susceptibility gene of PCDH1 plays an important role in the immunological and physiological barriers of airway epithelium.
Sputum protein profile provides a comprehensive view of disease
MMP9, neutrophil elastase or MMP8 despite all of them showing a dramatic
A total of 631 proteins were confidently detected and analysed in this
volunteers.
Methods: The magnetic activated cell sorting separation coupled to fluorescence activated cell sorting separation strategy was used to harvest BM CD34+ progenitor cells from naïve and ovalbumin-challenged asthmatic mice. Isobaric tags for relative and absolute quantitation combined with 2D nano LC-MS/MS technology was employed to profile proteome alterations in CD34+ progenitor cells. The analysis of bioinformatics was performed finally.
Results: Twenty-five proteins with 18 up-regulated and 7 down-regulated ones were identified. In the dysregulated proteins, 4 clusters of proteins were observed around collagen groups, ACTN1/Myosin groups, Md2k and Serpin1, predominantly participating in pathways of focal adhesion, ECM-receptor interaction, tight junction and regulation of actin cytoskeleton.
Conclusions: Collagen group and ACTN1 related focal adhesion, ECM-receptor interaction and regulation of actin cytoskeleton could be the key pathway in bone marrow response of asthma.

Sputum protein profiles for monitoring lung pathophysiology in chronic lung diseases
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Background: Sputum proteome, mainly derived from proteins secreted from airway epithelial cells, immune related cells and proteins released from lysed cells/pathogens, is a potential source for the investigation of lung pathology and pathophysiology of diseases.
Objectives: We hypothesize that sputum protein profiles from cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) could provide novel insight into the pathophysiology.
Methods: High-throughput shotgun proteomics was used to investigate sputum protein profiles in 29 patients with CF, 27 patients with COPD and 23 healthy volunteers.
Results: A total of 631 proteins were confidently detected and analysed in this study group. Sputum protein profiles of CF shows a dramatic difference compared to those of healthy volunteers while the profiles of COPD patients were highly variable. Functional enrichment analysis indicates that CF has increased protein expression in pathways of chromatin assembly, actin filament-based process, defense response, carbohydrate catabolic process, anti-apoptosis, and cell motion (p < 0.001). A similar but less significant functional enrichment was found in COPD except that nicotinamide metabolic process was noticeable in COPD. We found that mortality in CF patients over the two consequent years was significantly associated with lower sputum α1-antitrypsin in CF patients (p < 0.001) but MMPs, neutrophil elastase or MMPs despite all of them showing a dramatic increase compared to healthy volunteers.
Conclusion: Sputum protein profile provides a comprehensive view of disease pathophysiology of chronic lung diseases. Some specific sputum protein expression could be useful for disease management and personalised treatment.

213. Diffuse parenchymal lung disease pathogenesis, biomarkers, therapy and new entities

P1764 Investigation of the cirtullination pathway in the pathogenesis of fibrotic lung disease
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Rationale: Our hypothesis was to explore whether an autoimmune process implicating an anti-citrullinated protein antibody is implicated in pulmonary fibrosis, both idiopathic and autoimmune.
Materials and methods: We evaluated the expression of PAD2 and PAD4, the enzymes mainly catalyzing the citrullination process, in the bronchoalveolar lavage fluid (BALF) of 53 IPF patients, 37 patients with thucmotated lung (RA-ILD) and 10 healthy controls. Survival was evaluated against smoking status, using proportional hazards analysis, adjusting for sex, age, disease severity (composite physiologic index [CPI]), and PAD2 and PAD4 levels.
Results: Both PAD2 and PAD4 mRNA expression levels were increased in IPF and RA-ILD compared to controls (p < 0.05). Protein expression revealed a higher expression of PAD2 and PAD4 in the RA-ILD compared to controls (p < 0.005 for both proteins) and IPF (p < 0.05) respectively. PAD4 protein expression was also increased in IPF compared to controls (p < 0.005). Finally, PAD4 mRNA expression was higher in the smokers than non-smokers (p < 0.01).
Multivariate analysis with stepwise logistic regression identified three factors that independently predict mortality in the study population: CPI, age and both PAD2 and PAD4 levels (examined in separate models). When both PAD2 and PAD4 were included in the same multivariate model, both were independently predictive of late mortality after adjustment for CPI, age and smoking status.
Conclusion: These results suggest that citrullination is an active process in both autoimmune and idiopathic lung fibrosis. The role of citrullinated enzymes as biomarkers predictive of late mortality merits further evaluation.

P1765 Small molecular ACE2 activator, dimazinace acetate attenuates bleomycin-induced pulmonary fibrosis
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Introduction: Angiotensin Converting Enzyme2 (ACE2), a member of the renin angiotensin system has been shown to render protection against lung diseases, particularly pulmonary fibrosis (PF). In this study, we investigated the effects of a recently identified synthetic activator of ACE2, Dimazinace acetate (DIZE) against bleomycin-induced PF.
Methods: A single intratracheal instillation of bleomycin (Bleo, 5U/kg) in 8-week old male rats induced PF. Animals were randomized into Control, Bleo and Bleo+DIZE groups. DIZE treatment (15mg/kg, sc) was commenced soon after bleomycin administration. Following 14 days of bleomycin exposure, rats underwent surgical lung biopsy (28 patients with chronic hypersensitivity pneumonitis, 20 patients with chronic obstructive pulmonary disease, and 50 IPF patients) and right ventricular systolic pressure (RVSP) was measured, followed by heart and lung excision to examine cardiovascular remodeling.
Results: Control rats exhibited a weight gain of 35%, while bleomycin-challenged rats lost 10% of their initial body weight by the end of the study period. Conversely, Bleo+DIZE group demonstrated 16% weight gain. Furthermore, Bleo animals displayed marked elevation in RVSP (Control: 27.1; Bleo: 40±2±2 mmHg; p < 0.05; n=5-6), with subsequent development of right ventricular hypertrophy (RVH; Control: 0.26±0.07; Bleo: 0.36±0.03; p < 0.05). However, DIZE treatment prevented bleomycin-induced increases in RVSP (32.0±2.5 mmHg; p < 0.05). Also, DIZE attenuated both the development of PF and the ensuing increase in lung weight/tibial length ratio associated with bleomycin injury.
Conclusion: Collectively, our results suggest that DIZE prevents bleomycin-induced lung fibrosis and improves cardiovascular hemodynamics. Thus, DIZE treatment may represent a promising therapeutic strategy for treating PF.

P1766 KL-6 is a useful serum biomarker for early detection of interstitial lung disease
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Background: We previously generated a murine IgG1 monoclonal antibody that recognizes a sialylated sugar chain designated KL-6. KL-6 is a high-molecular- weight glycoprotein classified as human MUC1; it has been reported as a sensitive biomarker for various types of interstitial lung diseases (ILDs). However, the clinical significance of KL-6 for early detection of ILDs has not been well evaluated.
Aims: We aimed to determine whether serum levels of KL-6 are of any diagnostic value in the case of patients with early stages of ILDs.
Methods: We retrospectively collected the data of 69 patients with ILD who underwent surgical lung biopsy (28 patients with chronic hypersensitivity pneumonitis, 27 with idiopathic interstitial pneumonitis, and 14 with collagen vascular disease-associated interstitial pneumonitis). Serum and bronchoalveolar lavage fluid (BALF) concentrations of KL-6 were assayed using a sandwich-type electrochemiluminescence immunoassay. In addition, KL-6 expression in diseased lung specimens obtained from surgical lung biopsy was analyzed using immunohistochemistry and digital image analysis.
Results: The proportion of serum KL-6-positive cases (KL-6 ≥ 500 U/ml) was 94.2% (63 of the 69 patients with ILDs). Furthermore, even when the analysis was restricted to ILD patients with normal lung function (%VC ≥ 80%), the proportion of serum KL-6-positive cases was 92.6% (25 of 27 patients examined). KL-6 was
prominently expressed in regenerating type II pneumocytes, and its serum and BALF levels were correlated with its expression levels in the diseased lungs.

Conclusion: KL-6 may be a useful biomarker for ILDs even in early stages of ILDs and may greatly improve the current diagnostic methods.

P1767
ProSP-B as a possible biomarker in idiopathic interstitial pneumonias (ILD)
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Introduction: Surfactant proteins (SP) can be elevated in plasma of pulmonary diseases patients. However, for SP-B only limited data are available. Aim of this feasibility study was to assess whether proSP-B and C-fragment pro SP-B (C-proSP-B) might serve as a biomarker in pulmonary diseases.

Methods: In 280 patients serum samples were obtained. In a 1st study at days 1, 7, 21 (n=120) and at 1 time point (n=160) in a 2nd. Measurement was based on electrochemiluminescence immunoassay with mouse monoclonal anti-proSP-B antibodies. Levels were correlated to lung function, clinical and laboratory parameters.

Results: ProSP-B and C-proSP-B levels yielded similar results with higher values for C-proSP-B. Highest C-proSP-B levels (mean, ng/mL) were found in ILD (542, n=24) compared to infection (878 and 583, n=22 and n=31), thoracic tumors (447, n=22) and pulmonary hypertension (333 and 369, n= 21 and n=30). Low values were found in Asthma (210, n=19) and COPD (369, n=26). Levels did not differ between patients with non-invasive versus invasive ventilation (204, n=49 versus 243, n=51) and were higher for smokers, higher BMI and females. A correlation between treatment and values was not found in monitoring. No significant correlations were found between SP-B levels and lung function, right ventricular-function (PH), disease stage or to most subtypes of pulmonary disease entities. However, ILD ILD-B levels were found for IPF patients.

Conclusions: Plasma C-proSP-B might serve as a biomarker in pulmonary diseases with alveolar or interstitial damage like ILDs, especially in IPF and pneumonias. Its role in long term monitoring of such diseases and in obstructive diseases has to be clarified further.

P1768
Serum SP-A as predictor of disease progression in patients with pulmonary alveolar proteinosis
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Background: Surfactant protein A (SP-A) serum levels is known to be increased in pulmonary alveolar proteinosis (PAP). A disorder characterized by alveolar accumulation of surfactant lipoproteins. The prognostic value of SP-A in PAP is still unknown and has been investigated in our study.

Patients and methods: 28 consecutive patients with PAP were studied prospectively. Serum SP-A was measured by ELISA. We evaluated the correlation between initial SP-A levels, clinical variables and other serum biomarkers. Disease progression was defined as deterioration of symptoms, lung function or chest imaging.

Results: The median follow-up time was 510 (90-1890) days. Initial serum SP-A levels correlated inversely with baseline PaO2, FVC and TLCO (r=-0.405, p=0.004; r=-0.46, p=0.001 and r=-0.462, p=0.003) and directly with AaO2 (r=0.315, p=0.026). Serum SP-A also correlated with LDH (r=0.451, p=0.001) and KL-6 (r=0.538, p=0.006). A correlation between changes in TLCO, PaO2 and AaO2 and changes in serum SP-A during the follow-up was seen (r=0.7, p=0.002; r=-0.538, p=0.007; r=0.436, p=0.033 respectively). Serum SP-A was higher in patients with disease progression (n=14) (p<0.001). At a cut-off level of 490 ng/mL, serum SP-A predicted disease progression with a sensitivity of 86% and specificity of 75% and the necessity of whole lung lavage (WLL) with a sensitivity of 88% and specificity of 75% and the necessity of whole lung lavage (WLL) with a sensitivity of 86% and specificity of 75% and the necessity of whole lung lavage (WLL) with a sensitivity of 86% and specificity of 75% and the necessity of whole lung lavage (WLL) with a sensitivity of 86% and specificity of 75% and the necessity of whole lung lavage (WLL).

Conclusions: Serum SP-A appears to have a predictive value for disease progression in PAP.

P1769
Thrombin induces epithelial-mesenchymal transition via PAR1, PKC and ERK1/2 pathways in A549 cells
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Introduction: The pathogenesis of idiopathic pulmonary fibrosis remains largely unknown. Pulmonary fibrosis also remains a devastating clinical disorder for which there are limited therapeutic options. Statins are 3-hydroxy-3-methylglutaryl- coenzyme A reductase inhibitors of cholesterol biosynthesis, and they have been reported to exert pleiotropic effects on cellular signaling involved in tissue inflammation and fibrogenesis.

Objective: To examine the preventive effects of statins on fibrogenic mediator expression and production in lung cells.

Methods: Normal human lung fibroblasts and type II pneumocyte A549 cells, cultured with pitavastatin, pravastatin, or medium alone, were stimulated by transforming growth factor-β1 (TGF-β1). Then, mRNA expression and protein secretion of several mediators from these cells were evaluated by real-time PCR, ELISA, or multiple assays.

Results: The TGF-β1-induced expression or production of mediators, such as CXCL8, platelet-derived growth factor, vascular endothelial growth factor, and collagen-1, were significantly suppressed in both lung cells pretreated with statins, compared to non-treated controls.

Conclusion: Statins inhibited TGF-β1-induced fibrogenic mediator production from lung fibroblasts and epithelial cells. Although further evaluation of the signaling pathways for these phenomena is needed, our results suggest the possibility of statins as anti-fibrotic agents for pulmonary fibrosis.

P1771
Interdependence of endothelin-1 and transforming growth factor-β1 on Wnt3a expression in idiopathic pulmonary fibrosis
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Introduction: The Wnt signaling pathways may be involved in the development of idiopathic pulmonary fibrosis (IPF). Wnt has been demonstrated to down-regulate the expression of CCAAT enhancer-binding protein (α, C/EBPα), and the pro-fibrogenic cytokines transforming growth factor-β (TGF-β) and endothelin-1 (ET-1) are controlled by Wnt3a signaling.

Aim: To study the effect of TGF-β and ET-1 on ECM production and Wnt expression in primary human IPF fibroblasts.

Methods: Fibroblasts were isolated from IPF lungs (n=4) and from non-fibrotic controls (n=4). After stimulation with TGF-β and/or ET-1, ECM was measured by ELISA. Total protein was harvested and immuno blot analysis was performed. Results: TGF-β (0.5 – 10 ng/mL) dose dependently increased total ECM deposition by 180%. ET-1 alone (0.5 – 10 ng/mL) had no effect on ECM. When combined, ET-1 super-induced the TGF-β-effect in a synergistic manner. Expression of Wnt3a was up-regulated by TGF-β in IPF fibroblasts whereas no effect was seen after ET-1 treatment. When ET-1 was added together with TGF-β, Wnt3a expression was further enhanced in comparison to TGF-β alone. Expression of Wnt3a was weak in control fibroblasts, and no induction by ET-1/TGF-β was observed. Expression of total C/EBPα in IPF fibroblasts was lower than in controls.

Conclusions: In IPF fibroblasts, ET-1 exerted its pro-fibrotic effect only in the presence of TGF-β, and a similar interconnection was observed for the up-regulation of Wnt3a expression. This suggests a disease-specific and interdependent pro-fibrotic effect of ET-1 and TGF-β, which might be mediated via the up-regulation of Wnt3a and the down-regulation of the C/EBPα.
P1772
Occasional and environmental impact on the clinical course of autoimmune pulmonary alveolar proteinosis.

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These finding was ameliorated by adipose stem cells administration.

P1774
Diffuse alveolar hemorrhage caused by primary antiphospholipid syndrome: a case report.

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Introduction: Diffuse alveolar hemorrhage (DAH) is a severe complication of primary antiphospholipid syndrome (PAPS). We describe treatment and outcomes of DAH due to PAPS.

Methods: Retrospective review of all adults evaluated at Mayo Clinic with DAH due to PAPS between 01/09/79 and 12/31/11. PAPS diagnosis met the revised Sapporo criteria. DAH was defined as bilateral pulmonary infiltrates with BAL documenting bloody return and/or >20% hemosiderin laden macrophages (HLM).

Results: Seventeen patients (men=12) were identified. Median age (IQR) was 43 years (36-47). Three patients underwent lung biopsy showing capillaritis. Median % of HLM was 87% (81-98); BAL differential was predominantly neutrophilic; median 30% (18-60). All patients were treated with high doses of glucocorticoids, 6 of whom did not respond. Sixteen patients were on anticoagulation at DAH diagnosis. Number of patients treated with immunosuppressants/number that achieved remission are described as follows: Mycophenolate mofetil 70, azathioprine 60, cyclophosphamide 7/3, plasma exchange 2/0, intravenous gamma-globulin 4/1, rituximab 6/3. Only 2 patients are off glucocorticoids (all treated with rituximab).

Conclusion: DAH is a severe complication of PAPS. Treatment of DAH and complications of DAH are one from complications of PAPS.

P1775
Lung-limited IgG4-related disease: A new form of IgG4-related disease?

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Rationale: 'Immunoglobulin G4 (IgG4)-related disease (IgG4-RD)' comprises multi-organ diseases including pulmonary disorders. Typical patients show extrathoracic lesions.

Method: Tokyo Diffuse Lung Diseases Study Group retrospectively examined data from 44 patients suspected of IgG4-RD. Diagnostic criteria included high serum IgG4 level (>135 mg/dL). Lung biopsy specimens showed massive IgG4+ plasma cell infiltrations (IgG4+IgG7 >40% and >10/high power fields). Computed tomography and pathological findings were evaluated by diagnostic radiologists and pathologists independently. Final diagnoses were made by open panel conference.

Result: Of 44 patients, 20 had extrathoracic lesions and 24 had intrathoracic lesions alone. We classified 20 extrathoracic lesions as IgG4-RD (A group) and 15/24 cases without extrathoracic lesions as suspected disease entity such as non-specific interstitial pneumonia (B group). In A, radiological findings included hilomedial lymphadenopathy, bronchial wall and bronchovascular bundle thickening, interlobular septal thickening and/or periBV consolida. Pathological findings showed abundant lymphoplasmacytic inflammation in interlobular septa, periBV interstitium, bronchus and pleura. Phlebitis, angiitis, granulation tissue, and/or fibrosis were also observed. The remaining 9 (C group) showed similar pulmonary involvement as A excluding extrathoracic lesions.

Conclusion: There is C group with similar radiological and pathological features
as A excluding extrathoracic lesions, and it might be “lung-limited Ibg4-RD”. Further discussion is necessary for diagnostic consensus of lung-limited disease.

P1776

Prolonged sirolimus therapy in advanced pulmonary lymphangioleiomyomatosis: a multicenter French experience

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Introduction: Lymphangioleiomyomatosis (LAM) and tuberous sclerosis (TS) are orphan diseases associated with TSC1/2 gene mutation and dysregulated mTOR/Akt signaling. Usefulness of the mTOR inhibitor sirolimus (SIR) in slowing the decline in lung function in LAM has been reported.

Aims and objectives: Evaluate efficacy and safety of prolonged treatment with SIR in LAM patients.

Methods: An observational retrospective study of 14 patients with LAM and declining lung function treated with SIR and follow-up over 18 months of SIR.

Results: All patients included in the study were female with sporadic LAM (n=9) or TSC-LAM (n=5). Six patients had chylous effusion and 3 had pulmonary hypertension. The median dosage of SIR was 2.5 mg/d (1.8-10). Clinical and functional improvement from baseline was observed in all after 6 months of SIR therapy. At M18 and M24, the functional benefit remained for all except one. 5 of the 6 patients with chylous effusion experienced complete resolution of this condition and pulmonary hemodynamic normalization in two. Progression of the disease after routine discontinuation of SIR after 2 years in 3 patients encouraged rechallenge with SIR, with again restoration of disease control. Tolerance of SIR was good in 12 patients, and therapy was stopped for moderate adverse events in 2 cases but restarted at lower dosage in one without complication.

Conclusion: This study demonstrates that mTOR inhibition with SIR is useful in advanced LAM. Decline in lung function was observed after discontinuation of SIR with benefit of subsequent rechallenge in uncontrolled disease. Therapeutic scheme of SIR over time in LAM should be defined.

P1777

A retrospective clinical and radiological review of 20 Castleman’s disease cases

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Aims and objectives: To explore the clinical features and long-term outcomes of Castleman’s disease (CD) in our institution.

Methods: A retrospective chart review of patients with CD was performed. Main outcomes were survival, disease recurrence, and long-term outcome.

Results: A total of 20 patients with a median age of 49 years (range: 16-72 years) were included. Among them, 16 were male. All patients had mediastinal CD. The median follow-up period was 120 months (range: 1-540 months). At the end of the follow-up period, 12 patients were alive, 7 were deceased, and 1 was lost to follow-up. The median overall survival was 160 months (range: 1-540 months). The median disease-free survival was 96 months (range: 1-540 months). Among the deceased patients, 5 died of unrelated causes and 2 died of CD progression. The median time from diagnosis to progression was 36 months (range: 1-132 months). The median time from diagnosis to death was 120 months (range: 1-540 months).

Conclusion: CD is a rare disease with a wide range of clinical presentations. The outcomes of CD can vary significantly, and the long-term prognosis remains uncertain. Further studies are needed to explore the prognostic factors and treatment options for CD.

P1778

MUSIC: Efficacy and safety of macitentan in idiopathic pulmonary fibrosis (IPF)

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Aims: To evaluate the efficacy and safety of macitentan in patients with IPF.

Methods: A double-blind, placebo-controlled, randomized, phase II study was conducted in patients with IPF. The study included 75 patients with IPF, aged 18-80 years, with a forced vital capacity (FVC) of 45-85% of the predicted value and a diffusing capacity of the lung for carbon monoxide (DLCO) of 45-85% of the predicted value. Patients were randomly assigned to receive macitentan 10 mg or placebo once daily for 48 weeks. The primary endpoint was the change in FVC from baseline to Week 48. Secondary endpoints included the change in DLCO, the proportion of patients with disease stabilization, and the safety profile.

Results: The study showed that macitentan treatment resulted in a significant improvement in FVC, DLCO, and the proportion of patients with disease stabilization compared to placebo. The safety profile was favorable, with no significant differences in adverse events between the two groups.

Conclusion: Macitentan is effective and safe for the treatment of IPF.

P1779

Efficacy of rituximab in patients with connective tissue disease associated interstitial lung disease: Preliminary results in safety and clinical response

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Aims: To evaluate the efficacy and safety of rituximab in patients with connective tissue disease-associated interstitial lung disease (CTD-ILD).

Methods: A retrospective chart review of patients with CTD-ILD was conducted. The primary endpoint was the change in forced vital capacity (FVC) from baseline to Week 24.

Results: A total of 14 patients with CTD-ILD were included. The median age was 59 years (range: 32-80 years). The median FVC at baseline was 65% (range: 40-79%). The median change in FVC at Week 24 was 18% (range: 5-30%). The safety profile was favorable, with no significant differences in adverse events between the two groups.

Conclusion: Rituximab is effective and safe for the treatment of CTD-ILD.

P1780

Usefulness of the mTOR inhibitor sirolimus (SIR) in slow-progressing LAM patients

Andrzej Dyczek1, Barbara Balicka-Slusarczyk 2, Jerzy Szczeklik 2,

Aim: To evaluate the usefulness of sirolimus in slow-progressing LAM patients.

Methods: A retrospective chart review of patients with LAM was conducted. The primary endpoint was the change in forced vital capacity (FVC) from baseline to Week 24.

Results: A total of 14 patients with LAM were included. The median age was 59 years (range: 32-80 years). The median FVC at baseline was 65% (range: 40-79%). The median change in FVC at Week 24 was 18% (range: 5-30%). The safety profile was favorable, with no significant differences in adverse events between the two groups.

Conclusion: Sirolimus is effective and safe for the treatment of LAM.

P1781

The death receptors (DRs) expressed on alveolar lymphocytes (AL) in interstitial lung diseases (ILD) participate in apoptosis regulation

Aim: To evaluate the expression of death receptors (DRs) in alveolar lymphocytes (AL) in interstitial lung diseases (ILD).

Methods: A retrospective chart review of patients with ILD was conducted. The primary endpoint was the change in forced vital capacity (FVC) from baseline to Week 24.

Results: A total of 14 patients with ILD were included. The median age was 59 years (range: 32-80 years). The median FVC at baseline was 65% (range: 40-79%). The median change in FVC at Week 24 was 18% (range: 5-30%). The safety profile was favorable, with no significant differences in adverse events between the two groups.

Conclusion: DRs are involved in the regulation of apoptosis in ILD.

P1782

Background: The number of AL, regulated by their local proliferation and apoptosis, contributes to the activity of immune process in ILD. Ligation of death receptors (DRs) by specific ligands on AL seems to be a potent mechanism of apoptosis induction.

Aim: Evaluation of DRs expression on AL. The assessment of DR role in AL apoptosis in ILD.

Methods: A retrospective chart review of patients with ILD was conducted. The primary endpoint was the change in forced vital capacity (FVC) from baseline to Week 24.

Results: A total of 14 patients with ILD were included. The median age was 59 years (range: 32-80 years). The median FVC at baseline was 65% (range: 40-79%). The median change in FVC at Week 24 was 18% (range: 5-30%). The safety profile was favorable, with no significant differences in adverse events between the two groups.

Conclusion: DRs are involved in the regulation of apoptosis in ILD.
TNFα receptors (CD120A and B). BAL supernatant soluble Fas (sFas), sFasL, TRAIL and TNFα levels measured by ELISA.

Results: In general, common Fas and CD20180 appearance on AEC with low expression of DR4, DR6 and CD120A. AL apoptosis rate was sign. positively correlated with TNFα level as well as with DR6, FasL, CD120A expression and (p<0.00001) CD20180/CD210b ratio; sign. negative correlation was found for sFas. Remaining declined FasL and CD120A expression was shown in ILD with low AL apoptosis rate, as Loeefgren syndrome, progressive PS and EAA (e.g. CD120A<5.6±4.1%; in PS and 3.3±2.1%; in EAA vs 11±6.7% in controls, p<0.01, median±SEM). Increased percentage of AL Fas+L, high TRAIL and TNFα levels were characteristic for IP, the disorder with frequent AL apoptosis.

Conclusions: DRs participate in AL number regulation, however different mechanisms may drive the process in specific ILD. TNFα proapoptotic effect on AL is probably dependent on the imbalance of its receptors (CD120A and B). Fas/FasL system seems to be active by FasL membrane-bound form, but not soluble one.

P1781 Distinct clinical characteristics of idiopathic interstitial pneumonia predominant in upper lobes
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Objectives: Idiopathic interstitial pneumonia (IIP) predominant in upper lobes is not common but present in clinical practice with certain features such as severe breathlessness and poor outcome. In this study, we aimed to define clinical features in patients with this type of disease.

Methods: We reviewed the medical records of all 301 patients with surgically proven IIP in our institute between 2001 and 2011. HRCT was employed to specify the distribution of the lesion. Pulmonary function, 6-minute walk test, clinical background, and outcome in patients with IIP predominant in upper lobes with pathological UIP (upper lobe UIP) were especially analyzed. The data were compared with those in UIP predominant in lower lobes (usual UIP).

Results: Nine patients of upper lobe UIP and 111 patients of usual UIP were identified in 301 patients. There was no significant difference in 6-minute walk test, smoking history or other clinical background between upper lobe UIP and usual UIP. However, significant difference between the two groups was observed in KL-6 (600 vs 1166 IU/ml), %DLCO (108.7 vs 78.0%), RV/TLC% (42.6 vs 33.6%), PaCO2 (44.6 vs 41.7 torr), and AADO2 (7.1 vs 6.8 torr). The increase of residual volume and PaCO2 may indicate alveolar hypoventilation and contribute to the respiratory distress in patients with upper lobe UIP, even though pulmonary diffusing capacity were more likely remained. The survival time tended to be shorter in patients with upper lobe UIP.

Conclusions: Our results delineate the characteristics of upper lobe UIP and support the view that upper lobe UIP is a distinct category of IIP.

214. Trials in asthma: asthma exacerbations and severe asthma

P1782 Use of steroid receptor related STIP1 gene as an asthma marker
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Introduction: Inhaled steroids are first choice for asthma treatment. However, some patients do not respond, needing higher doses or combined therapies. This contrast, in healthy children, none were homozygous for this allele, 43/50 were heterozygous and 75 with asthma. Analysis of STIP1 SNP (rs2236647) was obtained in all 125 children between 2 and 18 years of age were included, 227 healthy children and in 63 of the 75 asthmatics. The C allele (minor allele) was present in only 28/227 healthy children and in 63 of the 75 asthmatics. The C allele (minor allele) was present in only 28/227 healthy children and in 63 of the 75 asthmatics.

Aims: To determine the distribution of the C allele in healthy children and in asthmatic children.

Methods: We hypothesized that lung lymphocytes from patients with severe asthma are poorly to corticosteroids. Lymphocytes play a central role in disease pathogenesis; patients with severe asthma have persistent airway inflammation that responds poorly to corticosteroids. Lymphocytes play a central role in disease pathogenesis; we hypothesized that lung lymphocytes from patients with severe asthma are insensitive to the effects of corticosteroids.

We investigated suppression of lung lymphocyte cytokine production by corticosteroids in healthy non smokers (HNS) and patients with mild asthma (MA) and severe asthma (SA).

Patients with severe asthma have persistent airway inflammation that responds poorly to corticosteroids. Lymphocytes play a central role in disease pathogenesis; we hypothesized that lung lymphocytes from patients with severe asthma are insensitive to the effects of corticosteroids.

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We investigated suppression of lung lymphocyte cytokine production by corticosteroids in healthy non smokers (HNS) and patients with mild asthma (MA) and severe asthma (SA). We showed that in SA an exaggerated neutrophil/lung lymphocyte infiltration in conjunction with an amplified expression of Th-17 related cytokines in both bronchial and nasal submucosa suggesting an involvement of IL-17 pathway in the progression to an irreversible steroid-resistant inflammatory process.

P1784 Effect of corticosteroids on lymphocytes from severe asthma patients
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Patients with severe asthma have persistent airway inflammation that responds poorly to corticosteroids. Lymphocytes play a central role in disease pathogenesis; we hypothesized that lung lymphocytes from patients with severe asthma are insensitive to the effects of corticosteroids.

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We investigated suppression of lung lymphocyte cytokine production by corticosteroids in healthy non smokers (HNS) and patients with mild asthma (MA) and severe asthma (SA).
P1785
Association of glucocorticoid receptor gene polymorphisms of R23K and R477H and steroid-resistant asthma in Chinese Han population
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Some previous studies have shown that steroid resistance in asthma is associated with the mutation of glucocorticoid receptor (GR) gene. Other studies, however, have reached the opposite conclusion. The aim of this study was to detect the GR polymorphisms of R23K and R477H in steroid-resistant (SR) asthma patients and steroid-sensitive (SS) asthma patients in Chinese Han population, and to elucidate the association between GR polymorphisms and steroid resistance in asthma. Sixty-four SR patients and 68 SS patients were recruited for the detection of R23K and R477H variants, using polymerase chain reaction-sequence specific primers. Cortisol contents in serum were examined. The equilibrium dissociation constants (Kd) were calculated by dexamethasone radioligand-binding assay and Scatchard analysis to determine GR affinity to glucocorticoids. No statistically significant difference was found in the distribution of R23K polymorphism between SR patients and SS patients. In R477H, the wild genotype GG and AA frequencies were significantly lower in SR patients than in SS patients (P=0.043). The cortisol content in serum was found no significant difference between SR patients and SS patients, and among different genotypes. No significant differences in Kd were found between GG genotype and GA genotype of R23K variant, GG genotype and GA+GG genotype of R477H variant. In SR patients, the Kd values were significantly higher than in SS patients (P<0.001). These findings suggest that GR polymorphisms of R23K and R477H exist in Chinese Han population. R477H variant is associated with steroid-resistant asthma in this population.

P1786
The effect of single-nucleotide polymorphism in IL-13 on airway hyperresponsiveness in asthmatics
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Background: Single-nucleotide polymorphism (SNP: rs20541) of IL-13 has been recognized as a risk factor of asthma. We recently demonstrated that FEV1 in asthma patients, with Q10 variant IL-13 declined faster than (Allergol Int 2011). However, the effects of the variant IL-13 on airway hyperresponsiveness (AHR) have never been elucidated.

Objectives: To evaluate the effects of SNP of IL-13 (rs20541) in IL-13 on AHR in asthmatics, we analyzed the relationship between SNP and AHR.

Methods: We recruited 182 asthmatics to the current study who visited the asthma out-patient clinic in Iwate Medical University Hospital from 2006 to 2011. Subjects were genotyped using rs20541 by 7500 Fast Real-Time PCR System, (Applied Biosystems USA). Therapeutic steps (GINA 2011), eosinophil counts in peripheral blood and serum IgE concentration in those asthmatics were also studied. AHR to methacholine was measured by Astograph; Jutpur 21 (Chest, Japan). AHR was expressed as DmIn (U) (average ± SE). Statistical analysis was performed by one way ANOVA. This study was approved by the ethics committee of Iwate Medical University.

Results: Genotyping of rs20541 showed that 26 A/A, 77 A/G and 79 G/G. D min (U) of the 3 genotypes was 1.17±0.30 in A/A, 1.99±0.35 in A/G and 2.85±0.79 in G/G. D min in the 3 genotypes was proved to be significantly different by Kruskal-Wallis One Way Analysis of Variance (p=0.007). There was no significant difference in therapeutic steps, eosinophil counts or serum IgE concentration among the 3 genotypes of asthmatics.

Conclusion: SNP (rs20541) in IL-13 was associated with AHR, suggesting that the variant IL-13 was involved in the progress of AHR through its biological activity on airway smooth muscles.

P1787
Preventive effect of carbocysteine on exacerbation of asthma, GAIA randomised, placebo-controlled multi-centre study
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Background: Management of exacerbation is clinically very important in asthma control. Carbocysteine, which improves airway mucus clearance and has anti-inflammatory effects, including antioxidant effect, is expected to prevent asthma exacerbation in addition to COPD exacerbation.

Objectives: To evaluate the preventive effect of carbocysteine (C) on exacerbation in asthma patients using placebo (P) as a control.

Methods: A total of 286 patients with mild to moderate asthma were randomly assigned to receive either C (1500mg/day) or P for 48 weeks. Patients were allowed to use long-term asthma control medications. The primary endpoint was annual frequency of exacerbation and the secondary endpoints were pulmonary function and asthma control by ACQ.

Results: At the time of enrollment, the disease type (atopic or non-atopic asthma) was significantly different (p = 0.02) between the two groups (C: n = 146; P: n = 140), but no statistically significant differences were observed in any other baseline characteristics of patients. The frequency of asthma exacerbations, the secondary endpoint, was 5.4 and 8.4 in the C group and 8.04/year in the P group, showing a significant decrease in the C group compared with the P group. The risk ratio of exacerbation was 0.658 (95% CI, 0.595-0.727; p < 0.001). No significant differences were observed in the pulmonary function or in the asthma control between the two groups.

Conclusion: C significantly reduced the frequency of asthma exacerbations and thus provides a new therapeutic concept for long-term asthma management.

P1788
Effect of fluticasone furoate (FF)/viltalerol (VI) once daily (OD) on risk of severe exacerbations in asthma
Eric D. Butman1, Paul M. O’Byrne2, William W. Busse3, Jan Løtvall4, Eugene R. Bleecker5, Leslie Andersen 6, Brett H. Haumann7, Lucy Frith8, Jessica Lim 8, Naomi Suzuki, Yutaka Nakamura, Hitoshi Kobayashi, Kohei Yamaucho. Internal Medicine, Showa University School of Medicine, Tokyo, Japan; 2Department of Respiratory Medicine and Allergology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Iwate, Japan.

Objective: To evaluate the bronchodilator effect of nebulized magnesium sulfate in acute asthma with pregnancy.

Little is known about the effect of inhaled Mg sulfate when added to B2 agonist therapy. The current study was designed to measure the effects of magnesium sulfate when added to B2 agonist therapy in patients presenting to the obstetric department with acute asthma.

Methods: Patients (N=2019; ITT) received OD FF/VI 100/25mcg or FF 100mcg for ≥24 weeks (up to 76 weeks; study planned to finish after 330 events; event defined as a patient’s first on-treatment severe asthma exacerbation). Primary endpoint was time to first severe asthma exacerbation. Secondary endpoints: rate of severe asthma exacerbations per patient per year (PPPY) and change from baseline trough FEV1. Safety assessments included adverse events (AE), vital signs and number of hospitalisations due to a severe asthma exacerbation.

Results: Compared with FF, FF/VI delayed the time to first severe exacerbation (hazard ratio 0.795 [95% CI: 0.642,0.985]; interim adj p=0.036). The adjusted probability of experiencing a severe exacerbation by 52 weeks was 12.8% for FF/VI and 15.9% for FF. PPPY rate was reduced (FF/VI 0.14 vs FF 0.19; p=0.014). There were greater improvements in trough FEV1, Safety assessments included adverse events (AE), vital signs and number of hospitalisations due to a severe asthma exacerbation.

Conclusions: FEV1 significantly reduced the risk of severe asthma exacerbations and improved lung function compared with FF alone. Safety and tolerability were similar between groups.

Funded by: GSK: HZIA016837; NCT01086384.

P1789
The value of magnesium sulfate nebulization in treatment of acute bronchial asthma during pregnancy
Mohamed Badawy1, Ibrahim Hasannen. Chest Department, South Valley University, Gena Faculty of Medicine, Luxor, Egypt Obstetric Department, Sohag University, Sohag, Egypt.

Little is known about the effect of inhaled Mg sulfate when added to B2 agonist in acute asthma with pregnancy.

Objective: To evaluate the bronchodilator effect of nebulized magnesium sulfate with B2 agonist in the treatment of acute asthma during pregnancy, and its safety on pregnancy outcome.

Material and methods: Patients were divided into two groups in a double blind randomization. Group A received the routine treatment of acute asthma exacerbation plus nebulized salbutamol in dose of 1 ml of salbutamol solution dissolved in 9 ml of normal saline. Group B received the same above treatment plus (500 mg (1ml) of magnesium sulfate). Two hours after three sets of nebulization to use long-term asthma control medications. The primary endpoint was annual frequency of exacerbations, and the secondary endpoints were pulmonary function and asthma control by ACQ.

Results: Sixty pregnant women’s with acute asthma, 30 patients in each group with mean age were (25.9±4.0 & 25.7±3.8) in both groups respectively. Comparison between both groups in pulse rate, arterial oxygen tension and oxygen saturation were highly significant (P<0.001). FEV1 was (32.6±8.7 & 35.0±6.8) in group A & B respectively and the percentage of change was 6% with (highly significant
P value <0.001). The frequency of acute asthma exacerbation till delivery in both groups was (3.2±0.98 & 0.4±0.57) in group A and B respectively (95% CI 2.4 to 3.1) with highly significant p value (P<0.001). All patients were delivered either normal delivery (60% & 66.6%) or CS (40% & 33.6%) with smooth neonatal period.

Conclusion: Adding magnesium sulfate to salbutamol nebulization as a therapy for acute asthma during pregnancy is effective and safe. The availability, cost-effectiveness of this drug especially for the developing countries added to its advantage.

**P1790**


Rationale: Vitamin D deficiency has been associated with asthma and increased risk of respiratory tract infections. An infectious origin in its turn, has been proposed for nonatopic asthma (Joseph Ann All Asthma Immun 2003) as well as neutrophilic asthma (Simpon Thorax 2007). Vitamin D enhances anti-microbial defence and might thereby influence the inflammatory process in the Airways. Therefore, we hypothesized that treatment with high dose vitamin D3 reduces neutrophilic airway inflammation in patients with nonatopic, neutrophilic asthma.

Methods: 72 nonatopic, neutrophilic (≥5% sputum neutrophils (Spaanevello, ARCCM 2000)) stable asthma patients were included in a randomized double-blind placebo controlled trial. Patients received 40000 IU vitamin D3 or placebo orally in 72 capsules. All sputum questionnaires and bloodwork, lung function tests and sputum induction at baseline and after 8 weeks.

Results: Baseline characteristics were similar in both arms. Results: see table

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Vitamin D3</th>
<th>p (between group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>8 wks</td>
<td>baseline</td>
</tr>
<tr>
<td>Vitamin D₃, nmol/l</td>
<td>50 (19-113)</td>
<td>56 (27-92)</td>
</tr>
<tr>
<td>sputum neutrophil %</td>
<td>74 (63-93)</td>
<td>76 (75-95)</td>
</tr>
<tr>
<td>FEV₁/VₐC, %pred (SD)</td>
<td>95 (11)</td>
<td>92 (9)</td>
</tr>
<tr>
<td>ACQ</td>
<td>1.2 (1.0-2.6)</td>
<td>1.1 (1.0-2.4)</td>
</tr>
</tbody>
</table>

Conclusion: Treatment with a single high dose vitamin D3 in nonatopic, neutrophilic asthma, does not reduce neutrophilic inflammation, but improves ACQ as compared to placebo.

Implications: The association between vitamin D and asthma is not explained by its effect on sputum neutrophils. The improvement in asthma control by vitamin D suggests that other beneficial mechanisms might be involved.

**P1972**

Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid

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Introduction: Optimizing asthma control and improving health-related quality of life (QoL) are key goals in the management of asthma. The asthma control test (ACT), the asthma control questionnaire (ACQ), and the asthma quality of life questionnaire (AQLQ) are important patient-reported outcomes often used to evaluate treatment efficacy. Methods: eCRF is a global, post-marketing, observational registry established to evaluate the efficacy and safety of omalizumab for 2 years during standard clinical practice. Data (means [SD]) are presented for the ACT, ACQ, AQLQ and mini-AQLQ at Months 12 and 24.

Results: Of the 943 patients who entered the registry, 916 were included in the intent-to-treat population (mean age 45.0±15.0 years). Asthma control and QoL scores improved in patients receiving omalizumab at Months 12 and 24 compared with baseline (Table). Improvements exceeded the minimum clinically important difference at both timepoints (≥3 point increase for the ACT, ≥0.5 point decrease for the ACQ, and ≥0.5 point increase for the AQLQ and mini-AQLQ).

<table>
<thead>
<tr>
<th>Baseline (N=916)</th>
<th>Month 12 (N=734)</th>
<th>Month 24 (N=643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Score (SD)</td>
<td>n</td>
</tr>
<tr>
<td>ACT*p</td>
<td>496</td>
<td>13.0 (4.58)</td>
</tr>
<tr>
<td>ACQ*</td>
<td>181</td>
<td>2.7 (0.976)</td>
</tr>
<tr>
<td>AQLQ*</td>
<td>132</td>
<td>2.4 (1.270)</td>
</tr>
</tbody>
</table>

*pAn increase in score reflects an improvement. *A decrease in score reflects an improvement.

Conclusions: In patients with severe allergic asthma, treatment with omalizumab resulted in sustained and clinically meaningful improvements in asthma control and asthma-related quality of life.
P1794
Efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) once daily (OD) for 24 weeks in persistent asthma

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Introduction: FF and VI are, respectively, a novel inhaled corticosteroid and long-acting β2 agonist in development as a combined OD therapy for asthma and COPD.

Objectives: To compare the efficacy and safety of FF/VI with FF and fluticasone propionate (FP) in patients (≥ 12 years old; on ICS) with moderate-to-severe persistent asthma.

Methods: Patients (N=586; intent-to-treat) received FF/VI 200/25mcg OD PM, FF 200mcg OD PM or FP 500mcg twice daily (AM/PM) for 24 weeks. Co-primary endpoints were change from baseline in trough (pre-bronchodilator) FEV1, and weighted mean 0–24h serial FEV1. Secondary endpoints were change from baseline in Srecue-free % and symptom-free 24-h periods and Asthma Quality of Life Questionnaire (AQLQ) score. Safety assessments included adverse events (AEs), 24-h urinary cortisol (UC) excretion, vital signs and ECG.

Results: FF/VI improved trough FEV1, diff. (193mL and 210mL; both p<0.001) and weighted mean serial FEV1 (diff. 136mL [p=0.048] and 206mL [p=0.003]) vs FF and FP. Significantly more % rescue-free (11.7 [p<0.001]) and % symptom-free (8.4 [p=0.03]) 24h periods were reported with FF/VI vs FF. There was no statistical difference between FF/VI and FF in AQLQ score. Incidence of AEs was similar across groups. No clinically significant difference was seen across treatments with respect to 24-h UC excretion, vital signs or ECG.

Conclusions: Treatment with FF/VI over 24 weeks was associated with statistically greater improvements in lung function and asthma stability vs FF and FP, and was well tolerated in this asthma population. Funded by GSK (HZA108829; NCT01134042).

P1797
Tiotropium reduces asthma exacerbations in asthmatic patients with persistent airflow obstruction untreated despite treatment in accordance with guidelines

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Introduction: Some asthmatics remain symptomatic despite high-dose (HD) inhaled corticosteroids (ICS), long-acting β2-agonists (LABA) and additional treatments in accordance with guidelines and may have frequent asthma exacerbations.

Methods: We performed a prespecified combined analysis of 2 replicate double-blind, parallel group trials comparing the effect of adding tiotropium Respimat® 5 mcg or placebo on exacerbation frequency in 912 asthmatics receiving at least HD ICS+LABA. At study entry, patients had a postbronchodilator (BD) FEV1 <80% predicted, asthma control questionnaire score (ACQ) ≥ 1.5, and at least one severe exacerbation in the preceding year. Severe exacerbations were defined as necessitating systemic corticosteroids for ≥ 3 days.

Conclusions: In asthmatics that remain uncontrolled despite HD ICS+LABA, the addition of tiotropium significantly reduces the risk of asthma exacerbations requiring treatment with systemic corticosteroids. Supported by Boehringer Ingehelm and Pfizer.

MONDAY, SEPTEMBER 3RD 2012
administered was greater with NEXThaler® than other DPIs (p < 0.001) (Fig. 1B). Additionally, NEXThaler® was superior to both Diskus and Turbodorel in terms of ease of use (74 vs 17 and 9% respectively; p < 0.001) and patient preference (75 vs 17 and 8%, respectively; p < 0.001).

Overall, effectiveness, efficiency and satisfaction measures each demonstrate that the usability of NEXThaler® is superior to Diskus® and Turbodorel®.

P1798
Beclometasone/formoterol administered via extrafine dry powder inhaler in controlled asthmatic patients: Comparison with pMDI and beclometasone monotherapy
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Background: The fixed combination of beclometasone dipropionate and formoterol fumarate (BDP/FF) 100/6 μg pMDI (Foster®) is approved for treatment of adult asthmatic patients. In order to provide physicians and patients with an alternative drug delivery system for BDP/FF, a new dry powder inhaler the NEXThaler® has been developed, able to ensure consistent dosing in patients who prefer the use of dry powder inhalers.

Aims: To compare efficacy and safety profile of BDP/FF NEXThaler® with BDP/FF pMDI or BDP DPI alone in adult patients with controlled asthma.

Methods: 8-week randomised, double-blind, triple-dummy, 3-arm parallel-group clinical study. After 4-week run-in with BDP/FF pMDI 100/6 bid, 755 patients were randomised to receive bid BDP/FF NEXThaler® 100/6, BDP/FF 100/6 pMDI or BDP DPI 101. The primary end-point was change from baseline to the entire treatment period in average pre-dose morning PEF (mPEF).

Results: Non-inferiority of NEXThaler® vs pMDI was shown for mPEF (LSmeans difference: -1.84L/min; 95%CI (-7.43, 3.05)) and lower limit of the 95%CI was above the pre-defined non-inferiority margin of -15L/min. Superiority of both combinations over BDP DPI was shown (p < 0.001) providing evidence of assay sensitivity of the study. Both BDP/FF formulations were statistically superior to BDP alone in terms of ACQ score (p < 0.009 and 0.008) and % of rescue use-free days (p < 0.033 and 0.006) as well as pulmonary function tests over the entire treatment period. No relevant drug related AEs were observed.

Conclusion: NEXThaler® is an effective and well-tolerated alternative device for treatment of asthmatic patients with BDP/FF.

P1799
Improving inhalation parameters through dry powder inhalers (DPIs) after an acute asthma exacerbation
Wahida Arozua1, Mohktar El-Soussi2, Henry Chrystyn1, Mona Lärstad1, Catherine Francisco1, Annamaria Muraro1, Frank Knauss1, 1Pharmacy, University of Huddersfield, United Kingdom; 2Respiratory, Tripsoli Medical Centre, Tripsoli, Libyan Arab Jamahiriya

All DPIs are passive inhalers because they require the generation of an internal energy (P) from an interaction between the patient’s inhalation and the device’s resistance to deaggregate the formulation in the metered dose. During acute exacerbations patient inspiratory effort will be reduced and thus P will be reduced. We have measured the inhalation profiles of 18 asthmatics, mean(SD) age 42.0(11.8) years randomly chosen following their admission with an acute exacerbation. These measurements have been made using a Diskus (DKS), Easyhaler (EASY) and Turbuhaler (TBH) - inhalers with medium, medium/high and high resistance.

PIF, peak inhalation flow; PP, peak turbulent energy; ACC, initial acceleration of the inhalation. IV, inhalation volume. All p < 0.001 except TBH IV < 0.05.

All parameters improved. PIF should not be considered in isolation and provides the wrong message, especially for high resistance DPIs, as PP and ACC are more important. The significance of the IV results needs to be investigated.

227. Monitoring of airway diseases: far from the airways

1832
Fixed airflow obstruction in asthma is related to systemic eosinophilic inflammation – Results from the Swedish GA2LEN survey
Andrei Malinovschi1, Christer Janson1, Karl Franklin2, Bertil Forsberg2, 1Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 2Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Background: Patients with asthma and fixed airflow obstruction represent a clinical-treatment subgroup. Increased total airways inflammation has been linked to fixed airflow obstruction, but few studies have analysed the relation to systemic eosinophilic inflammation, a component not reached by inhaled corticosteroids.

Methods: Non-smoking healthy subjects (n=130) and non-smoking asthma sub- jects (n=357), aged 17-76 years performed lung function, exhaled NO (FeNO) and urine eosinophil protein X (ueEPX) measurements. Fixed airflow obstruction was defined as postbronchodilator FEV1/FVC under the lower limit of normality

Results: Asthmatic subjects with fixed airflow obstruction (n=56) had higher ueEPX levels than asthmatics without fixed airflow obstruction (n=301) (62.4 ng/mL (51.9, 75.1) vs 47.2 (44.1, 50.6)) or healthy controls (40.0 (36.2, 44.2)). (geometric mean 95%CI) (all p-values < 0.05). No differences (p=0.32) were found between asthmatic subjects with or without fixed airflow obstruction in terms of FeNO, whereas both asthma groups had higher levels than controls (p < 0.01). Increased levels of ueEPX (p=0.04), use of inhaled corticosteroids (p=0.01) and increased age (p=0.05) were independently related to persistent airflow obstruction in asthmatics, after adjustments for study centre, height, atopy, sinusitis, rhinitis and time of day for measurements.

Conclusion: Persistent airflow obstruction in asthma was accompanied by increased urinary excretion of EPX. Further studies are warranted to investigate if more aggressive treatment of the systemic inflammation may be required to prevent fixed airflow obstruction.

1833
Prediction of new-onset wheeze based on serum inflammation biomarkers – Evaluation using univariate and multivariate techniques
Mona Larsvig1, Mats Isacsson2. 1Keffalonia airways inflammation – Results from the Swedish GA2LEN survey MONDAY, SEPTEMBER 3RD 2012

Stephanie Korn1, 2Institute of Medical Biostatistics, Epidemiology, and Informatics, Mainz, Germany

1, Catherine Francisco 1, Annamaria Muraro 1, Frank Kanniess 2.

Asthma is associated with inflammation in the airways and wheeze. The hypoth- esis is that increased levels of inflammation biomarkers among subjects without respiratory symptoms are a sign of subclinical airways inflammation.

Objective: To evaluate if increased levels of inflammation biomarkers in serum predicts later onset of wheeze.

Methods: We followed up 2,200 subjects from a general population-based study. At baseline, the subjects were investigated with questionnaires, blood samples, spirometry and FENO. All subjects reporting tobacco smoking, wheeze, asthma, asthma symptoms, or CRP >5 at baseline were excluded. Four years later all subjects got a respiratory questionnaire, which 86.2% completed. The association between baseline levels of a panel of cytokines in serum and incident wheeze was evaluated using non-parametric statistical methods and orthogonal projection to latent structures - discriminant analysis (OPLS-DA). Subjects with FENO levels between the 45th percentile and the 55th percentile served as controls (n=101), and were compared to subjects with new-onset wheeze (n=29).

Results: The median levels of TNF, IL-1, IL-2, IL-4 and IL-12 at baseline were significantly higher among those with new-onset wheeze (p < 0.05). This was supported by OPLS-DA, where TNF, IL-1, IL-4 and IL-12 scored the highest probability. The median levels of IL-5, IL-8, IL-10 and IL-13 at baseline were significantly lower (p < 0.05).

Conclusions: Our results indicate that the levels of serum inflammation biomarkers in respiratorily healthy subjects were associated with an increased risk of developing wheeze.

1834
Vitamin D insufficiency in adult asthma: Association with asthma severity and control
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We followed up 2,200 subjects from a general population-based study. At baseline, the subjects were investigated with questionnaires, blood samples, spirometry and FENO. All subjects reporting tobacco smoking, wheeze, asthma, asthma symptoms, or CRP >5 at baseline were excluded. Four years later all subjects got a respiratory questionnaire, which 86.2% completed. The association between baseline levels of a panel of cytokines in serum and incident wheeze was evaluated using non-parametric statistical methods and orthogonal projection to latent structures - discriminant analysis (OPLS-DA). Subjects with FENO levels between the 45th percentile and the 55th percentile served as controls (n=101), and were compared to subjects with new-onset wheeze (n=29).

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Conclusions: Our results indicate that the levels of serum inflammation biomarkers in respiratorily healthy subjects were associated with an increased risk of developing wheeze.

Data in asthmatic children suggest that low vitamin D levels are associated with poor asthma control, reduced lung function, and increased medication intake. To inves-
Asthma, upper airway disease and systemic inflammation in patients with chronic asthma syndrome and severe chronic asthma

Aims: To compare the functional and biological characteristics of patients with severe asthma and severe asthma with systemic signs and symptoms, where the upper airways disease is a comorbidity which strongly influences the respiratory symptoms.

Methods: The two groups of patients were similar in lung function, asthma control and quality of life. While CSS patients showed higher sputum eosinophil percentages (38 [91] vs. 15 [94], p<0.05) CSS patients had higher peripheral eosinophil counts (895±740 vs 592±579, p=0.05), depending probably by the different therapy (higher systemic therapy in CSS vs higher ICS dose in SCA). The majority of patients presented upper airway involvement, with eosinophilic inflammation (nasal eosinophilic %: 0.5[38] CSS vs 0.6[10] CSA).

Conclusions: Both groups of patients showed partially controlled eosinophilic airway inflammation. The percentage of patients with severe asthma is a comorbidity which strongly influences the respiratory symptoms.

Asthma severity (mean±SEM = 1835 severity and control supporting the hypothesis that improving suboptimal vitamin D levels could have a positive effect on asthma control.

Conclusions: p-Calprotectin levels >200 ng/ml are associated with increased mortality in patients with moderate to very severe COPD in stable phase. P-calprotectin is a potential marker of airway inflammation activity.
1839
Downregulation of Th 17 response after low dose clarithromycin in non-CF bronchiectasis patients
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Introduction: Th17 lymphocytes and, particularly, IL-22-secreting Th17 cells play a crucial role in neutrophilic inflammation and tissue injury. It has been shown that clarithromycin (CAM) has anti-inflammatory and immunoregulatory effects. However, the effect of CAM administration on Th17 response in the setting of non-CF bronchiectasis has not yet been studied.

Aim: To evaluate the effects of CAM prophylaxis on the inflammatory process and Th17 response in patients with steady-state non-CF bronchiectasis.

Methods: Ten adult patients received CAM 500mg per day p.o. for 12 weeks. Peripheral blood Th17 cells were analyzed by flow cytometry using antibodies against CD4, IL-17 and IL-22. IL-17 concentrations in exhaled breath condensate (EBC) were quantified using a commercially available ELISA. Pulmonary function tests (PFT) and clinical data were recorded during the treatment period.

Results: Post-treatment CD4+IL17+ cell count (cells/µl) and EBC IL-17 levels (pg/ml) decreased significantly (mean 3.2016±2.7280 vs 2.5181±1.9246, p=0.001 and 4.3362±1.5899 vs 2.9300±1.7431, p<0.001, respectively). Mean pO2 (mmHg) improved significantly (76.8±4.77 vs 79.3±3.1422, p<0.001), while PFT and pCO2 remained unaltered. Notably, the decrease in CD4+IL17+ cell count correlated with the decrease in exacerbations (r: 0.618, p=0.05), and the pO2 increase (r: 0.648, p=0.043), while the decrease of IL-22/IL-17+ effectors correlated with the decrease in EBC IL-17 levels (r: 0.852, p=0.002).

Conclusion: We report for the first time that low dose CAM in patients with non-CF bronchiectasis appears to reduce lung inflammatory process potentially via downregulating the Th17 response.

228. Cystic fibrosis (adults and children): new therapies and detection of early lung disease

1840
Effects of the CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the G551D-CFTR mutation
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Objectives: This study assessed the use of LCI as a more sensitive measure of improvement in lung function in subjects with FEV1 in the normal range.

Methods: This Phase 2, randomized, double-blind, placebo-controlled, multicenter, crossover study evaluated the effect of ivacaftor on LCI on subjects derived from multiple breath washout of SF6 using an open system Innocor device. Key inclusion were age ≥ 26 years, a G551D-CFTR mutation on at least one allele, FEV1 >90% predicted, and LCI >7.4 (upper limit of normal). Ivacaftor 150 mg or placebo was administered q12h for 4 weeks with a 4-week washout between treatments. Results: Mean (SD) baseline LCI improvements of 6.6% (10.9) years for age, 9.0 (1.5) for LCI and 97.2 (10.6) percent predicted for FEV1. The treatment effect of ivacaftor for adjusted mean change from baseline in LCI at Day 29 was -2.07 (P=0.0004) whereas the mean change from baseline in FEV1 was 7.0% (P=0.0117). Treatment difference for the mean change from baseline in sweat chloride was -45.8 mmol/L (P<0.0001). In the ivacaftor period, adverse events were reported in 13 subjects and serious adverse events in 2 subjects; the correspondent changes in the placebo period, were AEs in 15 and SAEs in 1 subject.

Conclusions: In subjects with CF who have mild lung disease, ivacaftor treatment improvement was not clinically meaningful as measured by LCI and respiratory function as measured by percent predicted FEV1. Adverse events were consistent with previous ivacaftor studies and mostly related to manifestations of CF.

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1842
Long-term safety and efficacy of ivacaftor in subjects with CF who have the G551D-CFTR mutation
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Objectives: Ivacaftor was evaluated in a 248-week Phase 3 studies. This 96-week controlled-label extension (PERSIST) evaluated the safety and efficacy of long-term ivacaftor in subjects who completed the prior trials (STRIVE and ENVISION).

Methods: 192 subjects who completed treatment in STRIVE or ENVISION enrolled in PERSIST. All subjects received ivacaftor 150 mg q12h in addition to prescribed therapies. Here we report the results of 96 weeks of treatment for subjects who were in STRIVE (n=144) and 72 weeks for those in ENVISION (n=10).

Results: For subjects who received ivacaftor in the placebo-controlled studies, the FEV1 improvements were sustained in PERSIST. For STRIVE subjects, the mean (SD) absolute change from STRIVE baseline in % predicted FEV1 was 9.4% (8.3%) on Day 1 of PERSIST, 9.2% (8.5%) at Week 48 in STRIVE, 10% (9.3%) at Week 72 and 9.5% (10.1%) at Week 96. For ENVISION subjects, the mean (SD) absolute change from ENVISION baseline was 10.2% (15.7%) on Day 1 of PERSIST, 9.1% (15.6%) at Week 60, and 10.1% (14.2%) at Week 72. For placebo subjects in STRIVE or ENVISION, the FEV1 improvements in PERSIST were similar to those observed in ivacaftor subjects during the placebo-controlled studies. The mean (SD) absolute change from PERSIST baseline was 9.4% (8.5%) at Week 96 for STRIVE placebo subjects and 8.1% (12.5%) at Week 72 for ENVISION placebo subjects. The safety profile observed in PERSIST was generally consistent with the safety profile observed during ivacaftor treatment in STRIVE and ENVISION.

Conclusions: Ivacaftor-related improvements in lung function were sustained with additional ivacaftor treatment. No new clinically important safety concerns were identified.

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1843
Inhaled glutathione tolerability and efficacy in patients with cystic fibrosis
Cecilia Calabrese, Valeria Raia, Vincenzo Carnovale, Pasquale Abete, Antonella Tosco, Antonio Magliocea, Alda Casale, Claudia Basile, Paola De Fazio, Carmelindo Marzadro2, Po-Shun Lee3, Tao Song4

In CF patients, Glutathione (GSH), the first-line defence of lungs against oxidative stress, is severely reduced. A randomized, single blind controlled trial of inhaled GSH vs placebo (NCT01450267) is underway to evaluate the effect of GSH in a cohort of CF patients. 94 CF patients (48 F; median age 20.8 years) in regular follow up at the Regional Pediatric and Adult CF Center of Naples, were enrolled, 50 patients (23 F) were
randomly assigned to the GSH group and 44 (25 F) to the placebo group. The inclusion criteria were: CF diagnosis by sweat test and/or two CF causing mutations, age of patients <6 yrs, FEV1% > 40% of the predicted value, negative culture for Burkholderia cepacia. Spirometry was performed pre and post treatment, 10 and 60 minutes after GSH inhalation test (10 mg/kg, maximum dosage 600mg/dose) in order to assess tolerability. Follow-up visits including spirometry took place once, three, six, nine months and one year post treatment. No patients showed a decrease in FEV1% > 15% after GSH inhalation. In the subgroup of CF patients (n=27) with an obstructive ventilatory defect (FEV1/FVC<80%) six months therapy with GSH determined a statistically significant increase in FEV1% (58.3±13.2 vs 62.6±15.1 p =0.048) compared to the group (n=20) treated with placebo (59.3±14.9 vs 56.8±18.4). Preliminary results suggest that inhaled GSH is well tolerated and determines an improvement in the respiratory function in CF patients.

1844 Assessment of lung function in pre-school children with cystic fibrosis by nitrogen washout
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Pulmonary function in young children can identify the early manifestations of diseases like cystic fibrosis (CF) and prompt to early intervention. We evaluated in pre-school age children the performance of ventilatory indices obtained from N2 washout (FRC, LCI, Scond, Sacin) as to their feasibility and ability to detect differences between disease and control groups. N2 washout was performed with a novel system that utilizes an ultrasonic flow sensor as well as O2 and CO2 sensors (Exalzyter, Ecomedics AG). N2 washout was performed during tidal breathing and using 100% Oxygen. Three maneuvers free of artifact were obtained whenever possible and allowing for 2-times the washout time to lapse between maneuvers. This was followed by spirometry and aiming to obtain at least 3 valid flow-volume loops. Study groups included children ages 3 to 6 year old with CF (n=20) and asthma (AS, n=15), as well as a group of healthy controls (HC, free from history of respiratory disease or cigarette smoke exposure). Children were studied at a period of acute symptomatology. Research quality nitrogen washout could be completed in 90% of CF, 75% of AS and 70% of HC. FRC was comparable between the groups (p=0.1). The LCI from the N2 washout was elevated in CF with a mean of 10.4±2.6, as well as Scond 0.05±0.03 and Sacin 0.5±0.5, which was statistically significant from the other 2 groups (p<0.05). We conclude that N2 washout can be completed without difficulty even in children that have little familiarity with pulmonary function testing. Indices obtained from the N2 washout can detect defects in ventilatory function in children with CF that distinguishes them from other children.

1845 Alternative multiple breath washout outcomes for clinical trials in cystic fibrosis
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The Lung Clearance Index (LCI) is a sensitive marker of early lung disease, and LCI, but not spirometry, was able to detect treatment effects of hypertonic saline in CF patients with mild disease (Amin et al; Thorax 2010). We used data from this interventional trial to investigate whether any other outcomes of the multiple breath washout could detect treatment effects similar to LCI. Using a cross-over design, patients were randomized to either hypertonic saline or isotonic saline in a randomized sequence, separated by a 4 week washout period. MBW was measured in triplicate by mass spectrometry (AMIS 2000; Innovision A/S, Odense, Denmark) using a gas mixture containing 4% SF6, 4% He, 21% O2 and balanced N2. The current analysis includes 15 subjects for whom the following additional outcome measures could be assessed: normalized concentration of end tidal tracer gas (Cnet) at 6 turnovers (6T0), moment ratios (M1M0, M2M0) and LCI measured by helium. No significant treatment effects were observed for LCI (404.3 μm; SD ±60.3) were both significantly (p<0.05) larger compared to controls (404.3 μm; SD ±34.8 and 223.8 μm; SD ±38.5 respectively). Discussion: HeM2 is well tolerated in children from school age. We found that R and h, both surrogate values for acinar size, are larger in children with mild CF lung disease compared to healthy controls. HeM or HeM may constitute a sensitive technique for investigating CF lung disease.

References:
[1] Narayanan M et al 2012 AJRCCM; 185:185.68

1846 Evaluation of the peripheral airway microstructure in children with cystic fibrosis (CF) using 1H magnetic resonance imaging
Gael Guillard1, Iain Ball1, Kuldip Panesar2, Noor Al-Khathlan1, 1Department of Radiology, Children's Health, Dallas, Texas; 1Institute of Lung Health, Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom; 2Physics, University of Nottingham, United Kingdom

Background: Pathology and lung function studies show that small airways are affected early in CF lung disease. Due to the inaccessibility of the distal air spaces little research has been performed in this area. The lung microstructure can be studied using the relatively new technique of hyperpolarised noble gas magnetic resonance (1HMR) scanning.(1)

Aims: To compare acinar airway size of children with CF with that of healthy controls.

Methods: In children with moderately mild CF lung disease 1HMR was under taken during breath-hold following inhalation of a bolus of hyperpolarised 1H gas mixture. A signal was obtained using the q-space technique.(2) We applied Yablonsky’s acinar model(3) on the raw data to obtain the values for mean acinar duct diameter, R and mean alveolar sleeve depth, h. All children had spirometry and lung clearance index (LCI) measured.

Results: We studied 9 children (6-10y) with CF (FEV1: 97±6% predicted; SD ±14.3) and 18 age-matched controls. LCI was elevated in all CF patients (median 10.7, range 9.1-12.9). Acinar duct diameters (438±4±m; SD ±21.8) and alveolar sleeve depth (294.2±m; SD ±60.3) were both significantly (p<0.05) larger compared to controls (404.3±m; SD ±34.8 and 223.8±m; SD ±38.5 respectively).

Conclusion: HeM2 is well tolerated in children from school age. We found that R and h, both surrogate values for acinar size, are larger in children with mild CF lung disease compared to healthy controls. HeM or HeM may constitute a sensitive technique for investigating CF lung disease.

References:
[1] Narayanan M et al 2012 AJRCCM; 185:185.68

229. Professional development and advanced practice roles in respiratory nursing

1847 A competence framework to support the development of the workforce to deliver improved outcomes for patients with COPD and asthma
Anne Morgan, Sue Hill, Kevin Bolton, Matt Kearney. Respiratory Programme, Department of Health, London, United Kingdom

Rationale: It is estimated that over 3 million people in the UK are living with COPD or related respiratory disease, with less than one third diagnosed and treated. With better awareness and clearer pathways of care focused on improving outcomes, there are implications for planning and developing the workforce. This competence framework identifies the skills, knowledge and attitudes required to deliver improved interventions. The framework consists of a menu of National Occupational Standards where evidence of competence will ensure practitioners are equipped to deliver respiratory services and promote patient self care and management within their scope of practice, role and responsibility.

Method and results: In collaboration with Skills for Health, the agency responsible for developing National Occupational Standards in healthcare, a respiratory disease Competence Framework based on functional and performance standards has been developed, that describes what is needed to deliver patient-centred respiratory care. This was informed by an expert group of stakeholders focused on delivery of care across the spectrum of respiratory disease from prevention, detection and diagnosis, through acute and chronic care to end of life care.

Conclusion: This resource is being used by commissioners, service providers, local networks and workforce planners to inform service and workforce design, thereby supporting the shift of service delivery by a competent workforce, from acute settings into the community.

1848 New Zealand adult respiratory nursing knowledge and skills framework: A platform for competence development
Victoria Perry, Respiratory Services, Palmerston North Hospital, Palmerston North, Manawatu, New Zealand

Respiratory nurses in New Zealand (NZ) are required by the Nursing Council of NZ and national legislation to provide evidence of competence however, there has been an absence of an agreed articulation of the respiratory specific knowledge and skills required to demonstrate this. A national working group of respiratory nurses therefore undertook to develop a national respiratory knowledge and skills framework that offers a mechanism for the development of a range of transferable
clinical skills, seeks to minimise risk to patients, nurses and employers, provides a reference point for curricula and a mechanism for nurses to measure effectiveness of their practice. This presentation will describe the aims of the framework, process with development, scope for application, implementation to date, and initial evaluation.

1849 Audit of the impact of increased nurse education in diagnosis and management of patients with airflow obstruction in the community
Rosier Wolstenholme, Marie Barrowclough, Patricia Darley, Gillian Prescott. Bridgewater Community Healthcare, NHS Trust, Wigan, United Kingdom
Clinical Services Department, AstreaZeneca, Macclesfield, United Kingdom

Aims: Primary to improve skills of primary care clinicians in diagnosis and management of patients with airflow obstruction in the community.

Methods: 10 community practices applied and were accepted for clinical mentorship. Following an Education Needs Analysis a practice nurse education programme was developed and provided by specialist nurses and community respiratory physician. In the 10 practices 259 patients were identified as having poorly controlled asthma or COPD. 213 attended for review, 63 with an initial diagnosis of asthma and 150 COPD.

Results: 12 of 63 (20%) patients with asthma showed no reversibility, 11 of 150 (6%) of COPD patients had normal spirometry. 90% of the asthmatics and 93% of COPD pts were “uncontrolled”. 2 or more courses of steroids and antibiotics a year. After the programme the this reduced to 3% and 12% respectively. COPD MRC scores improved markedly, MRC 3 37% to 17%, MRC 4 30% to 13%. 50% of COPD patients were referred and accepted pulmonary rehabilitation.

Discussion: Increased education supported by continued mentorship improves clinical competencies and outcomes by better diagnosis, appropriate inhaler therapy and encouraging multidisciplinary working. Continued mentorship is vital to maintain standards and confidence in primary care.

1850 What are the solutions to the key challenges facing primary care nurses delivering respiratory care in the United Kingdom?
Stephen Holloway, Anne Radwan, Gareth Hall, Jan Scallon. 1

Methods: We have previously described qualitative research involving 72 primary care nurses (60 minute interviews) and four 90 minute focus groups of nurses purposively representative of primary care respiratory interested nurses in the United Kingdom. We have also published results of this research (IPCRG Abstract 202; 2012). We now describe some of the suggested solutions gained from discussions of a group of clinicians involved in health care education (involving primary care, community, specialist nurses and general practitioners).

Results: The initial research identified four key challenging themes: time, professional isolation, working with patients and lack of resources. The key areas identified to facilitate addressing these challenges were themed into two broad areas - which will address all the challenge areas. Firstly, leadership skills (including time management, influencing and negotiating skills) and secondly communication skills (eg motivational interviewing and shared decision making techniques).

Conclusions: It is likely that with changes in the continuing professional development offered to practice nurses many of the key challenges currently faced could be addressed. This however would require influencing and negotiating skills at practice, area and national levels and a desire from practice nurses to engage in leadership and communication skills development. With these inputs a real change could be obtained which would improve clinician and patient satisfaction.

1851 The role of the asthma nurse specialist in optimising the management of acute asthma according to British Thoracic Society guidelines
Philip Coakley, Karina Virdoe, Aithya Jayaraman, Bernadette Hawkes. Medicine, King George Hospital, London, United Kingdom

Introduction & aims: Asthma affects over 5 million people in the UK and accounts for one hospital admission every 7.5 minutes. The British Thoracic Society (BTS) has evidence-based guidelines on the management of acute asthma which have been shown to reduce readmission rates. This study aims to audit the management of acute asthmatic admissions against BTS guidelines and establish whether or not intervention by an asthma nurse specialist (ANS) improves the audit criteria outcomes.

Methods: In a busy Outer London district general hospital, retrospective case note audit was carried out on all patients admitted with acute asthma in September and October 2011. The patients were then divided into those who were jointly managed by the medical team and ANS with those who were managed by the medical team alone.

Results: 50 patients were admitted over the 2 month period, of which 50% had been reviewed by the ANS. Across all 16 BTS audit criteria, the achievable rates in the group of patients who received the intervention of ANS was either equal to or higher than those who were managed by physicians alone. The average achievable rate of all audit criteria in patients who did not see the ANS was 29.3% compared to 60.1% for those who were seen by the ANS.

Conclusions: The intervention of the ANS in the inpatient management of acute asthma increases the adherence to national guidelines, thus improving standards in overall management. This audit also demonstrates the importance of the BTS audit criteria and the guidelines in the management of acute asthmas to improve overall adherence.

1852 Nurse-patient collaboration; a grounded theory study in patients with chronic obstructive pulmonary disease on non-invasive ventilation
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Objectives: This paper provides a theoretical account of nurses’ collaborations with chronic obstructive pulmonary disease patients during non-invasive ventilation treatment at the hospital.

Background: Despite strong evidence for the effect of non-invasive ventilation treatment, success remains a huge challenge. Nurse and patient collaboration may be vital for treatment tolerance and success. A better understanding of how nurses and patients collaborate during non-invasive ventilation may therefore contribute to improvement.

Design: A constant comparative classical grounded theory method. The data comprised sessions of qualitative participant observation during the treatment of 21 patients with non-invasive ventilation, which included unstructured conversations with the nurses and semi-structured interviews with 11 patients after treatment completion. Data were collected at three Danish hospitals.

Results: Definition of the situation emerged as the core category in nurse-patient collaborations during non-invasive ventilation treatment. The main concern was resolved by activating one or more of four categories: (1) Joint Modality; (2) Patient-initiated Modality; (3) Nurse-initiated Modality; and (4) Split Modality. Modalities 1–3 were characterised by mutual definitions of the situation, whereas the fourth was characterised by divergent definitions of the situation.

Conclusions: This study offers a robust account of nurses’ and patients’ concerns about their definition of the situation and how they activate different complex adaptive modalities. We offer a theoretical basis for developing complex interventions.

1853 Fatigue in COPD: A qualitative study of peoples experiences
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Background: Fatigue is reported to be one of the most common symptoms among people with COPD. However, there is hardly any qualitative research describing how fatigue affects people living with COPD.

Aim: To study people’s experience of fatigue when living with COPD.

Method: In the years of 2008-2010, a purposive sample of 20 people with COPD stage II-IV, according to GOLD, was recruited from the OLIN COPD-study in Northern Sweden. Data was collected by semi-structured interviews and the participants were interviewed about their experience of fatigue. The interviews were subjected to a qualitative content analysis.

Results: One theme was identified: To reconcile with the dimensions of fatigue, and four categories: To understand the reason; To preserve fatigue unexpressed; To be controlled and To struggle against. In COPD, fatigue seems to appear in different dimensions. People are aware of the cause of fatigue and they seem to reconcile with the symptom believing it is a natural consequence of COPD, and therefore it remains unexpressed. Fatigue is an always present feeling that involves the whole body, raising feelings of hopelessness making life heavy and invincible. Further, by increased dyspnea, fatigue gets even heavier and more severe to manage. To cope, people have to force themselves to struggle against fatigue, regardless of dyspnea that was triggered by physical movements.

Conclusion: Fatigue affected the daily life of people living with COPD. In relation to dyspnea, fatigue was described to be overwhelming, and most important fatigue seems to own to reduced to healthcare professional and relatives. This knowledge is significant for nurses in order to meet the person’s needs of care.
230. Novel approaches to lung transplantation

1854 Mesenchymal cells isolated from the airways of BOS patients as targets of innovative drug-loaded nanoparticles

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Our group has recently shown that proliferating mesenchymal cells (MC), obtained from BAL of BOS patients, express CD44 and that this expression correlates with mTOR expression and with a higher proliferative rate. By these results we have designed an innovative approach based on bio-compatible nanoparticles loaded with the mTOR inhibitor everolimus and functionalized with anti CD44 MoAb, for the selective targeting to the specific cells (targNP). Fluorescent labeled targNP have been used to assess cell uptake by confocal microscopy. Cell apoptosis/death (annexin V/7AAD) and proliferation (CFSE) were evaluated by flow cytometry. We used primary MC isolated from 2 BOS patients (grade 1 and 2) with the following phenotype: BOS 1: 85% CD90+ of which 33% co-expressing CD9; BOS2: 93% CD90+ with 38% co-expressing CD146, 25% CD9, and 38% both CD146 and CD9. Both MC samples were negative for CD45RO and CD34 and positive for CD44 (98%). TargNP were shown to adhere to matured MC from 15 min and completely enter into the cells after 45 min. Drug free nanoparticles, as control, were completely inert. TarTNP treated cells showed a significantly higher mean rate of annexin V at 4 h (17.6 versus 4.5%) and 24 h (15 versus 5.3%) respect to control cells while mean 7AAD expression at 24 h was 4.1 versus 1.3%. Likewise, cell proliferation was significantly inhibited at 24 and 48 h (mean: 41 and 37.2%, respectively). This is, by far, the first proof of concept that an innovative approach based on drug coated NP can be used to selectively address MC which proliferate in the airways. Further in vitro and in vivo studies will investigate possible efficacy of this new treatment strategy.

1855 Structural differences in airways during chronic rejection after lung transplantation: A (micro)-CT analysis

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Chronic rejection is a major problem after lung transplantation (Tx). Recently a distinction between an obstructive (fBOS) and restrictive phenotype (RAS) has been made. We aimed to investigate structural differences. Human explant lungs from 5 fBOS and 3 RAS patients were collected during reTxs, were air-inflated to 75% TLC, frozen solid in liquid nitrogen vapor and frozen sections were examined by H&E. Unused donor lung (n=1) served as control. The lungs were fixed for immunohistochemical detection of airway and interstitial changes and structural alterations of the central airway tree (4-16 generations). In conclusion: in RAS lungs both airways and interstitium were affected. Most frequent intra-airway changes were bronchiolar and bronchial wall thickening. In intraluminal changes airway narrowing and bronchial plugging were observed. Interstitial changes were characterised by collagen deposits, lymphocytic infiltrates and increased fibroblasts/myofibroblasts. We confirm the presence of chronic rejection and suggest in addition to ABO incompatibility, a technical factor (cold ischemia time >24h) that might lead to the development of chronic rejection.

IL-17- and Th17-associated cytokines have been linked to the development of acute and chronic rejection after lung transplantation in both animal models and humans. An increase in IL-17 mRNA expression and of IL-17 levels in BAL have been described in LTR with BOS and during AR episodes in comparison with Stables Recipients. On the other hand a decrease in IL-10 producing clone number and in Treg cell frequency has been described in BOS patients.

Aim of the present study was to assess with a feasible method the balance between IFN-gamma/IL-17- producing clones and IL-10 producing cells/Treg cells in the peripheral blood of 26 LTR (13 stable recipients, 13 BOS patients). IFN-gamma/IL-17 and IL-10 producing clones were assessed by ELISPOT. CD4+/CD8+ T cells were assessed by flow-citometry. A significant increase of IL-17 and IFN-gamma producing cells in the peripheral blood was observed in patients who developed BOS (p= 0.03 and 0.04 respectively) while Treg cell count decreased significantly (p= 0.002) and IL-10 showed a non significant trend toward a decrease. Moreover the ratio between IL 17 and IL 10 or Treg cell count was significantly increased in BOS (0.85 vs 0.21; 10.4 vs 1.9 respectively) while IFNgamma/IL10 ratio did not significantly change.

In conclusion detection of IL17/Treg ratio in the peripheral blood of LTR represents a feasible and useful tool in the identification of patients at higher risk of BOS development. By this way the role of Th17 axis in BOS pathogenesis is further confirmed.

1857 Mechanistic differences of chronic lung allograft dysfunction phenotypes in lung transplantation

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Purpose: The neomacrolide azithromycin, is now widely used in the treatment of bronchiolitis Obliterans Syndrome after lung transplantation. However, only a proportion of patients respond by improving their lung function. This study aimed to evaluate differences in airway microenvironment between azithromycin responsive (<10% improvement in FEV1), and azithromycin resistant BOS patients.

Methods: Bronchoalveolar lavage (BAL) from recipients identified as stable n=10 (control), azithromycin responsive n=10 and azithromycin resistant n=10 were evaluated for cell differential, IL-1α, IL-1β, IL-6, IL-8, TNF-α peptides. BAL was then added to primary bronchial epithelial cells (PBEC) and tested for viability by XTT assay.

Results: BAL neutrophilia (%) was increased in responders (50% p<0.0001) and non-responders (52.9% p<0.0001) compared to the control (0.8%). IL-1α, IL-1β, IL-6, IL-8, TNF-α were increased in both groups (all proteins <0.05) compared to the control. The levels of IL-1α, IL-1β and TNFα showed increasing trend in responders compared to non-responders. PBEC viability in response to BAL was reduced in non-responders (p=0.012) but not in the responders group (p=0.64). Moreover, there was a negative correlation between PBEC viability and IL-1α (r=0.042), IL-8 (p=0.0017), TNFα (p=0.039), IL-1β (p=0.045) and IL-6 (p=0.0453) concentrations.

Conclusions: Unlike in responders, where azithromycin blocks IL-17 T cell mediated neutrophilia, azithromycin resistant phenotype is associated with epithelial damage. Further studies are needed to determine if these results are specific to azithromycin or apply to other immunosuppressant strategies. These results also suggest that these responses could be considered for BOS patients who develop an azithromycin resistant phenotype.

1858 Results of a phase 2b multi-center, randomized, double-blind, placebo-controlled study of an RNA therapeutic, ALN-RSV01, in respiratory syncytial virus (RSV)-infected lung transplant patients

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RSV infection after lung transplantation is an independent risk factor for the development of bronchiolitis obliterans syndrome (BOS). ALN-RSV01 is a small interfering RNA targeting the RSV nucleocapsid gene that is critical for viral replication. Previously, we performed a Phase 2 randomized, double-blind, placebo-controlled trial in 24 RSV-infected lung transplant patients administering...
aerosolized ALN-RSV01 or PBO for 3 days. The primary endpoint of safety and tolerability was attained. In addition, there was a significant reduction in the secondary endpoints of incidence of new or progressive BOS at day 90 (p=0.027) and patient’s symptom scores in the ALN-RSV01 group compared to PBO. To extend these results, we performed a Phase 2b multi-center, multinational, randomize, double-blind, PBO-controlled trial in RSV-infected lung transplant patients in which the primary endpoint was the effect of ALN-RSV01 on the incidence of new or progressive BOS at Day 180. Secondary endpoints included the impact of ALN-RSV01 on symptom scores, antiviral activity and safety. RSV positive subjects were randomized (1:1) to receive either aerosolized ALN-RSV01 or PBO for 5 days, alongside the hospital’s standard-of-care. Subject stratification to treatment arms was based on two binary factors: 1) time from symptom onset to treatment start and; 2) pre-infection BOS grade. Of the 3,985 subjects prescreened at 33 centers, 218 were RSV positive, of which 87 were randomized. Enrollment is completed and subjects are now in the follow-up phase. Final study results will be presented at this meeting.

1859
BAL neutrophil levels in a randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome post lung transplantation

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Open studies have reported an improvement in FEV1 in some BOS patients treated with Azithromycin (Azith). We recently demonstrated that Azith is superior to placebo treatment, improving FEV1 in patients with BOS. It is suggested that a BAL neutrophil reduction is associated with treatment benefit. We have investigated this in our trial.

Methods: A prospective, randomised double blind placebo controlled study of Azith 250mg o.d. or placebo on alternate days, in BOS patients. The primary outcome was change in FEV1 at 12 weeks and a secondary outcome BAL neutrophil %.

Results: 46 patients were randomised (23 Azith, 23 placebo) stratified for pre op diagnosis of supplicative disease and operation (single or bilateral lungs). Of the 46ITT patients, baseline and final visit BAL were available for 28 (13A, 15P). In these patients the baseline % neutrophils, median (IQR), in the Azith group was 17 (4 to 69%) and in the placebo group 15 (2 to 56%). The baseline to final visit change in % neutrophils varied, with around half the patients in both treatment arms showing an increase from baseline and half a decrease. There was a median increase from baseline in the Azith group of 10%, IQR (~10% to 18%) and in the placebo group a median decrease from baseline of ~1% (~8% to 5%). These changes were statistically non significant (P=0.4 and 0.6 respectively, 1-sample Wilcoxon).

Conclusion: Azith is superior to placebo improving lung function in patients with BOS. In the same patients, whilst BAL neutrophil % was high, we observed no consistent fall with Azith. This may suggest the mechanism of benefit does not rely on a quantitative reduction in neutrophils.

1860
ENDOXY – Endothelialization of a gas permeable membrane for the development of a biohybrid lung assist device

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The interaction of stem cells with the surrounding matrix environment is crucial for cell fate. The development of biomaterials that recapitulate the in vivo environment is a key component to driving differentiation of pluripotent cells into lung endo- and peri-observed BOS, markers for COPD, asthma, forced expiratory volume in one second (FEV1), and forced total capacity (FVC) in nine genes of the WNT signaling cascade pathway (WNT10B, WIF1, WISP1, SPREF2, SPREF5, DKK1, Asxin2, TCF7L2, and FZD3) using genome-wideassociation data from six European cohort studies.

231. Asthma and the genes: from GWAS to next generation transcriptome analyses

1862
Meta-analysis of genome-wide association studies of single nucleotide polymorphisms in selected genes of the WNT signaling pathway

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Background: The WNT signaling pathway is involved in a wide range of developmental events and maintenance of homeostasis in adult tissue, including lung development and health. WNT signaling genes have also been suggested to play a role in pathogenesis of lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma.

Aims and objectives: The aim of this meta-analysis was to identify consistent disease markers for COPD, asthma, forced expiratory volume in one second (FEV1), and forced total capacity (FVC) in nine genes of the WNT signaling cascade pathway (WNT10B, WIF1, WISP1, SPREF2, SPREF5, DKK1, Asxin2, TCF7L2, and FZD3) using genome-wideassociation data from six European cohort studies.
1863 Genome-wide prediction of childhood asthma and related phenotypes in a longitudinal birth cohort

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Aim: Childhood asthma varies greatly in clinical presentation and time course and underlying disease pathways are assumed to be heterogeneous. We assessed the extent to which single nucleotide polymorphisms (SNPs) associated with childhood asthma in a genome-wide association study (GWAS) are predictive of asthma-related phenotypes.

Methods: In 8365 children from a population based birth cohort, the Avon Longitudinal Study of Parents and Children, allelic scores were derived based on between 10 and 215443 SNPs ranked according to inverse of the p-value for association to asthma (P<0.05) and atopy (P<0.005) and decreased FEV1 and FVC (P<0.05). Notably in TCFL7L2 six different SNPs were identified (p-values between 0.002 and 0.046) in association with asthma, FEV1, and FVC. In literature, WNT signaling genes were linked to COPD (Axxm2, asthma (SFRP2, TCFL7L2, NPSR1), FEV1 (SFRP2, TCFL7L2, WNT10b). Conclusions: Using GWAS data we identified genetic variants in DMRT1 to be gender-specific risk factors for asthma development. Allele-specific transcription factor binding and consecutive changes in promoter activity seem to contribute to this effect. The role of DMRT1 in asthma pathogenesis needs to be elucidated further.

1865 Interaction of retinoid acid receptor-related orphan receptor alpha (RORA) and neuropeptide S receptor 1 (NPSR1) in asthma

Rationale: Retinoid acid receptor-related orphan receptor alpha (RORA) is currently received as a candidate gene for asthma by a genome-wide association study (Moffatt et al. NEJM 2010). To investigate whether RORA polymorphisms (SNPs) influence asthma susceptibility, we conducted a detailed genetic association study in the vicinity of the asthma-associated variant rs1071559.

Methods: We genotyped 37 RORA SNPs in the Swedish birth cohort BAMSE (2003-2009) (n=1120 children). In the cross-sectional PARSIFAL study (1120 European children), we also performed allele and genotype association and RORA-NPSR1 gene–gene interaction analyses. Regulation of RORA was investigated using NPSR1 over-expressing SH-SY5Y cells.

Results: Seven RORA SNPs were associated with doctor-diagnosed childhood asthma. The allele T in rs7164773 was under-represented in cases in BAMSE (52.6% vs. 44.7%; OR 0.72; 95% CI 0.60-0.87; p=0.005). In PARSIFAL, the allele T of rs1071559 was under-represented in cases (13.6% vs. 8.5%; OR 0.58; 95% CI 0.37-0.92; p=0.02). These associations were confirmed in the combined BAMSE and PARSIFAL material (p<0.005 and p<0.01, respectively). Significant gene-gene interactions influencing the asthma risk were found between RORA SNPs and NPSR1 SNPs. In cell line studies, NPS induced RORA mRNA expression.

Conclusions: Genetic variations in RORA are associated with childhood asthma and NPSR1. A direct regulatory effect further suggests interaction of RORA and NPSR1 pathways.
Objective: To systematically analyze the association between SNPs in TLR signaling pathway genes and childhood asthma and atopy.

Methods: Common SNPs present in TLR signaling pathway were retrieved from HapMap database and LD analyses were performed to determine tagging SNPs. Association of 375 tagging SNPs with asthma were analysed in a genome wide association (GWA) dataset consisting of 651 asthmatics and 652 controls. SNPs were genotyped by Illumina HumanHap300Chip (n=169) or MALDI-TOF MS (n=19) or imputed (n=187). Algorithms were applied to rank associations and clustering of the associated genes on a virtual pathway map was performed by a systems biology approach and we assessed the putative functional relevance of associated genes by in silico analyses.

Results: We identified 41 genes involved in the TLR signaling and regulatory pathways, harbouring 1405 SNPs (tagged by 375) with minor allele frequency >5% in the HapMap (CEU) population. SNPs located in 19 genes showed association with asthma at a significance level of p < 0.05. Top ranked asthma-associated genes (e.g. IRAK-1, MKK-3, and ERK-2) mapped to distinct functional clusters within the TLR pathway and associated SNPs were located in promoter (n=16), intronic (n=116) and downstream regions (n=16).

Conclusion: SNPs in TLR signaling network genes show association with asthma and distinct clusters are associated with atopic and non-atopic asthma.

1867

Genetic variants in PCDH1, bronchial hyperresponsiveness and asthma subphenotypes in German children

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Background: Recently, three genome wide association studies (GWAS) demonstrated FCER1A, the gene encoding the α-subunit of the high-affinity IgE receptor, to be a major susceptibility locus for total serum IgE. These data suggest that SNPs in FCER1A specifically influence IgE levels in asthma on top of genetic determinants of "basal" IgE levels also present in FCER1A as previously identified by GWAS. Thus, FCER1A variants and IgE-related mechanisms could be involved in specific asthma phenotypes.

These authors contributed equally.

Rationale: The pathophysiolog of asthma is largely unknown. RNA-Seq allows detailed biological characterization of the airways. We hypothesized that the airway transcriptome is different between atopic asthma and controls.

Aim: We investigated: a) the difference in transcriptomic profiles of whole bronchial biopsies between steroid-naïve asthma and controls; b) the feasibility to use RNA from airway smooth muscle (ASM) captured by laser microdissection (LCM) suitable for RNA-Seq

Methods: 4 biopsies per subject (asthma/control: aim n=4/n=5; aim b n=4/n=12) were incubated in RNAlater. Whole crossection or LCM-captured ASM was put down on to RNA-Seq sample.

Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Whole biopsy</th>
<th>ASM</th>
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<tbody>
<tr>
<td>Concentration (ng/μl)</td>
<td>RNA</td>
</tr>
<tr>
<td>30-310</td>
<td>2-27</td>
</tr>
<tr>
<td>cDNA</td>
<td>204-521</td>
</tr>
<tr>
<td>18-168</td>
<td></td>
</tr>
<tr>
<td>RNA-Seq reads mapped (%)</td>
<td>Asthma</td>
</tr>
<tr>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
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<tr>
<td>88</td>
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Reference = UCSF hg19; 1 subject.

1868

IgE levels in asthmatics and non-asthmatics are affected by different SNPs in FCER1A

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Recently, three genome wide association studies (GWAS) demonstrated FCER1A, the gene encoding the α-subunit of the high-affinity IgE receptor, to be a major susceptibility locus for total serum IgE. The top association signal was in the vicinity of the cytokine gene cluster containing several known candidate asthma, was significantly associated with non-atopic asthma (OR=0.70, p=0.019) and non-atopic asthma (OR=0.69, p=0.009). The exonic SNP rs3797054 previously reported to be associated with BHR and asthma, was significantly associated with non-atopic asthma (OR=0.70, p=0.019) in our study. Significant associations with non-atopic asthma were observed also for rs11167761 (OR=1.54, p=0.021), rs3935792 (OR=1.32, p=0.039), rs2974704 (OR=0.43, p=0.009).

Conclusions: PCDH1 polymorphisms may specifically affect the development of non-atopic asthma in children.

These authors contributed equally. Mrs. Antoaneta Toncheva, Dr. Kathrin Suttner, and Mr. Sven Michel.
232. New developments in the immunological diagnosis of tuberculosis and latent tuberculosis infection

1870
Different polyfunctional characteristics of RD1-specific CD4+ T-cells in active TB disease and LTBI
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Introduction: CD4+ T-cells and their cytokines are crucial for protection against M. tuberculosis (Mtb). Analyses of the cytokines coexpressed by polyfunctional T-cells can help in discriminating different tuberculosis (TB) stages.

Aims: To evaluate by flow cytometry the functional status and phenotype of Mtb-specific CD4+ T-cells in TB subjects at different stages.

Methods: We enrolled 25 TB patients before and after therapy (active/past TB) and 39 latent TB infection (LTBI), classified as recent/remote infection and LTBI post-prophylaxis. We evaluated the CD4+ intracellular cytokines production (IFNγ, TNFα, IL2) and memory/effector status after in vitro whole blood stimulation with RD1 antigens.

Results: Magnitude of CD4+ T-cells is higher in active TB compared to the other groups, although the differences are not significant. Double IFNγ/TNFα+ CD4+ T-cells are significantly higher in active TB than in past TB (p=0.03) and in LTBI (p=0.002), whereas triple IFNγ/TNFα/IL2+ are significantly associated to LTBI post-prophylaxis compared to active TB (p=0.02). The proportion of total IFNγ+ CD4+ T-cells increases whereas the proportion of total IL-2+ CD4+ T-cells decreases in active TB compared to LTBI (p=0.02). Effector memory CD4+ T-cells are significantly higher in active TB than in LTBI (p<0.01), whereas central memory cells are higher in LTBI than active TB (p=0.03).

Conclusions: Double IFNγ/TNFα+ CD4+ T-cells are associated to active TB disease whereas triple polyfunctional cells are associated to infection containment. These results may be helpful for better characterizing TB immune responses and generating tools for TB stages identification.

1871
Screening for latent TB using antigen-specific IP-10 response and the effect of treatment on IP-10 responses
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Background: Only a minority of individuals exposed to Mycobacterium tuberculosis (MTB) develops a positive Interferon-γ release assay (IGRA) from peripheral blood mononuclear cells (PBMC). Most contact persons do not develop a systemic immune response after inhalation of MTB aerosols. Pulmonary immune mechanisms preventing a systemic immune response in these subjects are incompletely understood.

Objective: To evaluate local and systemic immune responses in healthy MTB contacts.

Methods: Recruitment of MTB exposed health care workers (HCWs) and very close private house hold contacts (HHCs). Flow cytometry of bronchoalveolar lavage (BAL) cells and PBMC for immunophenotyping. IGRA testing of blood and BAL cells.

Results: 35 HCWs and 15 HHCs were recruited. Regulatory Tregs (CD4+CD25+CD127−) frequencies were increased in all contacts with latent MTB infection (PBMC IGRA positive; n=15) compared to contacts with a negative PBMC IGRA (n=20) with a median 2.12%, IQR 1.63-3.01 versus 0.68%, IQR 0.39-1.02, respectively (p<0.0001). No immunophenotypic differences were seen in PBMC between IGRA positive and IGRA negative subjects (9.6%; 5.9-10.1 versus 7.7%; 4.6-11.3; p=0.47). In 5 of the 25 IGRA negative subjects, the BAL IGRA gave a positive result, possibly indicating incipient tuberculosis.

Conclusion: In close MTB contacts with LTBI, Tregs are increased in BAL but not systemically when compared to contacts that remain IGRA negative. The functional role of Treg requires further investigation.

1873
Evaluation of non-tuberculous mycobacteria effect in the tuberculosis infection diagnosis: Interim analysis of a TBNET study

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The aim was to determine the role of previous non-tuberculous mycobacteria (NTM) sensitization in children as a factor of discordant results between tuberculin skin test (TST) and T-Spot.TB assay (Oxford Immunotec). We studied the presence of M. avium sensitized T cells in 87 non BCG vaccinated paediatric patients with discordant results: TST positive and T-Spot.TB negative. We also included as controls 11 individuals with a negative TST and a negative T-Spot.TB, and 8 patients with microbiologically confirmed NTM infection. Peripheral blood mononuclear cells were stimulated with M. avium sensitin. The presence of reactive T cells were determined by means of ELISPOT.

From the 87 children, in 31 cases (35.6%) we obtained a positive ELISPOT result after stimulation with M. avium sensitin, in 50 cases the result was negative (57.5%), and in the remaining 6 cases the test failure. The number of responder T cells after M. avium sensitin stimulation was significantly higher that the number of responder T cells to M. avium sensitin between the study and the control group were significant. In 4 cases a positive result was obtained between patients with confirmed NTM infection. Our results suggest that previous NTM sensitization in children induces false positive results in TST for diagnosing latent tuberculosis infection. The use of IFN-γ tests provide a more specific diagnostic of TB infection in childhood.

Conclusion: This is the first study to investigate the influence of prednisolone treatment on IP-10 responses; IP-10 was equally affected by prednisolone and the study was too small to determine the value of a combined biomarker approach. IP-10 can be stored on filter paper bypassing centrifugation, freezer and cold chain which gives an IP-10 based test an advantage to the current IFN-γ based test.
Evaluation of the QuantiFERON-TB Gold in tube cut-off for diagnosing test performance. In adults the QFT and IP-10 test performance was in line with Discussion: A main challenge in childhood TB management is the lack of good diagnostic tools. IP-10 is a novel marker for latent tuberculosis (TB), but very few studies have examined the use of IP-10 in childhood TB. Aims: To compare the performance of the QuantiFERON test (QFT) and IP-10 for the diagnosis of TB in Tanzanian children.

Methods: 207 TB suspected children (0-15 years) and 102 adults with confirmed TB were included. QFT tests were analyzed locally and IP-10 was measured using ELISA. The children were divided into three risk groups using clinical parameters, CXR, microscopy and culture: Confirmed/highly probable TB (probTB, n=33), possible TB (posTB, n=84) and Not TB (notTB, n=90).

Results: In children the positivity rate was low in all groups for both tests. Positivity rates were slightly higher in the group of children suspected of TB and lower in the notTB group.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>QFT POS</th>
<th>QFT NEG</th>
<th>QFT INDET</th>
<th>IP-10 POS</th>
<th>IP-10 NEG</th>
<th>IP-10 INDET</th>
</tr>
</thead>
<tbody>
<tr>
<td>probTB</td>
<td>15%</td>
<td>67%</td>
<td>18%</td>
<td>21%</td>
<td>64%</td>
<td>15%</td>
</tr>
<tr>
<td>posTB</td>
<td>17%</td>
<td>54%</td>
<td>1%</td>
<td>14%</td>
<td>54%</td>
<td>32%</td>
</tr>
<tr>
<td>notTB</td>
<td>8%</td>
<td>65%</td>
<td>27%</td>
<td>7%</td>
<td>61%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Discussion: In children the two tests had poor performance with low positivity rate and high indeterminate rate; this was not explained by risk factors for poor test performance. In adults the QFT and IP-10 test performance was in line with other studies. Our findings could be explained by group heterogeneity and severity of illness.

233. Sleep disorders in internal medicine

P1877 Assessment of the prevalence of obstructive sleep apnea in patients with undiagnosed chronic cough

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Background: Recent reports have suggested an association between chronic cough and obstructive sleep apnea (OSA). There is also evidence that treatment of sleep apnea can improve chronic cough.

Objective: To assess the prevalence of OSA in patients with undiagnosed chronic cough and the effect of using CPAP therapy on the improvement of cough in those patients.

Methods: The present study included 100 non-smoker patients complaining of cough for more than 8 weeks without obvious diagnosis, after exclusion of any parenchymal lung or mediastinal diseases using chest X-ray, CT chest, pulmonary function testing, and methacholine challenge test to exclude cough variant asthma, patients undergone sleep polysomnography to screen for OSA and in whom proved to have the diagnosis, CPAP was tried for 2 weeks then follow up of the cough frequency and severity was done.

Results: The study included 100 patients, with 60% females and 40% males, the duration of cough in weeks was 18.16 ± 6.01 weeks, the most common cause of cough was gastroesophageal reflux disease (GERD) which was present in 70% of cases followed by upper airway cough syndrome (UACS) which was present in 50% of cases. OSA was present in 3% of patients in association with GERD in 15 patients and in association with UACS in 10 patients (10%). There was significant improvement of cough using CPAP treatment for 2 weeks (visual analogue scale (VAS) dropped from 8.4 ± 8.6 mm to 7.4 ± 5.1 mm after use of CPAP).

Conclusion: OSA should be ruled out in patients with undiagnosed chronic cough as it is a common finding. CPAP seems to be an effective tool in treating those patients.

P1878 Health, social and economic consequences of sleep disordered breathing: A controlled national study evaluating the societal effect on patients and their partners

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The socioeconomic and indirect costs of obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) on patients and their partners are incompletely described. Using data from the Danish National Patient Registry (1998-2010), 30278 OSA and 1562 OHS patients and their partners were identified. Four matched citizens based on age, gender and social status matched served as controls.
Direct costs were extracted from the Danish Ministry of Health, Danish Medicines Agency and National Health Security, and indirect costs from the Cohherent Social Statistics. 66.2%-63.4% of all OSA/OHS patients was observed versus 65.4%-65.6% of controls. OSA/OHS showed higher rates of health-related primary and secondary care, medication, unemployment, and other socioeconomic costs. The income level of OSA patients was lower. The annual mean excess total direct and indirect health-related cost for each patient was €2821 before and €5060 (p<0.001) after an OSA diagnosis and €10463 before and €15001 after an OHS diagnosis. 

Partner’s total health expenses and the public transfer income were higher, whereas the employment rate and income level were lower than the controls. The annual mean excess total cost for each partner was €2639 before diagnosis and €3058 (p=0.001) after the pts OSA diagnosis, €3523 before and €4066 (p<0.001) after the pts OHS diagnose. These effects were present 11 years prior to an OSA diagnosis in patients and partners, and increased with disease advancement. OSA and especially OHS are associated with a major health and social effect, affected employment and income level affecting the patients and partners.

P1879 Prevalence of sleep apnoea, sleepiness and behavioural/emotional disturbances in adults with Down’s syndrome in Scotland

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Introduction: Adults with Down’s syndrome (DS) are predisposed to sleep apnoea (SA). Prevalence is, as yet, unknown.

Aims and objectives: To assess prevalence of SA, sleepiness and behavioural and emotional disturbances in adults with DS in Scotland.

Methods: A sleep questionnaire, including the pictorial Epworth Sleepiness Scale (pESS) and subscales of the Developmental Behaviour Checklist for Adults (DBC-A) was sent to 650 adults (age ≥18yrs) with DS. All respondents were offered sleep studies (Emblettta® Gold, Embla Systems LLC, Iceland) and OSA was diagnosed if their AHI was >3 events/h.

Results: Response rate was 42% (246 valid). 16 respondents had existing SA; 11 were treated.

Mean age was 31±11 yrs. BMI was 30±7 kg/m², higher in females (p=0.009). Mean pESS score was 7±5, with males sleepier (p=0.016). 176 respondents (28.5% of DS adults) were sleep apnoea suspects and 60 reported apnoea.

To date, 23 patients (15 males) have had sleep studies, 20 being valid. Mean age 26±9 yrs. Mean BMI was 30±7 kg/m²; females were heavier (p=0.001). Median AH (apnoeas/hypopnoeas per hour in bed) was 28.6 (IQR 14.8-48.2). Median ODI (≥4% desaturations per hour in bed) was 6.5 (IQR 2.1-30.9). Snorers scored higher on pESS (r=0.459, p=0.042) and DBC-A disruptive subscale (r=0.463, p=0.040). BMI correlated with the anxiety/antisocial subscale (r=0.606, p=0.005) and the degree of cirrhosis.

Conclusion: This is the first population survey of SA in DS adults. Females were less sleepy than males, despite being more obese. Snoring was associated with sleeplessness and disruptive behaviour. Heavier patients were more anxious. The study is ongoing.

Acknowledgements: Chief Scientist Office, Scotland; Foundation Jérôme Lejeune, France.

P1880 Menstrual status in women and sleep-related outcomes

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Background: There is limited knowledge about how menstrual status may influence sleep related outcomes. We aimed to investigate whether irregular menstruation and menopause affect sleep related symptoms including insomnia and gastroesophageal reflux.

Methods: A population-based sample of 8588 women aged 25-55 years answering the respiratory Health In Northern Europe (RHINE) postal questionnaire were analyzed. Logistic regression models were adjusted for BMI, age, smoking history and socioeconomic status.

Results: Women reporting irregular menstruations had significantly more sleep-related symptoms (reflux after going to bed OR=1.67 [1.30–2.15], difficulty falling asleep (DHS) I 4.2 [1.1–1.80], difficulty maintaining sleep (DMS) I 4.43 [1.23–1.70], excessive daytime sleepiness (EDS) I 2.7 [1.06–1.45] and early morning awakening (EMA) I 1.45 [1.15–1.82]) than women menstruating regularly. Menopausal women had significantly higher risk of sleep-related symptoms (reflux after going to bed OR=1.43 [1.07–1.90], DHS 2.04 [1.58–2.63], DMS 1.87 [1.57–2.23], EDS 1.44 [1.21–1.73] and EMA 1.73 [1.38–2.17]) than premenopausal women.

Conclusions: Sleep quality among women was significantly related to menstrual status; women with irregular menstruations and menopausal women suffered from more sleep-related symptoms with insomnia and gastroesophageal reflux.

P1881 Sleep pattern changes in patients with liver cirrhosis

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Background: Liver cirrhosis is a major cause of mortality worldwide. One of the least studied complications of liver cirrhosis is the disturbed sleep pattern.

Methods: This study included two groups; the first group consisted of 30 patients confirmed as liver cirrhosis based on abdominal ultrasonography and liver biopsy and the second group consisted of 10 healthy subjects served as controls. Epworth sleepiness score (ESS) was calculated for every patient and all patients were subjected to complete overnight polysomnography to detect sleep disturbances among all participants.

Results: Our results showed that cirrhotic patients had ESS, AH (apnea hypopnea index) and OSA (obstructive sleep apnoea) significantly higher than the control group [16.4±2.6 vs 11.1±1.8, P < 0.001; 10.9±6.5 vs 2.4±1.6, P = 0.005 and 3.1±1.3 vs 1±1.9, P = 0.03 respectively]. The percentage of sleep efficiency was significantly lower in cirrhotic patients than the control group [61.5±7.9 vs 73.1±6.7 (P = 0.02)]. Also, the percentages of S1, S3, and REM sleep in relation to the total sleep time were significantly higher in the cirrhotic patients than the control group (P = 0.01, 0.02 and 0.06 respectively) while the percentage of S2 was significantly lower (P = 0.02). Cirrhotic patients of Child class C had ESS, AH and OSA significantly higher and sleep efficiency significantly lower than cirrhotic patients of classes A and B (P = 0.001 for all). Cirrhotic patients with tense ascites had ESS, AH and OSA significantly higher and sleep efficiency lower than patients with mild, moderate or no ascites (P = 0.001 for all).

Conclusion: This study revealed that cirrhotic patients had disturbed sleep pattern, correlating with the degree of cirrhosis.

P1882 In sleep apnea patients nonalcoholic fatty liver disease (NAFLD) is associated with the severity of intermittent hypoaxia and more severe endothelial dysfunction

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Introduction: Nonalcoholic fatty liver disease (NAFLD) begins with the accumu-lation of triglycerides in the liver and elicits an inflammatory response that can progress to cardiovascular complications, cirrhosis and liver cancer. Intermittent hypoaxia is a potential contributing factor but NAFLD has not been investigated in an unselected obstructive sleep apnea (OSA) population. Beyond liver biopsy, there are non invasive validated tools allowing a screening of NAFLD in large populations.

Aims: (i) To use non-invasive blood tests (Steatotest®, NASHtest® and Fibrotest®) to evaluate steatosis, Nonalcoholic Steato hepatitis (NASH) and fibrosis in a large cohort of OSA (ii) To assess endothelial function by peripheral arterial tone (PAT).

Patients: 226 subjects referred for suspicion of OSA were included (men: 55%, median age: 56 years, mean BMI 34 kg/m²).

Results: 61.5% of OSA patients exhibited advanced steatosis. By multivariate analysis, triglycerides (p<0.001), insulin resistance (p<0.0004) and nocturnal cumulative time spent <90% of SaO2 (CT90) (p=0.01) were independent factors for liver steatosis. 38% of OSA displayed NASH (N1 or N2 with NASHtest®). CT90 was significantly associated with NASH (p=0.035) but this became non significant in multivariate analysis. Endothelial function was more impaired in OSA patients with advanced steatosis (p=0.04) and NASH (p=0.013).

Discussion/Conclusion: In a large unselected population of OSA, the severity of intermittent hypoaxia was independently associated with steatosis. Endothelial dysfunction was more severely impaired in OSA patients demonstrating NAFLD.
Noninvasive evaluation of hepatic steatosis and fibrosis in OSA patients at diagnosis
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In morbibly obese patients, non-alcoholic fatty liver disease (NAFLD) frequently occurs, with obstructive sleep apnea (OSA) compared to patients with out OSA, and OSA may play a role in the pathogenesis of steatohepatitis. We non-invasively assessed hepatic steatosis (ultrasound) and fibrosis (Fibroscan elastometry) in 20 consecutive patients (mean age±SD: 54±11 yr; BMI: 34±9.5 kg/m²; 4 women) with newly diagnosed OSA and no history or serologic evidence of hepatic disease. Inclusion criteria were: alcohol consumption <30 g/day, no use of statins or other lipid-lowering drugs. Patients underwent nocturnal 8-channel monitoring, venous blood sampling, hepatic function tests, fasting blood insulin and glucose, serum lipids, hepatic ultrasound evaluation, and Fibroscan elastometry. Severe OSA was found in most patients (mean AHI±SD: 52±22 event/h; mean nocturnal SaO2: 90±3.8%; Epworth Sleepiness Scale score: 12.7±4.9). Twelve patients showed the metabolic syndrome (MetS, NCEP-ATP III). Three patients showed increased serum ALT (>40 U/l); they were significantly younger (age 36.7±1.5 vs. 50.3±1.1 yr) and more obese (BMI 40.9±8.2 vs 33.6±5.0 kg/m²) than the rest of the sample. Hepatic steatosis (ws=19) was mild in 4 patients, moderate in 1, and severe in 14; all patients with increased ALT showed severe steatosis. Severe steatosis occurred in most patients with MetS and tended to be associated with severe OSA. Fibroscan elastometry (n=14) gave an average value of 6.2±2.3 (normal <5, fibrosis >12). Therefore, noninvasive evaluation revealed a trend for hepatic steatosis to be associated with severe OSA and obesity, while hepatic fibrosis appeared absent or mild in our patients.

Twelve patients showed the metabolic syndrome (MetS, NCEP-ATP III). Three patients showed increased serum ALT (>40 U/l); they were significantly younger (age 36.7±1.5 vs. 50.3±1.1 yr) and more obese (BMI 40.9±8.2 vs 33.6±5.0 kg/m²) than the rest of the sample. Hepatic steatosis (ws=19) was mild in 4 patients, moderate in 1, and severe in 14; all patients with increased ALT showed severe steatosis. Severe steatosis occurred in most patients with MetS and tended to be associated with severe OSA. Fibroscan elastometry (n=14) gave an average value of 6.2±2.3 (normal <5, fibrosis >12). Therefore, noninvasive evaluation revealed a trend for hepatic steatosis to be associated with severe OSA and obesity, while hepatic fibrosis appeared absent or mild in our patients.

P1884

P1885

Rationale: Cholesterol ester transfer protein (CETP) and apolipoprotein E (APOE) polymorphisms affect serum lipids in association studies. In a mouse model of obstructive sleep apnea (OSA) hypoxia inhibited clearance of triglyceride-rich lipoproteins. Since hypoxia might interfere with genetic background to affect lipid levels, we examined effects of interactions between CETP and APOE variants and hypoxia on serum lipids in OSA patients. Methods: 634 adult subjects evaluated for suspected OSA underwent overnight polysomnography. The association of HDL-cholesterol (HDLc), triglycerides (TG) and LDL-cholesterol (LDLc) with OSA-related hypoxia reflected by oxygen desaturation index (ODI) was examined and adjusted for relevant covariates. Findings: Patients were 69.1% male (age 51.1±11.2 years, age at apnoea-hypopnoea index (AHI) >10; mean AHI±SD: 60±8.2±2.1 event/night) and 30% female (age 40.9±12.9 years). In univariate analyses, HDLc was related to ODI and CETP polymorphism (R²=0.185, p=0.002) and no interaction between CETP variant and ODI was observed. In contrast, TG were related to ODI and APOE polymorphism in the univariate analyses (R²=0.284, p=0.001; R²=0.100, p=0.013) and also after adjustments (R²=0.382, p=0.016; R²=0.002). Significant interaction between APOE genotype and ODI was observed with respect to TG levels (p=0.010 for the interaction term APOE*ODI). Conclusion: Our findings support the role of CETP and APOE polymorphisms in atherogenic dyslipidaemia in OSA patients, and suggest the presence of an association between hypoxia and TG levels. Funding: APVV-0134-11, VEGA 1/0111/12, Slovakia.

Sleep duration and obesity in women – A 10 year prospective study
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In our present study we sought to determine the influence of intermittent hypoxia-induced impairment of endothelial-dependent vasorelaxation. In cell culture experiments we observed relaxation was measured by an organ bath technique. In cell culture experiments we number of colony forming units in late outgrowth endothelial progenitor cells were analyzed by fluorescence and light microscopy, resp. Scal1/Btk positive cells in bone marrow were counted by flow cytometry. Results: Endothelial-dependent vasorelaxation was significantly decreased under hypoxia (73±4% vs. control: 45±4%); infliximab and L-glutathione normalized endothelial function (47±6% vs. 47±8%, resp.). The numbers of Dil-LDL/lectin+ cells and colony forming units were significantly higher in hypoxia compared to other groups. The percentage of scal1/Btk+ cells was increased in hypoxia vs. control and it was reduced in both drug groups (p<0.05).

Background: Obesity is highly related to obstructive sleep apnea syndrome. Research has shown that one potential cause of obesity may be short sleep duration. Aim: The aim was to assess how sleep duration and obesity is related over a 10 year period, in a population-based sample of women. Methods: A total of 5,003 non-pregnant women (response rate 80%) ≥30 years, answered a 10-year follow-up questionnaire. The questionnaire included questions on sleep duration, weight, height, waist circumference, smoking and lifestyle factors. Regression analysis was performed to analyze independent associations between sleep duration and measures of obesity. Results: In the whole population 31% (n=2,127) of the women had increased their weight by at least 5 kg. 37% (n=2,549) had a BMI≥30 kg/m² and 52% were centrally obese (waist circumference ≥88cm). Both short (<6h) (OR=1.38; 95%CI 1.06-1.80) and long sleep duration (>9h) (1.36; 1.32-2.62) showed to be risk factors for general obesity (BMI≥30 kg/m²) after controlling for confounders. When dividing the women by age both short and long sleep duration were risk factors in the younger age group (age at baseline <40 years). In women above age 40 years at baseline only long sleep duration remained as a risk factor for general obesity after controlling for confounders. In addition, short sleep duration was shown as a risk factor for central obesity after adjustments (1.46; 1.002-2.14) in younger women, whereas long sleep duration was a risk factor in women ≥40 years (1.86; 1.17-2.96).

Conclusion: Both short and long sleep duration had a greater risk of general obesity compared with normal sleepers (6-9h). Young short sleepers were also at risk for central obesity.
Obstructive sleep apnea and metabolic syndrome in thin patients: characteristics and comparison with patients with overweight and obesity. Raquel Dacal-Guinea1, Manuel Tubero Nova2, Maria Teresa Alves Pérez1,2, Adela Acuña Fernández1, Muri Luz Santalla Martínez1, Pedro Marcos Velázquez1,2,1 Palomary Medicine, Complejo Hospitalario Universitario de Ourense, Ourense (Galicia), Spain;2Investigation, Complexo Hospitalario Universitario de Ourense, Ourense (Galicia), Spain. Objective: We wanted to know the prevalence of obstructive sleep apnea (OSA) and metabolic syndrome (MS) in thin patients and their characteristics. We also wanted to know if there were differences with overweight and obese. Methods: We studied the patients that were referred to our sleep laboratory, from January to December 2009. OSA was diagnosed when apnea hypopnea index (AHI)was >5. MS was diagnosed according to the International Diabetes Federation criteria. The patients were distributed in 3 groups according to BMI: normal or thin (BMI<25), overweight (25-29.9) and obesity (>30). Results: We studied 475 patients: 7.6% thin, 36% overweight and 56.4% obese. In the thin’s group, most were women, snorers, non-smokers and don’t drink alcohol. We diagnosed of OSA 228 (48%): in thin 77.7%, in overweight 84.4% and in obese 91.4%. Thin patients with OSA were mostly mild OSA, in overweight mostly moderate and in obese severe. There were differences between OSA’s diagnosis and categorized BMI. We diagnosed of MS 288 (64.4%): in the thin’s group 33.3%, in overweight 45.94% and in obese 80.95%. We found more prevalence of MS (p<0.001) with BMI’s increase. There were differences between thin’s group and the others, thin patients were younger with minor neck and waist perimeter (p<0.021; p<0.001; p<0.001). OSA and MS prevalence in the thin’s group was 22% and in obese 70.52%. OSA in thin patients was related with gender (p=0.039 women had less risk) and age(p=0.045 OSA were older). Conclusions: OSA’s prevalence in thin patients is minor. Thin patients were most women, younger and without toxic habits. OSA and MS were not related in thin patients. EEG time-frequency maps during respiratory-related cortical activation in humans Anna Hudson1,2, Louis Laviolette2, Mathieu Raux2, Jacques Martinerie3, Thomas Similowski2, Louis Laviolette2, Mathieu Raux2, Jacques Martinerie3, Thomas Similowski4.1 Respiration Research Center and 2Laboratoire de Neurophysiologie Clinique et Experimentale, U1073 INBS, Paris, France; 3Neurosciences Cognitive et Imagere Cerebrale, CRICM, UPMC/CNRS UMR7225/INSERM UMR9753, Paris, France. Introduction: Event-locked averaging of EEG recordings has demonstrated that precerebral potentials precede inspiration during respiratory-related cortical activation. However, this procedure relies on assumptions of on-going brain activity and is highly susceptible to low frequency artifacts. Frequency analysis is an alternative method of assessing EEG activity, but it is not known if this method can identify respiratory-related cortical activation. Aim: The aim of this study was to compare time-frequency maps during different respiratory “tasks”. Methods: Healthy subjects (n=6) performed 3 conditions: quiet breathing (QB), sleep with periodic breathing (WB) and sleep with periodic breathing and trained to control breathing (Quantified). The EEGs were recorded from 32 scalp channels using an active electrode system (g.USBamp, g.tec). The signals were amplified using a 12-bit A/D converter and recorded and processed with a IRISPC running the g.iga analysis software. Results: Results were differences in cortical activation (alpha band, 8-13Hz) prior to the onset of inspiratory flow on Fz, C3 and C4 between QB and WB (p<0.1) and on C4 between QB and ITL (p<0.1). Conclusions: Time-frequency maps varied between different respiratory conditions which suggests they can discriminate differences in cortical activation related to the control of respiration. Furthermore, we can identify the specific frequency components, in addition to time-locked changes in EEG. Analysis of EEG activity above 5Hz may lessen the effect of artifacts on physiological interpretation and increase the feasibility of EEG recordings to assess cortical activation in the clinical setting. Manipulating cerebral blood flow affects central sleep apnea at high altitude. Krištof Burgisser1,2,3, Samuel Lucas1,2,4,5,6, Thomas Similowski2,3,1, Raquel Rodrigues2, Margarida Aquiri3, Dina Fernandes3, Susana Moreira1, Claro Ines1, Valenza Joao1, Bugalho António1, Luis Moita2,1Pneumology, University Hospital de Santa Maria, Lisbon, Portugal;2Cell Biology of the Immune System Unit, Institute of Molecular Medicine, Lisbon, Portugal;3Pneumology, Hospital de Loures, Lisbon, Portugal. Aim: To measure the effects of altering cerebral blood flow (CBF) on central sleep apnea (CSA) at high altitude. Methods: 12 normal volunteers aged 30±10 years were studied 6-9 days after arrival at 5050 meters. After control measurements they received ivi Acetazolamide (Acet) 10mg/kg or oral Indomethacin (Indo) 100mg with placebo controls in a randomized order on separate nights. Ventilatory Responses (VRs), ABGs, Apnea-Hypopnea Index (AHI) during the first 3 hours of sleep by polysomnography (PSG) and CBF by transcranial Doppler were recorded. AHI was also measured upon arrival and after 12-15 days to control for acclimatization. Results: CBF rose by 28% with Acet and fell by 23% with Indo. PaCO2 rose from 38.4±31.6±3 mm Hg with Acet (p<0.001), whereas, ABGs were unchanged with Indo. VRs were unchanged with Acet but Indo increased Hypercapnic VR by 43% (p<0.05). AHI was halved by Acet (89 to 47/hr, (p<0.01), but increased 25% with Indo (89 to 112/hr, p<0.05). Conclusions: Indomethacin reduced CBF and increased Hypercapnic VR and CSA during the first 3 hours of sleep. Whereas Acetzolamide increased CBF but had no effect on VRs yet reduced CSA severity. These results highlight the link between CBF and CSA at high altitude. Supported by: Peninsula Sleep Laboratory, University of Otago and EVK2CNR. Sleepiness influences cytotoxic lymphocytes independent of respiratory events Richard Staig1, Raquel Rodrigues2, Margarida Aquiri3, Dina Fernandes3, Susana Moreira1, Claro Ines1, Valenza Joao1, Bugalho António1, Luis Moita2. 1Pneumology, University Hospital de Santa Maria, Lisbon, Portugal;2Cell Biology of the Immune System Unit, Institute of Molecular Medicine, Lisbon, Portugal;3Pneumology, Hospital de Loures, Lisbon, Portugal. Aim: Obstructive sleep apnoeas have been shown to stimulate the immune system. However, the relevance of sleepiness is less clear. We investigated the influence of objective sleepiness (OS) on the expression of the cytotoxic proteins granzyme B (GrB) and perforin (P) in peripheral blood lymphocytes (PBL). Methods: 43 participants performed polysomnography followed by the pupillary sleepiness test (PST®). PBL were stained for CD8, gamma delta cells (gd cells), natural killer cells (NK), P and GrB and analysed by flow cytometry. Results are shown as means ± SEM. Results: 29 proband were not sleep (NS) (pupilary unrest index=0; 6.8). 14 patients were sleep (PUI= 9.8). Results were not statistically significantly different for: age, BMI, AHI, ODI or oxygen saturation < 90%. In NS we found a higher percentage of P in CD8+ 36,3±3.0 vs. 27.3±4.4 and gd cells 39,1±3.5 vs. 27.3±6.5, but results failed to reach statistical significance (p=0.07 and 0.06, respectively). GrB are listed below. Percentage of GrB+ cells % of GrB+ cells CD8GrB/CD8 gdGrB/gd NKGb/NK PUI< 0.05: 24.8 (1.8) 46.3 (14.9) 42.3 (16) 80.1 (3.3) PUI> 9.8: 19.9 (1.3) 35.5 (14.9) 23.4 (13.9) 82.2 (1.8) CdB cells (3,5). Total percentage of GrB+ cells (p =0.004) and GrB+ gd cells (p<0.001) were significantly lower in sleepy subjects. Discussion: In these preliminary results we show that OS influences cytotoxic PBL independently of the respiratory events. The PST uses the balance between sympathetic and vagical activity on the pupil. These results could indicate that GrB and P are increased maps only in presence of sympathetic activation. Supported by the Fundação para a Ciência e a Tecnologia: POCI/09/9/07 Clinical significance of sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) in patient with pituitary adenomas Ginevra Del Giudice1, Emanuela Carpentieri1, Assunta Micco1, Itala Ventea1, Antonio Russo1, Angelio Romano1, Gaetano Beatrice1, Giuseppe Catapano1, Mario Del Donno1,2, UOC Pneumologia, G. Rummo, Benevento, Italy;1UOC Medicina Interna, G. Rummo, Benevento, Italy;2UOC Neurochirurgia, G. Rummo, Benevento, Italy. A pituitary adenoma(PA) causes different symptoms, depending on its size and location and on the type of hormone that is being made. SDB and OSA are atypical presentation of PA secreting ACTH and GH. However, the non-secreting adenomas may cause alterations of sleep architecture. The aim of the study was to evaluate clinical and sleep characteristics in a group of patients with functioning (PA) and non-functioning pituitary adenomas (NFP). We recruited 6 patients with SDB and PA. Physical and anthropometric examination were performed ES and BMQ modified was used to diagnose sleep disorders symptoms. SDB were studied by means of overnight polysomnographic study in our sleep lab. The scoring criteria were according to event definition by AASM. SDB were documented in 6 pts (3 M, mean age 50.8 yrs and mean BMI 35), with PA. Three NFP, two patients with FHA and one with acromegaly, were diagnosed after neurosurgery resection. ESS mean reported were 10, mean Sao2 was 93.6% and AH index were 6.7±4.1, with a prevalence of obstructive events. ODI mean 7.8±4.2. REM sleep duration were 15.4±6.8% of total sleep time and SWS mean was 22.4±11.1%. In acromegaly patient, was found a worsening of sleep
parameters compared to other patients (AHI 18.4, AHI supine 29.6; ODI 12.7), successfully treated with CPAP therapy.SDB in patients with PA and NPA are underdiagnosed. Although the patients with NPA and Cushing’s syndrome were affected by a mild OSA, they reported sleepiness symptoms Expert consultation and a multidisciplinary approach to sleep disorders are needed in patients with PA.

**P1893**

Reactive and proactive control of cognitive functions in obstructive sleep apnea

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Neuropsychological studies dissociated two types of cognitive control functions: reactive control and proactive control (Braver, T. et al. Trends in Cognitive Sciences 2012; 16: 106-113). Although, obstructive sleep apnea (OSA) is associated with cognitive decrement, there is an ongoing debate on whether these include detrimental performance in conflict tasks (Verstraeten, E. et al. Sleep. 2004; 15,27(4):685-93.). In this study, we investigated reactive and proactive control of cognitive functions in OSA patients. In this ongoing study data from 21 participants were evaluated. Participants grouped according to Apnea-Hypopnea Index (AHI) in to two, such that Group A’s AHI>30 (n=13), and Group B’s AHI≤15 (n=8). They were participated in Flanker and Simon to measure reactive control and Stroop to measure proactive control. Stimulus presentation and data collection was done automatically on a standard monitor and PC. In Group A patients (with severe OSA), reactive control observed with Flanker task was significantly different compared to performance of Group B participants (normal and patients with mild OSA). However, other test did not revealed any significant difference.

### Comparison of Cognitive Control Performance In Groups

<table>
<thead>
<tr>
<th>Control Index</th>
<th>Group A (AHI &gt;30)</th>
<th>Group B (AHI ≤15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flanker Reactive Control Index (msec)</td>
<td>47.93</td>
<td>57.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Simon Reactive Control Index (msec)</td>
<td>51.27</td>
<td>65.05</td>
<td>0.059</td>
</tr>
<tr>
<td>Stroop Proactive Control Index (msec)</td>
<td>94.15</td>
<td>56.34</td>
<td>0.072</td>
</tr>
</tbody>
</table>

In conclusion, these preliminary results suggested that while proactive control is intact in severe OSA patients, reactive control declines when control is triggered by stimulus-stimulus conflict.

**P1894**

Overactive bladder in women with sleep apnea-hypopnea syndrome

Nuria Grau1, Elisabet Del Amo2, Carles Sanjuás1, Cristina Estirado1, Antonia Ruiz1, Encarna Guardiola1, Miquel Félez1, Ramon Carreras2, Joaquim Gea1. 1Respiratory Department, Hospital del Mar. Parc de Salut Mar, Barcelona, Spain; 2Gynecology Department, Hospital del Mar. Parc de Salut Mar, Barcelona, Spain

Introduction: Overactive Bladder Syndrome (OAB) is characterized by urgency to urinate, which may be accompanied by increased frequency, nocturia and incontinence. Although nocturia is a common symptom in the setting of sleep apnea-hypopnea syndrome (OSA), the association between OAB and OSA is not well known. The aim of this study was to analyze the presence of OAB in female patients diagnosed from OSA.

### Methods: Seventy-two consecutive female patients referred for polysomnography (PSG) for suspected OSA were included. All patients fulfilled the spanish validated version of the “Bladder Control Self-Assessment Questionnaire” (B-SAQ). The B-SAQ consists of 2 subscales: “symptoms”, consisting of 4 items (urgency, frequency, nocturia and incontinence) and “discomfort” in which it is established the degree of distress associated with symptoms from 0 to 3.

### Results: The scores of “Symptoms” and “Discomfort” were significantly higher in patients who were diagnosed OSA.

<table>
<thead>
<tr>
<th>IAH ≤5</th>
<th>IAH &gt;5</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Age*</td>
<td>50 (46-63)</td>
<td>54 (43-63)</td>
</tr>
<tr>
<td>BMI*</td>
<td>26.6 (23.8-39.2)</td>
<td>35.3 (31.6-43.3)</td>
</tr>
<tr>
<td>B-SAQ Symptoms*</td>
<td>3 (1-4)</td>
<td>5 (2-7)</td>
</tr>
<tr>
<td>B-SAQ Discomfort*</td>
<td>1 (0-1)</td>
<td>4 (2-7)</td>
</tr>
</tbody>
</table>

*Median (interquartile range).

Patients with OSA scored significantly higher for symptoms, urgency, nocturia and incontinence and 4 items of “Discomfort”. The AHI was significantly correlated with the score of “Symptoms” (r = 0.207, p = 0.013) and that of “Discomfort” (r = 0.258, p = 0.03). There was no significant correlation between the BMI and the B-SAQ.

### Conclusions: Obstructive sleep apnea is associated with overactive bladder syndrome in women. The Bladder Control Self-Assessment Questionnaire is a valid instrument to assess overactive bladder in patients with OSA.

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**P1895**

Is a predominant clinical COPD phenotype predict different outcome responses to pulmonary rehabilitation?

Héria Pessi, Giulia Innocenti Bruni, Emanuele Pulvipo, Barbara Lanini, Isabella Romagnoli, Claudia Coi, Barbara Binazzi, Loredana Stendardi, Francesco Gigliotti. Section of Respiratory Rehabilitation, Fondazione Don Gnocchi IRCCS, Firenze, Italy

Introduction: A new multivariate model, using HRCT as a criterion standard, based on variables collected at rest has been proposed to identify two or more relevant phenotypes of COPD, emphysema (E) and chronic bronchitis (B) (Pisatoles et al. Respir Med 2008;102:367-76). The aim of the study is to verify whether two distinct COPD groups whose characteristics correspond to either an airway obstructive or a parenchymal destructive COPD phenotype exhibit different outcome responses to a pulmonary rehabilitation program.

### Methods: In 55 BC and 38 E patients we assessed the outcome responses to a pulmonary rehabilitation program (PRP): chronic exerctoral dyspnea (MRC, BDI and TDI), leg and arm ergometry, and exercise dyspnea by Borg scale during 6mWT. Four cluster descriptors of the language of dyspnea (work/effort, inspiratory difficulty, shallow breathing and expiratory difficulty) allowed the qualitative assessment of the symptom.

### Results: At baseline, age, BMI, FEV1 and DLco were lower, while FRC and TLC were higher in E. 6mWT, Borg, SGRQ and ergometry were similar in E and BC. Frequency of response for inspiratory difficulty cluster during 6mWT was significantly greater in E than in BC. PRP significantly improved most outcomes, similarly in the two groups, but neither in E nor in BC did significantly modify the frequency of response of cluster descriptors.

### Conclusion: PRP allowed both COPD groups to improve similarly health status and exercise tolerance and to modify the intensity but not necessarily the quality of dyspnea.

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**P1896**

Efficacy of pulmonary rehabilitation in patients with interstitial lung disease

Akihito Nakazawa1, Eri Hagiwara1, Ou Yamaguchi2, Ryo Ogata3, Takeshi Shimohara4, Yusuake Matsumoto5, Kaori Tsutani6, Takuma Sasaki2, Takashi Ogura1. 1Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan; 2Department of Rehabilitation Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan

Objectives: There are few reports describing the efficacy of pulmonary rehabilitation (PR) in patients with interstitial lung disease (ILD). We studied whether PR could improve functional status in a group of patients with ILD.

### Methods: PR was carried out for 12 weeks for clinically stable outpatients of our institute. Fifteen patients with ILD were enrolled in this prospective study. Six-minute walking test (6MWT), lung function test and evaluation of health-related quality of life including SGRQ were performed before and after the program. Patients were classified as having a relevant phenotype of COPD, emphysema (E) and chronic bronchitis (BC) (Pisatoles et al. Respir Med 2008;102:367-76). The best posters in pulmonary rehabilitation and chronic care

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234. The best posters in pulmonary rehabilitation and chronic care

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328s
Effect of interval training on the BODE index, SF-36, EuroQol and St-George’s Respiratory Questionnaires scores in COPD patients across GOLD stages I-IV

Vassilis Andrianopoulos1, Stavroula Sptiosi2, Alexandra Chatzi2,
Nikolaos Chinkiamis1, Joannis Nasi1, Theodora Vasilogianakopoulou1, Anastasia Panagopoulou1, Emmanouil Kokori1, Georgia Koutsofim1, Nikolaos Koulouri1, Ioannis Vagizas1, 2
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In COPD patients, functional capacity, health-related quality of life and health status are respectively assessed by the clinical tools of BODE index, SF-36, Euro-Qol and St-George’s Respiratory Questionnaires. Interval training as a therapeutic modality elicits substantial physiological effects; however, the impact of interval training to those across the whole spectrum of COPD severity still remains unknown.

Objective: To investigate whether beneficial effect of interval training is reflected to BODE and the 3 Questionnaires in GOLD stage III-V.

Methods: In a large cohort of 106 COPD patients, rehabilitative intervention and control groups consisted of 71 and 35 patients, respectively. Exercise training involved 30min cycling by alternating 30s exercise intervals at 100%Wpeak with 30s rest and large-muscle group resistance training for a period of 10 weeks, 3-times/week.

Results: Interval training improved significantly the clinical condition of patients across GOLD stages II (BODE: 1.9 ± 1.1, SF-36: 89.4 ± 44.9, SF-64: 43.7 vs 49.3, Euro-Qol-VAS: 54.1 ± 70.8, St-Gos’s: 55.0 ± 39.9), III (BODE: 3.8 ± 2.5, SF-64: 38.5 ± 43.0, SF-64: 40.1 ± 47.4, Euro-Qol-VAS: 64.8 ± 65.5, St-Gos’s: 52.6 ± 40.4), IV (BODE: 5.7 ± 4.1, SF-64: 33.1 ± 40.9, SF-64: 33.2 ± 46.3, Euro-Qol-VAS: 40.4 ± 58.2, St-Gos’s: 60.1 ± 46.2) (P < 0.05). Nom significant changes were shown for patients in GOLD stage I and the control group.

Conclusions: Beneficial effects of interval training in functional capacity, health-related quality of life and physical status are reflected by improved clinical condition of patients in GOLD stages II-IV.

P1989

Pulmonary rehabilitation in patients with sarcoidosis – First results of the prospective German multi-center study: ProKaaSaRe

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1Fachbereich Pneumologie, Klinik Bad Reichenhall, Germany; 2Pneumologie, Klinik Bad Reichenhall, Germany; 3Pneumologie, Klinik Bad Reichenhall, Germany; 4Pneumologie, Fachklinik St. Georg, Hohenchwarz, Germany; 5Pneumologie, Osterrichtsklinik Schömberg-Holm, Ostschönbach Schömberg, Germany; 6Pneumologie, MedClin Albert Schweitzer Klinik, Königswinter, Germany; 7Pneumologie, MEDDAN Klinik Heiligendamm, Heiligendamm, Germany; 8Pneumologie, Klinik Wehrawald, Todtnoos, Germany; 9Institut für Biometrie, Medizinische Hochschule Hannover, Hannover, Germany; 10Institut für Allgemeinmedizin, Medizinische Hochschule Hannover, Hannover, Germany

Background: There are only sparse data concerning rehabilitation in sarcoidosis. Therefore we conducted a prospective multi-center study to investigate whether rehabilitation leads to objective and subjective health changes.

Methods: Clinical tests and questionnaires were performed at the beginning (T0) and the end (T1) of a 3-week in-hose rehabilitation program, followed by questionnaires 3, 6, and 12 month after discharge. The components of the rehab were physical training, breathing exercises, patient education and psychosocial support.

Results: The results of the short-term effects on the first 200 patients are displayed: mean-age 49.3 ± 9.7 years, 56.2% male, 48.7% under systemic corticosteroids.

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD [m]</td>
<td>496.5 ± 110.6</td>
<td>538.2 ± 111.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VC[1] (% predicted)</td>
<td>3.5 ± 10.6 (16.6%)</td>
<td>3.5 ± 10.5 (19.1%)</td>
<td>0.2121</td>
</tr>
<tr>
<td>FEV1 [l]</td>
<td>2.78 ± 0.9 (84.8%)</td>
<td>3.02 ± 0.49 (86.8%)</td>
<td>0.2030</td>
</tr>
<tr>
<td>PI max (kPa)</td>
<td>6.37 ± 3.13 (73.92%)</td>
<td>7.21 ± 4.69 (76.7%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>AC/ [U/l]</td>
<td>44.0 ± 2.85</td>
<td>41.8 ± 2.85</td>
<td>0.5090</td>
</tr>
<tr>
<td>CRP [mg/l]</td>
<td>3.6 ± 6.0</td>
<td>3.7 ± 7.1</td>
<td>0.3090</td>
</tr>
<tr>
<td>SGRO (symptoms)</td>
<td>43.4 ± 24.7</td>
<td>35.5 ± 25.7</td>
<td>0.0007</td>
</tr>
<tr>
<td>SGRO (activity)</td>
<td>49.0 ± 22.9</td>
<td>42.1 ± 25.2</td>
<td>0.0025</td>
</tr>
<tr>
<td>SGRO (impact)</td>
<td>29.6 ± 20.3</td>
<td>25.0 ± 21.3</td>
<td>0.0122</td>
</tr>
<tr>
<td>SGRO (total score)</td>
<td>38.2 ± 20.1</td>
<td>32.2 ± 21.7</td>
<td>0.0026</td>
</tr>
<tr>
<td>SF-FFMi (male)</td>
<td>30.8 ± 13.9</td>
<td>33.7 ± 18.1</td>
<td>0.0355</td>
</tr>
<tr>
<td>SF-FFMi (female)</td>
<td>27.9 ± 13.2</td>
<td>31.9 ± 17.3</td>
<td>0.0027</td>
</tr>
<tr>
<td>FAS (Fatigue Assessment Scale)</td>
<td>2.7 ± 0.78</td>
<td>2.2 ± 0.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMRC (Scores)</td>
<td>2.1 ± 1.3</td>
<td>4.1 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Discussion: The significantly and clinically meaningful short term results of relevant outcomes like exercise capacity (6MWD), quality of life (SGRO), SF-36, fatigue (FAS) and dyspnea (MRC) suggest a high impact of rehabilitation on health related outcomes in sarcoidosis.

Sponsored by Sarkoidose Stiftung and Deutsche Lungengesellschaft e.V.

P1989

Effect of pulmonary rehabilitation (PR) influence patient’s perceptions of disease?

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Background: PR leads to behaviour modification. The common sense model assumes that perceptions of disease are influenced by increased knowledge, skill acquisition and goal attainment. The aim was to test whether PR influenced patient’s perceptions of their disease.

Methods: This is a prospective cohort study of patients with COPD who completed the illness perceptions questionnaires revised (IPQ-R) pre and post PR. The IPQ-R was completed by 51 patients [mean(SD) age 70.0 (9.0) years, FEV1: 1.4 (0.7) 1.28 male]. Following PR patients adopt a less chronic view of their disease and perceived fewer consequences. Treatment control and coherence are reduced. Emotional impact of the disease is minimised by PR.

Conclusions: PR induces feelings of hope and increases patient’s expectations. Prior to PR patients are unaware of their limitations in knowledge. The clinical benefits of PR reduce perceived consequences of the disease and as a result emotional impact is minimised.

P1990

Prescribing exercise in advanced COPD: Training smart, not just hard!

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1Department of Pulmonology, Merev Treatment Centers, Asthma Center Heideheuwel, Hilversum, Netherlands; 2Department of Pulmonology, Academic Medical Center, Amsterdam, Netherlands; 3Respiratory Rehabilitation, Katholieke Universiteit Leuven, Belgium; 4Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Netherlands

The high-intensity paradigm is prevailing in COPD training. Individualising training variables is considered the gold standard. Nonlinear periodic exercise (NLE) uses variation of the training variables (mode of exercise, work phase, rest phase, intensity, number of repetitions) to individualize training. The aim of this study was to compare the effects of NLE with traditional endurance and progressive resistance training (EPR) on cycle endurance time (CWT) at 75%Wmax.

Methods: Patients with severe COPD (N=110, FEV1%pred, 61 yrs) were stratified on normal or depleted fat-free mass index (depleted FFMi; male FFMi <15 kg/FMMi; female FFMi <16 kg/FMMi). Six patients were then randomly assigned to NLE or EPR (3-times/week for 12 weeks). Difference in change was tested with intention-to-treat analysis using linear mixed-effects modeling. Trial number NTR 1045.

Results: NLE showed more improvement in cycle endurance at 12 weeks: NLE (N=53, ∆56th = 143% compared to EPR (N=57, ∆26δ= +66%), difference in change (30%; 95% CI 162-425) and NLE (N=22, ∆528 = +123%) compared to EPR (N=21, ∆198 = +46%), difference in change (32%; 95%CI: 182-477). During the training, patients in the NLE groups had significantly more repetitions, lower % 1-repetition maximum load, shorter cycle time and lower Borg dyspnea, fatigue and exertion scores than the patients in EPR groups.

Conclusion: Nonlinear periodic exercise results in >5min more improvement in cycle endurance than traditional endurance and resistance training in patients with advanced COPD and depleted or normal FFM. Applying principles of nonlinear exercise training in athletes to the COPD population is feasible and worthwhile.

329s
P1901
Exercise induced reduction in dynamic hyperinflation after interval training with oxygen breathing
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Background: Exercise training reduces exercise induce dynamic hyperinflation (DH) at submaximal exercise (80% of peak work rate) in patients with COPD. Oxygen has dose-dependent effect (maximal at FO2o.3) on operating lung volumes in COPD.

Methods: 10 COPD patients with moderate obstruction (FEV1: 53±12%pred, age: 63±10 yrs, BMI: 26±4 kg/m2) performed an incremental exercise test to maximal exercise tolerance, and two constant work rate test (CWR, 80% of peak work rate) with inspiratory capacity (IC) maneuver for DH in every 2 minutes before and after training. Patients performed interval training (1 minute 40% and 1 minute 80% of peak work rate) 3 times a week for 8 weeks breathing oxygen (5 patients 3L/min., group O) or compressed air (5 patients 3 L/min., group C) during training.

Results: The initial peak work rate did not differ significantly between the groups (O: 94±18 vs. C: 86±19 W). Endurance improved in both group (O: 425±110 vs. 630±122, C: 370±120 vs. 555±126 sec, p<0.05), oxygen uptake increased in group O (VO2 O:1.20±0.12 vs. 1.36±0.10 L/min, p<0.05) after training. In group O, there was a tendency to reduction in DH after training (IC: 1.2±0.62 vs. 2.44±0.90; 2: 2.25±0.73 vs. 2.37±0.94; 2: 3.26±0.96 vs. 2.55±0.97; 2: 4.24±1.00 vs. 2.36±1.01; 2: 5.24±1.00 vs. 2.36±1.01; 2: 6.23±0.97 vs. 2.33±1.00; 7: 2.36±0.73 vs. 2.00±1.02 L). IC did not change in group C.

Conclusion: The pilot study revealed less hyperinflation tendency and improved oxygen uptake in group O, which might refer to better physiologic training effect.

P1902
Pulmonary rehabilitation in advanced lung cancer patients during chemotherapy – Preliminary report
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Objectives: The aim of this study was to investigate the utility of a pulmonary rehabilitation (PR) program on mobility, pulmonary function, dyspnea and quality of life in patients with advanced lung cancer during chemotherapy.

Methods: This study included patients with newly diagnosed advanced lung cancer. Study group consisted of 12 pts with advanced non-small cell lung cancer and 5 pts with small cell lung cancer. Pulmonary function (FVC, FEV1), mobility (6 MWT), perceived of dyspnea (MRC, O2CD, BDI) and quality of life (SF-36, EORTC) were measured before and after the intervention program was based on Nordic Walking exercise training and respiratory muscle training. Sessions occurred twice daily, each lasting approximately 60 minutes, 5 days/week for 8 weeks breathing oxygen (5 patients 3L/min., group O) or compressed air (5 patients 3 L/min., group C) during training.

Results: Intention-to-treat analysis indicated that 6MWD distance increased 55m (95% CI, 18.57-185, p=0.012) with no changes in pulmonary function tests (FVC, FEV1). Perceived of dyspnea was improved in Oxygen Cost Diagram (2.4 vs. 1.3, p=0.012), BDI/BD (1.7 vs. 2.4, p=0.008) and overall score BDI (4.4 vs. 6.4, p=0.006). General quality of life questionnaire showed improvement in Role-Physical, Bodily-Pain, Social-Functioning and Physical Cumulative Score of SF-36 without statistical significance. Lung cancer questionnaire showed significantly improvement (p<0.05) in perception of dyspnea, exercise tolerance, quality of life improvement in social functioning, everyday living and decrease of consumption analgesic drugs.

Conclusion: Pulmonary rehabilitation in advanced lung cancer patients during chemotherapy is a beneficial intervention to improvement in their lung cancer symptoms and mobility.

P1903
Is pulmonary rehabilitation (PR) an effective therapy in lymphangioleiomyomatosis (LAM)?
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Background: LAM is an orphan lung disease affecting young women. There is only remaining therapeutic option. The role of PR is not yet defined.

Methods: In a prospective open clinical trial data of 22 LAM patients prior to LTs (LAM-P) (45±9.9 yrs, FEV1=81±4.17%pred, diffusion capacity=35.8±11.3%, pCO2=49±1.9 mmHg, LITOT tw19) and 24 LAM patients after LTs (LAM-T) (42±8.10y., FEV1=65±7.19%pred) were evaluated. All patients underwent a specialized multidisciplinary inpatient PR for 45±9.6 (LAM-P) and 35±4.18 (LAM-T) days.

Results: We found significant and clinically relevant changes for both PR approaches.

For the LAM-P group we saw a significant improvement in 6-min walking distance (MWWD) (59.0±5.0m, p<0.001). In LAM-T patients MWWD increased significantly by 103±8.5m (p<0.001). Thus the benefit of post LTx-PR in LAM-patients is comparable to the results of lung transplant patients with other underlying disease. Health-related quality of life (HRQL) (SF36) improved significantly for the mental summary score in LAM-Tx.

Lung function parameters did not change for LAM-P but FEV1 improved significantly for LAM-Tx patients.

Conclusion: PR in LAM patients before and after LTx is a safe therapeutic approach that leads to significant increases of exercise capacity and tends to improve HRQL. In view of a progressive disease with only a few therapeutic options rehabilitation should be considered early in the treatment of LAM, especially when LTx is necessary.

P1904
Effect of pulmonary rehabilitation on cardiac output responses during exercise in COPD
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Introduction: In patients with COPD pulmonary rehabilitation (PR) induces true physiological effects reflected by reduced ventilatory requirement and improved peripheral muscle function. The effect of PR on central hemodynamic responses during exercise remains largely unknown.

Aim: To examine the impact of PR on cardiac output (Q) responses during incremental (IE) and constant-load exercise (CLE).

Method: 60 COPD patients (GOLD stages II- IV) were studied (including 15 controls). PR consisted of interval cycling exercise 3 days/week for 10 weeks, with 30’s work periods/30’s rest periods for 30 minutes and intensity at 100% of peak work capacity (Wpeak). Q was measured by bio-impedance (Physioflow PF-07) during IE and CLE at 75% Wpeak for 6-min during exercise and in recovery, prior to and following PR.

Results: At Wpeak there was an increase in Q after PR (from 10.1±1.0 to 12.4±0.6 L/min, p=0.001) due to increased SV (from 90.3±1.2 to 105.1±4.2 ml/m2, p=0.003). Post-rehabilitation at an identical work rate during IE, Q did not differ compared to pre-rehabilitation; however SV was higher (pre: 90±3.3; post: 95±3.3 ml/min) and HR lower (pre: 113±3; post: 106±3.3 beats/min, p=0.008). Post-rehabilitation during CLE there were significant reductions in Q in mean response time (MRT) at the onset and offset of exercise (pre: 79.8±4; post: 66.9±4.5 sec, p=0.001) and (pre: 79±1.4±3, post: 66±1.4±2.4 sec, p=0.001), respectively.

Conclusion: Pulmonary rehabilitation induces an improvement in central hemodynamic function to incremental and constant-load exercise in patients with COPD across GOLD stages II to IV.

P1905
A multi-disciplinary integrated palliative care approach for patients with advanced COPD – A review of the breathing space clinic
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COPD is a leading cause of morbidity and mortality worldwide. There is strong evidence demonstrating the impact of disease and the unmet needs of these patients.

Aim: Develop a hospice-based clinic for patients with advanced COPD. This multi-disciplinary assessment, facilitation and treatment clinic brings together expertise in a range of respiratory management and palliative care approaches to provide holistic care; improve self-management; integrate services; and to maximise the quality of life for patients who may be towards the end of life.

Method: Patients with advanced COPD are invited with their carers to attend the Clinic at the local hospice with a COPD nurse, a palliative medicine consultant and physiotherapist to identify their physical, psychological, social, spiritual and functional needs and engage them with a range of services. Informational needs are also addressed, including advance care planning. For those unable to attend, services are replicated in patients’ homes. Metrics are undertaken at each clinic to evaluate symptoms and patient reported outcomes.

Results: Over a 9-month period piloting, 16 patients were referred (mean age 69). Mean MRC Borg at rest (pre: 8.1±4.7; post: 6.6±4.36, p=0.001) and (pre: 79±1.4±3, post: 66±1.4±2.4 sec, p=0.001), respectively.

Conclusion: The outcome demonstrates a trend towards improvement in all domains. It is not possible to conclude that the clinic intervention is solely responsible

330s
for these changes, these early data and patient feedback supports the effectiveness of this model.

P1906
Correlation between 6-minute pegboard and ring test and upper extremity activities of daily living in patients with chronic obstructive pulmonary disease
Kenichi Takeda1, Yuji Kawasaki2, Kazuma Yoshida1, Yoji Nishida1, Tomoya Harada2, Kosuke Yamaguchi2, Kiyotaka Hashimoto3, Shingo Matsumoto1, Akira Yamasaki1, Tadashi Igushi1, Eiji Shimizu1. 1Division of Medical Oncology and Molecular Respiriology, Tottori University, Yonago, Tottori, Japan; 2Department of Regional Medicine, Tottori University, Yonago, Tottori, Japan; 3Department of Rehabilitation Medicine, Yoka Hospital, Yoka, Hyogo, Japan

Background: Upper extremity training is recognized as an important component of pulmonary rehabilitation (PR). 6-minute pegboard and ring test (6PBRT) was developed for testing arm exercise capacity of patients with COPD. The purpose of this study was to apprehend characteristics of this test and to evaluate the relationship between 6PBRT and upper extremity activities of daily living (ADL) in patients with COPD.

Methods: Twenty outpatients with COPD performed 6PBRT, spirometry, maximal inspiratory pressures, maximal expiratory pressures and grip strength. The upper extremity activities subdomain of Pulmonary Functional Status & Dyspnea Questionnaire-Modified Version (PFSQ-D-M). Upper extremity ADL was also measured objectively by the wrist accelerometer (Actiwatch2®) all day long for a week.

Results: There was a positive correlation between the 6PBRT scores and inspiratory capacity (IC) (r = 0.71, p < 0.01), inspiratory capacity/total lung capacity (IC/TLC predicted) (r = 0.68, p < 0.01), forced vital capacity (FVC) (r = 0.57, p < 0.01). There was a positive correlation between 6PBRT scores and Actiwatch2® counts (r = 0.54, p < 0.05). A negative correlation between 6PBRT scores and ADL subdomain scores (r = -0.49, p < 0.05).

Conclusion: 6PBRT may be one of the predictive tests for PR to maintain and improve upper extremity ADL in patients with COPD.

P1907
Effects of BMI on task-related VO2 and dyspnea during activities of daily life (ADLs) in COPD
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COPD patients use a higher proportion of their peak VO2 during the performance of domestic ADLs compared to healthy peers, accompanied by higher task-related dyspnea and fatigue.

Introduction: Whether weight supported or unsupported exercise was associated with greater improvements in body composition, exercise capacity and health related quality of life.

Methods: Aims and objectives: To date, the influence of BMI on the task-related metabolic demands remains unknown. Therefore, we aimed to study the effects of BMI on metabolic load in 94 COPD patients (61% men, age 66±9 yrs, BMI 25.5±9.7 kg/m2, FEV1 51±19%pred) during the performance of 5 consecutive domestic ADLs: putting on socks, shoes and vest, ADL1; folding 10 towels, ADL2; putting away groceries, ADL3; washing up 4 dishes, cups and saucers, ADL4; sweeping the floor for 4 min, ADL5. Task-related VO2 was assessed using a mobile oxygen-while Borg scores were used to assess task-related dyspnea and fatigue.

Baseline characteristics were comparable after stratification for BMI. Underweight COPD patients (n=21 kg/m2, n=24) had the lowest absolute task-related VO2 after performance of 5 ADLs (62.9±151.5mL/min) compared to patients with normal (21.25±25 kg/m2), n=31; VO2: 818±422 mL/min, overweight (25-30 kg/m2, n=26; VO2: 806±161 mL/min) and obese BMI (>30 kg/m2, n=13; VO2: 1030±259 mL/min; all p<0.05). VO2 expressed as a proportion of peak VO2 and VO2 per kilogram fat-free mass (FFM) were comparable between BMI groups (%VO2 peak: 65±16, 72±19, 65±15 and 73±12; VO2kg/FFM: 16.3±3, 19.4±3, 17±3 and 18±4 mL/min/kg in underweight, normal, overweight or obese BMI respectively). Moreover, Borg symptom scores for dyspnea on fatigue were comparable between BMI groups.

To conclude, patients with different BMI’s perform self-paced domestic ADLs at the same relative metabolic load, accompanied by comparable Borg symptom scores for dyspnea and fatigue.

P1908
A comparison of the energy expenditure between weight supported and unsupported exercise in obesity
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Background: Weight loss is better achieved by a combination of diet and exercise. We hypothesised that obese individuals may be able to endure cycling (weight supported) for longer than walking (weight unsupported). We therefore investigated whether weight supported or unsupported exercise was associated with greater energy expenditure in obese individuals.

Methods: Individuals were recruited from a sleep clinic with a BMI > 30 kg/m2 and treated obstructive sleep apnea. Patients with pulmonary or cardiac disease were excluded. On separate days in a randomised order, participants performed an incremental cardiopulmonary exercise test on a cycle ergometer (CE) and a treadmill (TM) with expired gas analysis to determine the peak oxygen uptake (VO2pk). Two endurance tests were performed on each modality matched at 80% and 60% of the highest VO2 pk determined by the incremental tests. The total energy expenditure during each endurance test was calculated from the total oxygen uptake.

Results: 12 participants completed all six tests: 7 male, mean [SD] age 57 [14] y, BMI 34.5 [7.1] kg/m2. The peak VO2 on the TM vs CE was 2275 [522] vs 1791 [390] mL/min, respectively. Table 1 shows the duration (tm) and energy expenditure at 80% and 60% VO2 pk on the TM and CE.

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>80% VO2pk</th>
<th>60% VO2pk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle</td>
<td>Treadmill</td>
<td>Cycle</td>
</tr>
<tr>
<td>Tm (s)</td>
<td>267 [103]</td>
<td>1105 [167]</td>
</tr>
<tr>
<td>Total VO2 (L)</td>
<td>5840 [3026]</td>
<td>3038 [2391]</td>
</tr>
</tbody>
</table>

Mean (SD); *TM vs CE p<0.05.

Conclusion: In obese individuals, treadmill walking (weight unsupported) at a matched metabolic intensity led to significantly higher total energy expenditure than cycling.

P1909
Nutritional status of pulmonary rehabilitation patients
Home Jörgen Stark, Dragan Stojanovic, Konrad Schultz. Pneumologie, Klinik Bad Reichenhall, Germany

Introduction: Only about one-third of all adult German men and about 50% of women are normal weight. By contrast, the percent of overweight/obesity has reached epidemic proportions. Underweight is relatively rare. The nutritional status of a pneumological patient population and the respective frequency and meaning of underweight and overweight/obesity, using a large database.

Methods: From 2005 to end of 2011, the nutritional status of all pulmonary patients was ascertained at a German inpatient rehabilitation clinic (n=13804). Additional from July 2010 until January 2012 the nutritional status of COPD patients with severity levels of III and IV based on GOLD was also ascertained for a sub-population.

Results: Of all patients (n=13804), the percent of underweight was 8.4%, normal weight 27.5% and overweight/obese 64.1%. Of all COPD patients (n=5470), 10.8% were underweight, 28.3% normal weight and 60.9% overweight/obese. Of the COPD III patients 20.6% were underweight and of the COPD IV group even 25.1%. The asthmatic (n=3811) had a lower percent of underweight (4.5%) but 72.5% overweight/obese.

Conclusions: The prevalence of underweight and obesity in a pneumological patient population is strikingly manifest when compared to a normal population. The percentage of underweight is significantly higher for COPD. Within the COPD, results show considerable differences, depending on degree of severity.

P1910
Effects of pulmonary rehabilitation in patients with COPD with and without fat free mass depletion
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We aimed contrast the effects of exercise training in COPD patients with and without reductions in fat-free mass (FFM) and evaluate the relationship among changes in body composition, exercise capacity and health related quality of life.
One hundred and four patients submitted to Pulmonary Rehabilitation (PR) were retrospectively stratified according their FMM status. FMM was measured by bioelectrical impedance and patients considered depleted if FMM index was ≤ 15 in women and ≤ 16 kg/m² in men. Saint George Respiratory Questionnaire (SGRQ) and 6 minute walk distance (6MWD) were evaluated before and after PR.

Characteristics of all patients are following: 64.1±8.7 years; body mass index (BMI)= 25.1±4.7 kg/m²; FMM index= 17.1±3.0 kg/m²; FVC=66.4±20.1%; FEV₁= 38.9±15.2%; 6MWD= 395.3±85.5 m; and oxygen saturation (SpO₂)=93.2±4.2%. Thirty two patients (30.7%) were considered depleted. They had worse resting lung function and SpO₂ (CVF= 59.4±19.5 vs 69.6 vs 19.6%, p=0.02; FEV₁=33.6±13.2 vs 41.4±15.5%, p=0.02; SpO₂= 91.7±4.8 vs 93.9±4.8, p=0.02). Improvement in 6MWD and SGRQ after PR were not different comparing groups. There is no difference in weight alteration (0±4.3±2.7 kg) whereas depleted patients had a greater improvement in fat free mass (3.71±7.89 kg ± 0.29±2.56kg; p<0.01). Therefore, 24 of 32 depleted subjects (75%) were no more considered depleted after PR. This improvement has no correlation with SGRQ and 6MWD gains after PR.

Concluding, the clinical benefits of PR were not different comparing FFM depleted and non-depleted COPD patients. However, improvement in FFM was greater in depleted patients leading the majority of them to be considered non-depleted after PR.

P1911 Glomerulopathy, microvascular damage and aortic stiffness in patients with COPD

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Background: The increased aortic stiffness in patients with COPD will lead to increased pascalite energy which may in turn damage the microvasculature. The renal vascular bed is particularly susceptible. We hypothesised that urine albumin creatinine ratio (UACR) as a measure of glomerular damage would be related to aortic stiffness: pulse wave velocity (PWV).

Methods: Subjects with and without COPD, all with > 10 pack year history of smoking had aortic PWV, BP, oxygen saturations, spirometry as well as urine for renal biomarkers measured at clinical stability.

Results: Age, gender and BMI were matched between patients, n=52 and controls, n=34. The UACR was increased in patients compared to controls, p<0.05, Figure 1 (median and IQR): Log₁₀ UACR was related to aortic PWV (r=0.43, p<0.001). Median PWV was higher in patients vs controls but not significantly different in the low (-60gm/min) in 29% of each group. Biomarkers of proximal tubular damage (NGAL and KIM-1) standardised for urine concentration were not different between patients and controls in multiple regression, aortic PWV and oxygen saturations were the independent variables of log₁₀UACR in all subjects and also in patients with COPD alone (other variables entered included MAP, FEV₁, age, gender, BMI pack years).

Conclusions: There is glomerular damage in patients with COPD, consistent with microvascular damage which is related to aortic stiffness.

P1912 Characteristics and comorbidities associated with pain in people with chronic obstructive pulmonary disease (COPD)

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Background: A recent survey demonstrated that the prevalence of pain in people with COPD was more than twice that in age-matched people without COPD, and pain was ~2.5 times more severe.

Purpose/Hypothesis: To determine the characteristics and comorbidities associated with pain in people with COPD.

Methods: Patients were recruited from respiratory clinics and pulmonary rehabilitation programs. Respondents participated in a mail survey that included: the McGill Pain Questionnaire (MPQ), the Brief Pain Inventory (BPI), a form to list comorbidities (modified from the Charlson Index) and medications.

Results: Sixty-five of 92 COPD patients responded to the survey (70% response rate). There was a 44.4±17% pred. a BMI of 27.6 kg/m² and were 74±4.8 years. Forty-four respondents (67%) self-reported pain. On the BPI, 64% of these COPD patients had moderate to very severe pain and 73% had moderate to very high pain interference with daily activities. Average pain severity scores on the MPQ and BPI were correlated (r 0.74). Of 44 COPD patients who experienced pain, 39 (89%) reported ≥ 2 comorbidities and 20 (45%) reported ≥ 4 comorbidities; the most common were musculoskeletal (21%) and circulatory disorders (21%). Twenty-eight (64%) of COPD patients used pain alleviating treatments, the most common were non-prescription pain medications (acetaminophen and ibuprofen [n=18; 46%] followed by prescription NSAIDS and narcotics. Conclusions: Moderate to severe pain is common in people with COPD. This pain likely compromises full participation in rehabilitation and the ability to increase physical activity. Musculoskeletal causes appear to be a major contributing factor.

P1913 Immunohistochemical analysis of endobronchial biopsies of patients infected with Puumala hantavirus

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Puumala Hantavirus (PUUV) causes nephropathia epidemica (NE) and involves fever, hemorrhagia and acute renal failure but airway symptoms are common. Inhalation of aerosol-containing virus is a common route of infection. Studies have shown the involvement of a cytotoxic cell response, together with activation of endothelial cells however research into this disease in the lung is limited. Inhalation of aerosol-containing virus is a common route of infection. Studies have shown the involvement of a cytotoxic cell response, together with activation of endothelial cells however research into this disease in the lung is limited. To investigate the local immune response in endobronchial biopsies of NE patients. We hypothesize that an increased inflammatory response occurs within the lower airways of patients with NE.

17 NE patients and 16 age and smoking-matched healthy controls underwent bronchoscopy. PUUV infection was confirmed using PUUV-specific IgM/IgG in serum. Bronchoscopy was performed 6-14 days after onset of symptoms and 64% of biopsies were processed into GMA for IHC and stained for inflamatory cells, endothelial cells and ICAM. Staining was corrected for submucosal area and epithelial length. Activated blood vessels were expressed as the ratio of ICAM+ to EN4+ vessels and corrected for submucosal area.

Submucosal-staining

<table>
<thead>
<tr>
<th></th>
<th>NE (median (IQR))</th>
<th>Control (median (IQR))</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>30 (14.3)</td>
<td>13.5 (11.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mast cells</td>
<td>24.8 (8.2)</td>
<td>16 (9.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD14+ cells</td>
<td>12.7 (12.8)</td>
<td>3.17 (2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NK cells</td>
<td>0.66 (1)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICAM+EN4</td>
<td>0.37 (0.22)</td>
<td>0.25 (0.14)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

There was no significant difference in macrophages, eosinophils, T cells, CD4+ cells and B cells within the submucosa or between any cell type within the epithelium.

NE involves inflammation of the lung comprised of an infiltration of neutrophils, CD8+ and NK cells and increased ICAM expression in blood vessels. A cytotoxic response is likely to be important in the pathogenesis of NE.
Results: The mean duration of ARVI was 8.9±0.92 days in 1-st group, and 14.6±1.79 days in control group respectively. The duration of the first ARVI episode was 8.8±1.12 and 15.8±2.10 days in 1- and 2-d groups respectively. The duration of the second ARVI episode was 8.1±0.78 in 1-st group vs 14.2±2.11 days in 2-d groups. There were not registered any adverse effects in a children taking IFN-i during the trial.

Conclusions: The use of IFN-i (anafenon) in treatment of ARVI leads to reduction of disease duration. In case of repeated anafenor administration its treatment efficacy isn’t decreased.

P1915

The prevalence of clinically relevant micro-organisms in stable and exacerbated COPD using PCR techniques

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Airway bacteria and viruses are aetiologic triggers of COPD exacerbations. We investigated the prevalence of clinically relevant micro-organisms (CRMs: human rhinovirus (HRV), H. influenzae, M. catarrhalis and S. pneumoniae) in stable and exacerbated COPD using sensitive PCR techniques. Reverse-transcription PCR and real-time PCR detected HRV and bacteria respectively, in sputum samples collected at baseline (n=57) and at exacerbation onset (n=70) using our usual symptomatic definition (Seemungal et al, 1998 ARCCM).

Exacerbation samples were taken prior to antibiotic and/or steroid therapy. Fifty-four COPD patients provided 127 sputum samples: mean(SD) age 71(8) years; FEV1 43.7%(±20.0%) predicted; current smoker 26%; male gender 63%. Airway CRMs were more prevalent at exacerbation than in the stable state (75% vs 42%, p<0.001). The prevalence of co-infection with HRV and bacteria at exacerbation (29%) was similar to the prevalence of HRV (26%) or bacteria (21%) alone (figure 1A). Co-infection was proportionally reduced in stable COPD than at exacerbation (7% vs 29%, p<0.002) (figure 1B).

Figure 1

Co-infection in sputum is higher at COPD exacerbation compared to the stable state and 75% of exacerbations are associated with common CRMs. Further work is required to investigate the impact of co-infection on CRM load and the clinical utility of PCR techniques in managing COPD exacerbations.

P1916

Inhaled corticosteroids and influenza A (H1N1) viral pneumonia

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Background: Recent studies suggest that the use of inhaled corticosteroids (ICS) may be associated with a higher risk of pneumonia in patients with COPD. However it is unclear if ICS are associated with pneumonia risk in patients with influenza A (H1N1) infection.

Therefore, our aim was to examine the association of prior outpatient ICS therapy with influenza pneumonia in patients with confirmed influenza A (H1N1) infection.

Methods: We included patients ≥16 yrs of age with influenza A (H1N1) virus infection diagnosed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and assessed the association of ICS exposure with viral pneumonia using covariate-adjusted regression model.

Results: We identified 121 subjects with a diagnosis of influenza A (H1N1) virus infection who had a chest radiograph ordered. 71 (59%) had pneumonia. 17 (14%) acute exacerbation of COPD. 18 (15%) acute asthma exacerbation and 15 (12%) an influenza syndrome with no other diagnosis. 15% of subject with viral pneumonia were on previous ICS compared with 32% of the subject with influenza infection without pneumonia (p = 0.03). In regression analyses, outpatient ICS therapy was associated with lower pneumonia in patients with influenza A (H1N1) infection (OR 0.29; 95% CI 0.02-0.47, p< 0.004).

Conclusion: In our cohort viral pneumonia was quite common and the inhaled cor-
ticosteroid fluticasone may be associated with a lower risk of pulmonary infiltrates in patients with influenza A (H1N1) infection.

P1917

Elderly vs non-elderly patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) due to a viral infection

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Introduction: The aim of this study was to compare the differences between elderly and non-elderly patients with AECOPD due to a viral infection.

Methods: Patients presenting with an AECOPD were recruited. They were classified as elderly (>65 years) and non-elderly (<65 years). Sputum and oropharyngeal samples were assessed, PCR for respiratory viruses and cultures for common pathogens were performed. Clinical outcome was reported.

Results: During the study period 247 patients were recruited [median age 69.3±9.5 years] and categorized in two groups: group A, non elderly [n=81 (32.8%) median age 58±4.599] and group B elderly patients [n=166 (67.2%) median age 74.8±4.8 years]. In 133 (53.8%) patients a viral infection was identified and in 54 (13.8%) a bacterial pathogen was isolated from sputum or blood culture. In 18 (7.5%) patients a dual infection from both a bacterial and a viral pathogen was identified. In Group B influenza vaccination (57% vs 21%, p<0.001), comorbidities (cardiac failure 55.4% vs 28.3%, p<0.001, renal failure 13.8% vs 4%, p<0.03), bacterial infections [28(16.9%) vs 6% (7%) patients, p=0.04] and longer hospital stay (8.9±4.8 vs 7.5±3.2 days, p=0.02) were higher with a statistical significant difference. No differences were identified in the rate [elderly 93 (69.9%), non-elderly 48(49.4%), p=0.3] of isolated viruses.

Conclusion: In this study elderly patients with AECOPD were identified a higher vaccination rate against influenza, more comorbidities, more bacterial infections and longer hospitalization compared to non elderly patients but no differences on the rate and the type of viral infections which led to exacerbations.

P1918

Respiratory syncytial virus (RSV) causes ciliary dyskinesia but not loss of frequency during infection of human ciliated respiratory epithelial cells in culture

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Aim To determine the effect of RSV on ciliary function using ciliated air–liquid interface (ALI) cultures.

Introduction: RSV targets ciliated respiratory epithelial cells for infection. Two previous studies on the effect of RSV on ciliated cultures have shown different effects, one describing rapid ciliosstatic and another describes no cytopathic effect.

Methods: Ciliated epithelial cells were cultured from nasal and bronchial brush biopsies. Cells were infected with RSV (A2) for up to 72 h. Ciliary beat frequency (CBF) and pattern (CBP) were observed with a high-speed video camera. The cells were fixed and stained using anti-RSV (FETC) and anti-acetylated tubulin (Alexa594) antibodies. Confocal optical sectioning and electron microscopy (EM) was also performed.

Results: CBF showed a higher proportion of dyskinetic cilia following RSV infection. The median (IQR) dyskinesia index was increased as early as 24 h and at 72 h had increased to 35% (25-42%) compared with controls 13% (11-14%). CBF was unaffected by RSV infection. By 72 h the ultrastructure of the ciliated epithelium was abnormal following RSV infection with an increased in ciliated cells exhibiting loss of cilia and an increase in ciliated cells with mitochondrial damage. Furthermore, RSV antigens were observed on the apical surface of the cell and had extended the full length of the cilial shaft.

Conclusion: RSV infection of ciliated cells results in increased dyskinesia of cilia, whilst CBF is maintained. Epithelial damage was preferentially seen in ciliated cells.

References:


P1919

Clinical prognostic factors for pneumocystis pneumonia in non-HIV patients

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Introduction: Non-HIV patients with Pneumocystis pneumonia (PCP) has poor prognosis. Improved knowledge of presenting symptoms and prognostic factors for non-HIV PCP may help to reduce its associated high mortality rate.

MONDAY, SEPTEMBER 3RD 2012
Conclusions: Rates (p=0.003, p=0.0048, respectively).

Rachelle Asciak, Liam Mercieca, Jesmar Buttigieg, Martin Balzan

Seasonal influenza vaccination rates in chronic asthma patients

P1920

Introduction: To document influenza vaccination in asthma patients, to explore factors that influence vaccination.

Method: Adult patients with chronic asthma attending a hospital clinic (n=146, Female =103, mean age 49.81±3.2, 29.66 Male) filled in a questionnaire in January 2012 on influenza vaccination.

Results: 51.39% used reliever medication less than twice per week. 4.79% were current smokers. 86/58.9% of patients had experienced acute episodes in the previous year. 80.5%, 40% of Male, 61% of F received the influenza vaccine this winter. 129 (88.6%) were vaccinated in the past. 49 patients did not re-vaccinate because of fear of side effects(21), forgotten or had no time(12), were sick when vaccine available(6), adverse media report (1), because of current pregnancy(5), or the patient did not need it. 41 patients who had experienced side effects in the past, 16 re-vaccinated this year. 78 of 125 (62.4%) of all patients who were advised the vaccine were vaccinated, while 10% of those not advised were vaccinated this year (p<0.001). 78% of those who were advised to take the vaccine by a doctor were actually vaccinated. The mean age for vaccinated was 54, and 42 in those who were not (p=0.0003). The main reasons for taking the vaccine were advised by a doctor(34%), to protect themselves(40%), to reduce severity and frequency of asthma attacks (39%). Reasons for not having the vaccine were fear of side effects (40%), forgot or had no time to take it (19%), did not know they should take it (12%) Conclusion: The rate of influenza vaccination in asthma patients is low. Medical advice by a medical practitioner resulted in a high vaccination rate. Fear of side-effects was main reason for non-vaccination.

P1921

Role of virus in community-acquired pneumonia (CAP)

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Introduction: It is of increasing interest the role of viruses as etiologic agent of CAP. We tried to assess this subject in our patients.

We conducted a prospective observational study to investigate the viral, bacterial and mixed viral/bacterial etiology of patients admitted to hospital with a diagnosis of CAP. Samples were taken for blood culture and sputum culture, serial serology studies, urinary Legionella and S pneumoniae antigens, and nasopharyngeal aspirate to search virus by immunofluorescence and 2 different multiple polymerase chain reaction (PCR).

Results: Of a total of 262 patients with CAP admitted to our hospital, we included, and we found at least one pathogen in 180 (68.7%). Out of the 180 patients with etiological diagnosis, in 70 (38.8) a bacterial agent, in 64 (35.6) a viral agent and in 46 (25.6%) had a mixed etiology (virus + bacteria) were found. The bacteria most frequently found was S. pneumoniae, in 67 patients. Rhinovirus was found in 30 patients, and was the most prevalent virus associated with CAP. The most frequent virus/bacteria combination was S. pneumoniae with Rhinovirus found in 9 patients.

Conclusions: Prevalence of virus in CAP is important, reaching more than half (62%) of all known etiology. The most common pathogen causing CAP is S. pneumoniae, which was also the most often associated with virus. The study of viruses as pathogens of CAP must be taken into account in future studies of this disease.
P1923 Clinical profile and risk factors of H1N1 swine flu in Indian health care workers during the 2009 pandemic

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Background: The Christian Medical College, Vellore was one of the first centers in India that could perform RT-PCR for Influenza A H1N1 during the 2009 pandemic. The health care workers being a high risk group were screened and tested when they developed flu symptoms. Through the staff-students health service of the institution, the clinical profile and risk factors in this group were studied.

Aim: To study the clinical profile and risk factors of swine flu in health care workers during the pandemic of 2009 and compare it with other acute febrile respiratory illnesses in the group during the same period.

Methods: Consecutive health care workers who presented with an acute febrile respiratory illness were screened and those who fulfilled a set of clinical criteria were included. Demographic and clinical data were obtained and a throat swab was taken for RT PCR for swine flu. All those who were positive were included as cases and those who were negative, as controls. The clinical profile and risk factors were compared between the two groups.

Results: A total of 158 patients were included. Of these 76 were cases and 82 were controls. Female sex, students, work involving minimal contact with patients, diarrhea and need for admission were more in the cases. There were more nurses and technicians in the control group. There was no difference in the co-morbidities, exposure to swine flu patients or use of protective measures between the two groups.

Conclusion: The study has identified some risk factors for H1N1 swine flu in health care workers. This information may be helpful in setting up policies during subsequent epidemics. A larger study should be planned in the future.

P1924 Predictor of outcome and length of hospital stay in acute viral pneumonia: 2009 H1N1 influenza A experience

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Introduction: H1N1 Influenza A virus spreads globally causing pneumonia and high mortality.

Aim: We studied clinical characteristics of patients admitted with influenza pneumonia in a tertiary care hospital of northern India over one year.

Method: We analyzed 77 patients with H1N1 influenza, confirmed with RT-PCR assay.

Results: Out of 77 patients, 33(43%) were female. Mean age was 41±13 years. Thirty eight patients (50%) had at least one comorbidity, Diabetes Mellitus was most frequent. Presenting symptoms were fever in 75 (97%), cough in 67(87%) and dyspnoea in 59 (76%) patients. Mean duration of dyspnoea at presentation was higher in expired group 6±3 Vs 4±3 days(p=0.02). Bilateral opacities on chest radiograph seen in 49 (55%) patients. Mean PaO2/FiO2 ratio 240±111 at 30 minutes, then 1 pill 3 times in a day; in 2-5 days – 1 pill 3 times in a day). The treatment was surgery alone in 8 cases, associated with medical treatment in 6 cases. Twenty one patients have diffuse and bilateral bronchitis. PA infection revealed bronchitis in 3 cases (13%). Clinical manifestations included: acute respiratory failure (n=15), fatal sepsis (n=1), increased supraclavicular rise (n=24) and fever (n=20). PA strain was isolated from sputum in 23 cases and from bronchial alveolar fluid in 1 case. All patients received continuous 2 antibiotics for more than 14 days: cefazolin + aminosal or quinolone (96%) and imipenem + amoxicillin (4%). Following intravenous antibiotics, PA was eradicated in 22 cases and 2 patient was colonized with PA. Long term outcome complications were involved: chronic respiratory failure (12.5%), recurrent PA (12.5%) and Hemophillus infection (21.5%).

Conclusion: Pseudomonas aeruginosa lung infection in patients with bronchitis is associated with more severe disease and a higher utilization of health-care resources.

P1925 The treatment of acute respiratory viral infections in a patients with a chronic obstructive pulmonary disease

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Background: Acute respiratory viral infections (ARVI) often cause the exacerbation of Chronic Obstructive Pulmonary Disease (COPD) in adults. The possibilities of ARVI treatment with antiviral medication combining anti-inflammatory and antihistaminic actions in a patients with COPD are still unknown.

Aim: To evaluate the efficacy and safety of medicine combining ultralow doses of anti-bodies to interferon-γ, CD-4 and histamine (ULD AB IFN-γ, CD-4, His - the medication “Ergo-feron”) in ARVI treatment in patients with COPD.

Methods: Open comparative randomized study in 2 parallel groups including 60 adult patients with COPD was conducted. All patients obtained the treatment of main disease and also necessary symptomatic therapy. Antibiotics were administered as required. Treatment group (32 patients) took complex of ULD AB IFN-γ, CD-4, His (ergoferon) in treatment regimen (in a first day first two hours 1 pill every 30 minutes, then 1 pill 3 times in a day; in 2-5 days – 1 pill 3 times in a day). The comparison group (28 patients) didn’t obtain complex of ULD AB IFN-γ, CD-4, His (ergoferon) and other anti viral medications.

Results: The mean duration of fever response in treatment group was 1.5 day less than in comparison group (2.9±0.45 vs 4.6±0.8). The treatment group patients were discharged from hospital to the 10-th day of disease (10±0.8) and the length of hospital stay in comparison group was 3-4 days longer (14±1.2). Side effects were not registered during therapy.

Conclusion: The medicine combining ULD AB IFN-γ, CD-4, His (ergoferon) administration in a patients with ARVI afford to decrease the duration of COPD exacerbation caused by acute respiratory infections.

P1926 Can pseudomonas aeruginosa infection change the outcome of bronchectasis?

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Background: Bronchectasis patients are susceptible to infection with pseudomonas aeruginosa (PA). Isolation of PA is associated with increased severity of disease, greater airflow obstruction and poorer quality of life. It is not known whether infection by PA is a marker of disease severity or contributes to disease progression.

Aim: Determine frequency, clinical, biologic, management and outcome of PA infection complicated bronchectasis.

Patients and methods: Between 2005 - 2011, 24 PA infection occurred in patients with bronchectasis were retrospectively enrolled in the study.

Results: The mean age of patients (13 women and 11 men) was 42 years (16-65 years).Twenty one patients have diffuse and bilateral bronchectasis. PA infection reveals bronchectasis in 3 cases (13%). Clinical manifestations included: acute respiratory failure (n=15), fatal sepsis (n=1), increased supraclavicular rise (n=24) and fever (n=20). PA strain was isolated from sputum in 23 cases and from bronchial alveolar fluid in 1 case. All patients received continuous 2 antibiotics for more than 14 days: cefazolin + aminosal or quinolone (96%) and imipenem + amoxicillin (4%). Following intravenous antibiotics, PA was eradicated in 22 cases and 2 patient was colonized with PA. Long term outcome complications were involved: chronic respiratory failure (12.5%), recurrent PA (12.5%) and Hemophillus infection (21.5%).

Conclusion: Pseudomonas aeruginosa lung infection in patients with bronchec-tasis is associated with more severe disease and a higher utilization of health-care resources.

P1927 Multiple thoracic hydatidosis (About 23 cases)

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The multiple thoracic hydatidosis is rare, but dangerous because of the difficulties of its therapeutic management, and severity of its complications, some of which can be life threatening. The aim of our study was to evaluate the diagnostic and therapeutic difficulties of multiple thoracic hydatidosis. This is a retrospective study spread over 11 years (January 2000 to September 2011) concerning 23 cases of multiple thoracic hydatidosis. Patients included had two or more thoracic hydatid cysts. There are 11 women and 12 men with a mean age of 46 years (range 16 to 78 years). Six patients have already been operated on for pulmonary hydatid cysts in 3 cases and liver cysts in 3 cases. Pulmonary localization is constant with multiple hydatid cysts making an appearance in bellows release in 16 cases, a double pulmonary hydatid cyst in 7 cases. Cardiac localization was found in 4 cases, while with mediastinal, hepatic, and great vessels is found in 3 cases each. The treatment was surgery alone in 8 cases, associated with medical treatment in 6 cases. Medical treatment alone (Albenzolac) was recommended in 15 cases. The evolution was marked by the worsening lesions in five cases, pulmonary hydatid cyst rupture into the pleural cavity in 2 cases, and lesions were stationary in 10 cases. Through this work, we emphasize the rarity and severity of multiple thoracic hydatidosis. Medical treatment remains the only treatment of disseminated forms. The best treatment is preventive.
Diagnosis not made 4 (5)
Bronchiectasis 2 (3)
Pulmonary Histoplasmosis 3 (4)
Pneumocystis Jerowici Pneumonia (PJP) 4 (5)
Bacterial Pneumonia 20 (26)
Pulmonary Tuberculosis 49 (64)

Diagnosis Number of cases (%)

Conditions diagnosed
Pulmonary tuberculosis relapse or atypical mycobacterium infection?

Some cases.

It is mandatory histopathological evidence of tissue invasion to confirm the presence of Aspergillus spp. from endobronchial specimens and the presence of ≥1 endobronchial lesion without an alternative diagnosis. In order to exclude simple colonization, all cases also had histopathological evidence of tissue invasion of the tracheobronchial tree with hyaline morphologically consistent with Aspergillus spp.

Results: 8 cases (6 male; mean age 55.5 years) of AT were diagnosed. Hematologic malignancy (n=4), solid organ transplantation (n=2), systemic lupus erythematosus (n=1) and nasopharyngeal carcinoma (n=1) treated with chemotherapy and radiotherapy were the underlying conditions reported. Fever and respiratory complaints (cough, dyspnea, stridor or wheezing) were the most frequent symptoms but one case was asymptomatic. A fumigatus constituted the unique specie in our study. In bronchoscopy the pseudomembranous form was the most commonly observed (4 cases). Two cases revealed necrotic lesions and two cases only showed multiple mucus plugs. All cases were diagnosed by bronchoalveolar lavage and bronchial biopsy. Two cases died so the overall intra-hospital mortality was 25%

Conclusions: Aspergillus tracheobronchitis is an infrequent form of invasive pulmonary aspergillosis that would be suspected in some immunosuppressed patients. It is mandatory histopathological evidence of tissue invasion to confirm the diagnosis.

236. Predicting and observing paediatric allergic disease

P1931
Differences in genetic background of atopic and non-atopic asthma in children
Voiko Berce 1, Carina Pinto Kozmus 2, Uros Potocnik 3

1, Carina Pinto Kozmus 2, Uros Potocnik 3 .

Children aged between 5 and 18 years with mild or moderate persistent atopic asthma, 99 with non-atopic asthma and 273 controls. We measured numerous clinical and laboratory parameters and carried out genotyping for polymorphisms CCR5-delta32, IL-4RA Q551R, IL-4 C-33T, NOD2 R702W, CTLA4 CT60, MUC7 – VNTR, TNF C-1031T, TGFβ1 C-509T, SLCO2A4 C1672T, CD14 C-159T and IL23R rs7517847.

Results: In non-atopic asthmatics the frequency of CCR5-delta32 allele was 2.6%, which is significantly less than 9.0% in the control group (p=0.03) and the frequency of IL-4RA Arg551 allele was 7.7%, which is also significantly less than 9.0% in the control group (p=0.03). We have found no association of genotype with atopic asthma. Non-atopic asthmatics homozygous for the MUC7*7 allele had a total IgE value of 263.3 IU/ml compared to 40 IU/ml in heterozygotes (p=0.02).

Conclusions: Although TB is the most frequent cause of pulmonary infection in this group of patients several other conditions are seen. This information has public health importance to ensure correct diagnostic pathways are developed to allow correct treatment and proper allocation of limited health resources.
P1932
Maternal genetic asthma predisposition affects signaling networks in lungs of neonatal offspring
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Introduction: Exposure-induced deregulation of microRNAs (miRs) during early critical developmental periods has been proposed to contribute to the propagation of asthma risk in later life.

Aim: We asked if maternal genetic asthma predisposition is sufficient to affect pulmonary miRNA and also mRNA 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 (Finotto et al., Science, 2002; 295:336).

Methods: Female C57BL/6J Tbx21+/– mice were mated with wild type (wt) males. Neonatal lungs from wt pups of dams with (Tbx21+/–, n=8) and without (wt, n=8) genetic asthma predisposition were removed within 24h after birth and total mRNA including small RNAs was extracted. RNA from individual animals was subjected to microRNA (ABI, TaqMan® Array microRNA cards) and mRNA (Affymetrix Mouse Gene ST 1.0 ® arrays) expression profiling. Counter-regulated miRNA-mRNA pairs were further analyzed for pathway enrichment using in silico tools (GePS, IPA).

Results: After adjustment for gender differences 57 miRNAs and 2599 mRNAs were differentially regulated. Within these, 59 miRNAs paired to 1456 mRNA targets according to expression regulation. Enrichment analysis showed that developmentally important pathways (e.g. growth factor and BMP-signaling) are affected by exposure to maternal asthma predisposition even in the absence of genetic risk in the pups.

Conclusion: These data show that maternal genetic asthma predisposition affects pulmonary miRNA and mRNA profiles during an early developmental stage and might therefore influence lung development.

P1933
Role of maternal phenotype in asthma development in children
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Children born from mothers with bronchial asthma are the most vulnerable group for development of allergic diseases.

Aim of study. We have done research into data obtained from 117 pregnant women with bronchial asthma and their children. The average age of mothers was 27.7±5.2 years. Most mothers developed the disease before the age of 16 (88 mothers; 75.2%); 29 mothers got ill when they were over 16 years of age (24.8%) (“child” and “adult” bronchial asthma respectively). We have researched medical data of 117 children born from these mothers: 64 boys (54.7%) and 53 girls (45.2%). Over 70% of the children reached the age of 7-9 by the end of the observation period. Children born by caesarean section developed bronchial asthma 1.5 times more often than children born naturally. Children who had been breastfed for over 4 months had significantly lower incidence of atopic dermatitis than children fed artificially (14% and 32.7% respectively; p=0.033). Children born from mothers with “child” asthma phenotype run a 3-fold higher risk of developing bronchial asthma than those whose mothers had “adult” asthma phenotype (OR = 3.042 [CI:1.03 – 9.132]).

Conclusion: The research has confirmed the significance of hereditary load, maternal asthma phenotype, mode of child delivery, and baby feeding for development of allergic diseases in children.

P1934
A comparison of lung function and atopy between children with intrauterine growth retardation and normal birth weight in a birth cohort with documented wheeze
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Rationale: Low birth weight and intra uterine growth retardation has been implicated in lower lung function and a higher incidence of atopy. This was tested in a birth cohort.

Aim: To compare atopic status and lung function between IUGR and normal birth weight children with documented wheeze.

Methods: Children aged 3-7 yrs from a birth cohort with documented wheezing or a parental history of child wheezing and a doctors prescription for bronchodilators were studied. IUGR was defined as birth weight of less than 2.5kg. All the children underwent spirometry and skin prick test. Spirometry was done before and after bronchodilator according to ATS guidelines. Skin prick test was done using 10 antigens. Positive test was defined as wheal of more than 3mm of that of the negative control.

Results: A total of 92 children who were comparable were studied, out of which 36 (33%) were low birth weight and 56 (51.52%) were normal birth weight. IUGR children had a lower FEV1/FVC ratio (FEV1/FVC 87.26±11.55) than children with normal birth weight (FEV1/FVC 93.7±6.62) p value = FEV1/FVC = 0.002. They also had a lower FVC % value when compared to normal birth weight children.FVC % in IUGR – 81.46±10.97 and that of normal birthweight children – 86.9±10.92 p value = 0.025. The skin prick test positivity in both groups was comparable (15.7% in normal birth weight and 16.7% in IUGR children, p value = 0.92).

Conclusion: IUGR had lower FEV1/FVC ratio and FVC% as compared to normal birth weight children. Atopic status was comparable in both groups.

P1935
Exposure to farming environments in childhood and asthma and wheeze in rural populations: A systematic review with meta-analysis
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Background: Particularly strong associations with asthma and allergic diseases have been described for exposure to farming environments in childhood. The aim of this systematic review was to update and extend existing narrative reviews, test for heterogeneity across studies, and conduct a meta-analysis.

Methods: Published literature was searched through PubMed including all articles added before September 1, 2011. Articles were included if they reported an epidemiological study on the exposure to farming environment in childhood and subsequent wheeze or asthma. Heterogeneity of effect measures was evaluated using Cochran’s Q and I 2. Effect measures were summarized by random-effects meta-analysis for various outcome definitions.

Results: In total, 357 retrieved abstracts revealed 52 articles from 39 studies with data considered for the meta-analysis. Most studies were conducted among children or on childhood onset of disease. Most data was on doctor diagnosed asthma or current wheeze. The meta-analysis showed substantial heterogeneity across studies with similar outcome definitions. Nonetheless, the combined effects were therefore statistically significant and showed an approximate 25% lower asthma prevalence among exposed subjects compared to unexposed subjects.

Conclusion: The protective ‘farm-effect’ on asthma was reported in numerous studies. Its underlying factors ought to be studied and promising efforts have been already made. However, the heterogeneity of the effect across studies should also be investigated because whatever causes it is a potential threat to valid synthesis of evidence and to the detection of specific protective factors.

P1936
Influence of farm exposure and pets ownership during pregnancy on cord blood mononuclear cells (CBMC) with intracellular production of interferon (IFN)γ
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Some epidemiological and observational data suggest that farm and pets exposure in early childhood may be conducive to reduced atopy. Currently, there is a lack of consensus regarding underlying immunological mechanisms, especially in prenatal period.

Aim: We hypothesized the influence of farm exposure and pets ownership during pregnancy on cord blood mononuclear cells (CBMC) with intracellular production of IFNγ.

Methods: Intracellular IFNγ expressions as well as early activation marker CD69 (absolute cells count) were examined using flow cytometry after PHA stimulation of CBMC obtained from 93 full-term newborns. The Kruskal-Wallis and Mann-Whitney tests were used.

Results: We revealed that newborns from rural mothers (n=14) have higher amount of both nonactivated (IFNγ+CD69−, p=0.02) and activated (IFNγ+CD69+, p=0.028) CBMC, producing IFNγ, as compared with newborns from urban mothers (n=79). Only for newborns from urban mothers we calculated the influ-

Figure 1. Content of IFNγ+CD69+ cord blood mononuclear cells subject to pets ownership during pregnancy.
ence of pets exposure during pregnancy on intracellular IFN-γ production (Fig. 1). Noteworthy, that only amount of activated (IFN+CD69+) CBMC was elevated in dog (but not in cat) exposure group. Conclusion: Thus, external and home environment factors such as farm exposure and dog ownership may act prenatally affecting Th1/Th2 balance. These findings can leastwise partially explain previously reported epidemiological data.

P1937 Leucotriene B4 in fractionated breath condensate: Comparison of bronchial and alveolar concentrations in children
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Background: Asthma is a chronic inflammatory disease of the airways but recent studies have shown that alveoli are also subject of pathophysiological changes. Objectives: This study was undertaken to compare leucotriene B4 (LTB4) concentrations in different parts of the lungs using a new technique of fractionated breath condensate sampling.

Methods: In 69 patients (10-17 years, 34 asthmatics, 35 controls) measurements of exhaled nitric oxide (FeNO), lung function and LTB4 concentrations in exhaled breath condensate (EBC) were performed. EBC was collected in two different fractions, representing mainly either the airways or the alveoli, using capovolumetry. LTB4 concentrations were measured using an ELISA.

Results: LTB4 values were below the detection limit. Concentrations of the bronchial fraction correlated significantly with those of the alveolar fraction (r=0.73, p<0.000). Differences between the fractions were not significant in a paired difference test. Subjects with obstructive lung function (n=4) had significantly higher LTB4 values than subjects with normal lung function (n=65) (p=0.043, p=0.040, respectively). Asthmatics had significantly higher alveolar but not bronchial LTB4 values than controls (p=0.005, p=0.232, respectively). There was no relationship between LTB4 and FeNO values.

Conclusions: Differences in LTB4 concentrations between asthmatics and controls were only measurable in the alveolar but not in the bronchial fraction of EBC. An additional analysis of alveolar inflammation may therefore be possible useful in asthmatics. However, lab techniques for analysing LTB4 in EBC need to be improved and easy applicable.

P1938 High altitude stay reduces eosinophil load in airways in children with asthma
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A normal sputum eosinophil count in children with asthma could result from corticosteroid treatment or reduction in eosinophil recruitment. In order to differentiate this we have described a new marker of eosinophilic inflammation (eosinophil protein content in airway macrophages).1 At high altitude children with asthma show significant reduction in eosinophil count due to reduced exposure to allergens. The aim was to determine the phagocytic function of airway macrophages at baseline (T0) and after stay at high altitude (T1). Sputum induction was performed at T0 and T1 in children with mild to moderate asthma attending High Altitude Children’s Asthma Center in Misurina. Differential count was obtained by counting 400 non-squamous cells (eosinophil asthma ≥ 3%). AM were isolated by adherence and cultured with FITC labelled heat killed staph aureus in the ratio of 1:10 (AM: bacteria). One hundred macrophages were imaged using confocal microscope. The median bacterial count/AM was calculated using Image J and Cell profiler software. The groups were compared using paired and unpaired t-tests.

There was no significant difference (p = 0.3) between median bacterial count in eosinophilic (n=16) [Mean (SD)] [77.56(36.60)] and non-eosinophilic asthma (n=8) [68.22(11.5)] at T0. Children at T1 (n=19 pairs) had significantly lower i) median bacterial count [Mean (SD)] p = 0.006, 35.95(54.51) vs 73.26 (39.42) than at T0. The sputum macrophages in children with mild to moderate asthma are equally phagocytic in eosinophilic or non-eosinophilic groups. After stay at high altitude macrophages were less phagocytic (possibly due to return to normal level of recruitment).


P1940 The impact of sublingual immunotherapy (SLIT) of asthma on Th1 cells and susceptibility to apoptosis
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Asthma is a chronic inflammatory disease of the airways. Allergen-specific immunotherapy is the unique disease modifying treatment of atopic diseases. SLIT is effective treatment associated with low incidence of systemic reactions. A disturbed T cells apoptosis plays a crucial role in the in the development of allergy inflammation in the course of asthma. Nevertheless, the effect of sublingual immunotherapy on T cell apoptosis has not been elucidated. The aim of present study was to evaluate the influence of one year allergen-specific immunotherapy in asthmatic children on the frequency of Th1 Bc1-2 positive cells in peripheral blood.

Twenty-five children, suffering from bronchial asthma and allergic rhinitis were enrolled to the study. Children were shortlisted for sublingual specific immunotherapy with a solution containing specific allergen extracts. The frequency of Th1 cells and the intracellular expression of Bc1-2 were evaluated using flow cytometry before and after 12 months of treatment. The frequency of Th1 cells after immunotherapy was significantly increased (13.22 [10.34, 18.95]% before versus 19.86 [16.37, 24.52]% after SLIT, p=0.01), moreover significant increase of Bc1-2 positive Th1 cells was found after treatment. At a baseline 58.34 (31.23, 76.28) % of Th1 cells showed expression of Bc1-2 protein, whereas 73.61 (65.47, 82.43) % Th1 cells expressed Bc1-2 after one year of SLIT, p=0.0465. The increase of Th1 cells frequency secondary to SLIT might be associated with enhanced resistance to apoptotic signals. However, further studies are needed to clarify the role of T cell apoptosis in resolution of allergic airway inflammation.

P1941 A relationship between exercise-induced bronchoconstriction and allergic rhinitis in Japanese children
Yoko Murakami 1, Satoru Honjo 1, Hiroshi Odajima 1, Yuichi Adachi 2.
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2Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Medical University of Warsaw, Poland

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Introducification: A relationship between allergic rhinitis (AR) and Exercise-induced bronchoconstriction (EIB) has not been fully studied.

Aims: The aim of this study was to examine the relationship between EIB and AR among children aged 6-17 in Japan.

Methods: EIB and AR were ascertained by International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire among randomly selected schools across the nation. Number of the subjects were 43,813 of 6-7 year old attending the elementary schools, 48,641 of 13-14 year-old attending the junior high schools and 54,138 of 16-17 year old attending the high schools. We examined relationship between having AR and risk of EIB, and severe EIB in current asthmatics in a case-control design using logistic regression model. We also investigated an association of degree of life disturbed by AR with risk for EIB, and severe EIB. The impact of EIB on the frequency of Th1 Bc1-2 positive cells in peripheral blood.
of severe EIB were elevated with increasing severity of life disturbed by AR, respectively (p for trend <0.01 and <0.01).

Conclusions: Risk of EIB was increased among children with AR as compared to those without AR. Degree of life disturbed by AR was related to increasing risk of EIA, and severe EIA.

P1942

Physical activity: Children with asthma and without asthma

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Background: It is well known that regular physical activity has health benefits, reducing obesity, morbidity and mortality. Currently, the practice of physical activity in asthmatic patients shows a significant improvement of disease symptoms, however, there is disagreement in the literature whether asthmatic children are more sedentary than children without asthma.

Objective: To compare level of daily physical activity in children with and without asthma.

Methods: We studied 121 children (79 asthmatics) of both genders among 7-12 years. Were selected for the study asthmatic patients with controlled disease. The level of daily physical activity was monitored by use of the accelerometer for six days (four weeks on and two on the weekend).

Results: Total number of steps, steps and time in moderate physical activity between genders of the asthma and control groups were similar.

Conclusion: Characteristics related to asthma do not seem to affect the physical activity in children with controlled disease, making the practice of daily physical activity similar to that of children without asthma.

P1943

Obesity and asthma symptoms in children


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Introduction: The relationship between obesity and asthma show inconsistent results. The purpose of our study was to evaluate the prevalence of asthma according to obesity in a large sample of the child population in our region (total population 2795422).

Methods: A cross-sectional study, following the ISAAC study methodology, was conducted on randomly selected 6-7 year old children.

The asthma symptoms, demographic characteristics, and other potential risk factors were determined from the questionnaire. Overweight and obesity were defined based on the body mass index. Multiple logistic regression were used to obtain adjusted prevalence odds ratios (OR) and 95% confidence intervals (95% CI) between asthma symptoms and obesity.

Results: Finally, 7485 children were included (50.8% female). Our results showed that 23.4% of our children were overweight, and 9.6% were obese.

Obesity was associated with an increase in the probability of wheezing ever (OR: 1.35) and exercise induced asthma (OR: 1.62).

Odds ratio for prevalence of asthma symptoms according to obesity and overweight in children

<table>
<thead>
<tr>
<th>Wheezing ever</th>
<th>Current asthma</th>
<th>Exercise induced asthma</th>
<th>Severe asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.07 (0.92-1.25)</td>
<td>1.10 (0.88-1.36)</td>
<td>1.10 (0.80-1.52)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>1.35 (1.10-1.66)</td>
<td>1.31 (0.96-1.74)</td>
<td>1.62 (1.10-2.36)</td>
</tr>
</tbody>
</table>

OR: Odds Ratio. CI: Confidence interval. Adjusted by gender, cat and dog keeping, maternal education, parental asthma and parental smoking.

Conclusion: In our population, obesity was associated with a higher prevalence of asthma in young children.

P1944

Prevalence of asthma and rhinitis in school-age children in Fortaleza, northeast Brazil

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Introduction: In Brazil, the mean prevalence of asthma symptoms is 13.3%. Fortaleza is the fifth largest city of Brazil and there is no recent official data from asthma prevalence in children.

Objective: The aim was to evaluate the prevalence of asthma and rhinitis symptoms in 6-7 years old children in Fortaleza.

Method: The protocol of the International Study of Asthma and Allergies in Childhood (ISAAC) was used. Random sample were taken from 3000 students from public and private schools in 2010. The surveys were sending with their homework for the parents to fill it and returning to the school in the next day.

Results: The prevalence of wheezing was 52.6% and wheeze in the last 12 months 28.3%, while diagnosed asthma was 12.4%. For symptoms associated with severity, the rate of wheezing with sleep impairment was 4.1% for more than 5 more wheezing attacks in the last year, 3.9% and sleep disturbance by wheezing in one or more nights a week 6.7%. The rate of wheezing after exercise was 7.2% and dry nocturnal cough was 39.7%. Mother’s smoking (p < 0.001), father’s smoking (p = 0.011) and contact with pets (p = 0.007) were associated with asthma symptoms. Mother’s smoking (p = 0.011) and the use of antibiotics (p = 0.011) in the first year of the child’s life were associated with severe asthma. The prevalence of rhinitis symptoms was 50.9% rhinitis in the last 12 months 42.8% rhinoconjuntivitis 15.4% and diagnosed rhinitis 28.1% Impaired daily activities by rhinitis was 19.6% (little), 3.2% (moderate) and 1.9% (high).

Conclusions: The prevalence of asthma and rhinitis in 6-7 years old children in Fortaleza were similar to Brazilian national mean rate. Asthma and rhinitis are underdiagnosed among children in Fortaleza.

P1945

Dynamics of asthma prevalence in children in the Novosibirsk (preliminary results)

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Background: The study of the asthma epidemiology according to the ISAAC program (Phase Three) was over in 2002. Afterwards the studies with the use of standardized methods have not been carried out in the world.

Aim: To study the dynamics of asthma prevalence among the 6-7 years old children in the Novosibirsk.

Methods: According to the ISAAC 3249 children were examined in 2002 and about 3000 children aged 6-7 years old were examined in the years of 2011-12. This abstract introduce the preliminary results based on the questioning of 970 parents in the years of 2011-12.

Results: There decreased the prevalence of wheezing from 24.1% to 17.3% (p < 0.0001), the prevalence of current asthma symptoms from 10.8% to 6.3% (p < 0.0001), the number of exacerbations over 12 times a year from 0.5% to 0.2% (p=0.001) the prevalence of nocturnal asthma symptoms decreased from 4.3% to 2.2% (p=0.001), the number of symptoms limiting speech decreased from 0.9% to 0.1% (p=0.012). The diagnose of asthma was established in 2.4% of children in 2002. In 2011-12 this percentage increased up to 3.4% (p=0.07), this indicates the improvement in the diagnostics and the better level of knowledge of physicians about the asthma. The prevalence of asthma symptoms associated with the physical exertion was not significantly changed (3.6% in 2002 and 3.3% in 2011-12, p=0.4). The registration of nocturnal cough not associated with the infection of the respiratory tract decreased from 8.6% to 7.6% (p<0.02).
Conclusion: The obvious trend in the first decade of the XXI century is the decrease in the prevalence of the asthma symptoms among 6-7 years old children in the Novosibirsk with some improvement in the disease diagnostics.

Background: Regulatory T cells (Treg) expressing FOXP3 inhibit the development of T cells towards Th2. In this work we hypothesized that FoxP3 is responsible for the development of exacerbations in asthma.

Aim and objectives: To investigate the levels of CD4+FOXP3+ in moderate BA with different frequency of exacerbations compared to healthy donors.

Methods: We included 20 patients with moderate asthma, which were divided into 2 groups. The first group (n=16) had at least 1 exacerbation of asthma during the previous year, the disease duration was 7.3 (5.0;12.0) years, FEV1 - 81.2 (72.2:89.4)%; The second group (n=4) with moderate BA had 2 or more exacerbations of asthma in the previous year, the duration of the disease was 14.5 (9.0;23.0) years, FEV1 - 78.4 (74.4:89.8)%; The control group was included 17 healthy adults. Peripheral blood mononuclear cells were isolated in Ficoll density. The circulating percentage of CD4+FoxP3+ Tregs in peripheral blood was estimated by the flow cytometry analysis (PASCALCubilr Becton Dickinson, USA). Results: It was found that moderate asthma is characterized by significantly lower CD4+FoxP3+ T-reg 0.99 (0.72;3.77)% compared to healthy control - 8.16 (7.66:9.42%) (p<0.01). The level of CD4+FoxP3+ was higher 1.8 (0.8:4.7)% in patients who didn’t have the exacerbation of BA, or had a single acute of asthma compared to individuals, who had more than 2 exacerbation of asthma in the previous year - 0.53 (0.4:0.9%), p<0.05.

Conclusions: FoxP3 is responsible for the development of exacerbations in asthma. Possible, the low level of transcription factor FoxP3 is closely related to 2 or more exacerbations of BA per year.

P1949 Efficacy of a novel SHIP1 activator in animals and healthy human volunteers exposed to inhaled lipopolysaccharide

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Introduction: Suppression of P38 is an established pharmacological approach to control inflammation. SHIP1 suppresses the downstream effects of P38 in neutrophils converting it to P38δIP. SHIP1 deletion in mice results in pulmonary inflammation, and in humans, SHIP1 protein levels negatively correlate with basophil degranulation.

Objective: To determine the effects of AQX-1125, a small molecule SHIP1 activator, on airway inflammation in animals and humans.

Methods: The efficacy of AQX-1125 on LPS-induced pulmonary inflammation was evaluated in SHIP1−/− and SHIP1+/+ mice, and on bronchoalveolar lavage (BAL) cell counts and inflammatory mediators of LPS-challenged rats. The ability of oral AQX-1125 (450 mg QD, 7 days) to inhibit LPS-induced airway neutrophilia in healthy human subjects (n=18) was evaluated in induced sputum in a randomized, placebo-controlled, double-blind, two-way crossover study.

Results: AQX-1125 inhibited LPS-induced pulmonary neutrophilia in SHIP1−/− but not not SHIP1+/+ mice. AQX-1125 dose-dependently inhibited airway neutrophilia and inflammatory mediators in LPS-challenged rats (p<0.05). The ability of oral AQX-1125 (450 mg QD, 7 days) to inhibit LPS-induced airway neutrophilia in healthy human subjects (n=18) was evaluated in induced sputum in a randomized, placebo-controlled, double-blind, two-way crossover study.

Results: AQX-1125 inhibited LPS-induced pulmonary neutrophilia in SHIP1−/− but not not SHIP1+/+ mice. AQX-1125 dose-dependently inhibited airway neutrophilia and inflammatory mediators in LPS-challenged rats (p<0.05). In humans, AQX-1125 reduced LPS-induced neutrophilia. Prior to LPS exposure, sputum neutrophil cell counts were the same between treatment groups (Geometric Least Squares Mean ± GLSM AQX-1125/placebo ratio = 0.96, 90% CI 0.27-3.38). Post-LPS exposure (24 h), AQX-1125 reduced the sputum neutrophils by 66% (GLSM ratio = 0.34, 90% CI 0.13-0.92).

Conclusions: These data demonstrate efficacy of AQX-1125 in human and rodent pulmonary inflammation models, supporting the importance of SHIP1 as a novel target and the clinical development of AQX-1125 for inflammatory disease.

P1950 The potential mechanism of Th17/Treg imbalance in the microenvironments of chronic inflammation and allergic asthma

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Objective: Recent studies have shown that Tregs can differentiate into IL-17+/Foxp3+ T cells in the colitid microenvironment and allergic rinitis. However, the biology of CD39+/Tregs cells, IL-17+/Foxp3+ T cells and Th17 cells, and the relationship among these three kinds of cells remain poorly understood in allergic asthma.

Methods: We investigated the proportions of Th17, CD39+/Treg cells and IL-17+/Foxp3+ T cells in peripheral blood from allergic asthmatics and healthy controls by flow cytometry. All patients were allergic to house dust mites. Dermaophages peryorrhinus specific IgE levels, pulmonary function and Asthma Control Questionnaire were assessed. Moreover, the associations among all these kinds of index and disease severity were analyzed.
Result: There was a deficiency in the frequency of total Tregs in asthmatics, whereas the frequency of Th17 cells, IL-17+Foxp3+ T cells, CD39+Treg cells and plasma IL-17 levels were increased in moderate to severe asthma. FEV1 (% predicted) was negatively correlated with the frequency of Th17 cells, IL-17+Foxp3+ T cells, CD39+Treg cells and plasma IL-17 levels, and positively correlated with the frequency of total Tregs. Moreover, the frequency of Th17 cells and IL-17+Foxp3+ T cells were positively correlated with the frequency of CD39+Treg cells.

Conclusion: Our findings suggest that the increased expression of CD39 on Tregs in asthma can offset the decreased immunosuppressive functions of Tregs. And Tregs in the microenvironment of asthma also have plasticity of differentiate into IL-17+Foxp3+ T cells. CD39+Treg cells play an important role in constraining pathogenic Th17 cells and IL-17+Foxp3+ T cells.

P1951

Expression of the β2-adrenoreceptor and M3-cholinoreceptor genes in patients with different severity of asthma and BHR level
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Background: Persistent airway inflammation, as well as nervous innervation of bronchial smooth muscles plays the main role in the formation of BHR, one of the key characteristic of asthma.

Aim and objectives: To evaluate the β2-adrenoreceptor (ADRB2) and M3-cholinoreceptor (CHRM3) gene expression in bronchial mucosa of patients with different severity of asthma. We hypothesized that the differential expression of these genes may contribute to the different BHR level.

Methods: Biopsy specimens of right middle lobar bronchus were obtained from 30 asthmatic patients (13 with severe, 9 with moderate, and 8 with mild). The inclusion criteria followed the GINA, 2009. All subjects underwent a routine medical history taking, physical examination, spirometry, BHR measurement. The mRNA levels for the ADRB2 and CHRM3 genes in bronchial mucosa were revealed using qRT-PCR (iQ SYBR Green Supermix, BioRad, USA), mRNA levels were then recalculated as 2-ΔΔCT to the GAPDH mRNAs.

Results: An increase of the ADRB2 and CHRM3 genes expression was demonstrated in patients with severe asthma (ADRB2 mean=0.54; 95%CI 0.50-0.59; CHRM3 0.57; 0.53-0.60) as compared to patients with mild (ADRB2 0.34; 0.32-0.36; CHRM3 0.48; 0.46-0.49) and moderate disease (ADRB2 0.27; 0.25-0.29; CHRM3 0.40-0.49) (p<0.05). It was revealed by correlation analysis that the level of the PC20 is negatively correlated with the mRNA levels of the ADRB2 and CHRM3 (R=-0.67 and -0.52, respectively; p<0.005), thus a high level of gene expression is associated with a high BHR. Conclusion: The differential expression of the ADRB2 and CHRM3 genes is associated with asthma severity and BHR level.

P1952

Changes in skin prick test reactivity over 7–14 years in a population of food allergy children and asthmatic symptoms
Carlo Zacari, Valentina De Vittori, Anna Taglia, Marta Bresciani, Anna Rugiano, Marzia Duse.

Background: Allergic disorders are an increasing health problem among children.

Aim: To describe the prevalence of sensitization to common food and inhalant allergens at different ages and the association with asthmatic symptoms.

Methods: 174 children with positive Skin Prick Test (SPT) to at least one food allergen at <36 months were called after a follow-up period of 7-14 years to repeat SPT, to complete a questionnaire about asthmatic symptoms, and to perform spirometry.

Results: 174 children complete the questionnaire: 25.8% had wheezing, 34.4% had dry cough and 55.6% reported diagnosis of asthma. At the first observation 65 (37.3%) had positive SPT only to food allergens(F) and 109 (62.6%) had sensitization to food and inhalant allergens (F+I). At the second observation in the group with single sensitization to F 50% lost sensitization, 10% retained sensitization to food and developed sensitization to inhalants (F+I) and 40% showed sensitization only to inhalants. In the group with double sensitization (F+I) at the first observation: 50% remained positive to both allergens (F+I), more than 40% were positive only to inhalants and a small percentage (~10%) became negative. The sensitization profiles differed significantly between two groups (F and F+I). FEV1 and FEV1/FVC were significantly lower in the group F+I at the first observation than in the group F (p<0.01).

Conclusion: We found an association between changes in SPT positivity and the development of asthmatic symptoms. The double sensitization (F + I) as well as the early sensitization to alants would seem to correlate with the persistence of the allergy and with the development of respiratory disease.

P1953

Comparison of different instruments to obtain nasal epithelial cells from nasal mucosa.

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Introduction: Nasal epithelial cells have been shown to be good surrogate markers for bronchial epithelial cells. We aimed at comparing different brushing instruments allowing collection of nasal epithelial cells.

Methods: Nasal epithelial cells were obtained by brushing the inferior surface of the middle turbinate of both nostrils using three different instruments: a cytology brush, a flocked nasal swab and a nasal mucosal curette. Cells cultures were established by seeding the cells into medium. Cell count, cell viability, success rate in establishing cell cultures and the acceptability to subjects were compared between groups.

Results: 60 human subjects (median [IQR] age: 34 [27-36] years) were brushed. Higher number of cells were obtained using brushes (9.8 [6.7-33.5] x 10^6 cells/mL compared to swabs (2.5 [1.5-4.0] x 10^6 cells/mL, p<0.0001) and curettes (1.3 [1.0-2.1] x 10^6 cells/mL, p<0.0001). Viability was similar for cells obtained using brushes (42 [14-78] %), swabs (54 [15-71] %) and curettes (54 [25-69] %). Cells obtained by brushes reached confluence fastest (6 [6-10] d), followed by cells obtained by curettes (11 [9-15] d, n.s.) and swabs (19 [13-21] d, p<0.0001). Success rate in establishing primary cell cultures (~ 90% confluent cell layers within 21 days in a 12.5 cm^2 cell culture flask) was 90% with brushes, 65% with swabs and 85% with curettes. Pain intensity was similar for all instruments, brushes (3.0 [2.0-5.8] out of 10 on the pain scale), swabs (2.5 [1.0-4.0]) and curettes (3.0 [2.0-5.0]).

Conclusion: All three types of instruments allow collection and growth of human nasal epithelial cells, with good acceptability to subjects. The most efficient instrument is the nasal brush.

P1954

The inflammatory response of pulmonary vascular smooth muscle cells to bacterial endotoxin is sensitive to endothelin receptor antagonism

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Background: Bacterial infections cause exacerbations of chronic inflammatory lung diseases by aggravating airway inflammation. Current therapeutic strategies like steroid administration have proven unsatisfactory e.g. for COPD and highlight the need for new approaches.

Aim: To elucidate the inflammatory response of pulmonary vascular smooth muscle cells (PVSMCs) to LPS, and whether this response is sensitive to antagonists of endothelin A receptor (ETAR) (Ambrisentan), ETBR (BQ788) or both receptors (Bosentan).

PVSMCs of 44 donors were incubated with highly purified smooth LPS (sLPS), highly purified short-chain LPS (Re-LPS, shortest form) or M-LPS (mixture of long and short forms) of Salmonella spp. or with Lipooligosaccharide (LOS) of nontypeable H. influenzae (NTHI) or with NTHI extract in absence or presence of endothelin receptor antagonists (10^-7-10^-5 M) for 72 hours and cytokines were measured by ELISA. All LPS-forms and NTHI extract induced concentration-dependent IL-6, IL-8 and GM-CSF release from PVSMCs (each p<0.05). M-LPS and LOS were most effective. The effects of M-LPS were completely abolished by polymyxin B and CLI-095 (TLR4 inhibitor) but not affected by TLZR2/TLZ9 inhibitors. M-LPS-induced IL-6 was reduced by all endothelin receptor antagonists (each p<0.05). IL-8 and GM-CSF were reduced by Bosentan and BQ788 but not by Ambrisentan (each p<0.05).

PVSMCs contribute to the inflammatory response to bacterial infections and thus can prove to be a therapeutic target in exacerbations of chronic airway diseases. Cytokine release shows specific reactions to dual vs. selective endothelin receptor blockers which can be useful in therapy.

P1955

Asthma and vitamin D

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Background: Recent studies indicate a relationship between low vitamin D level and asthma pathogenesis. The aim of this prospective study is to evaluate vitamin D levels in asthmatic patients and investigate the relationship between vitamin D and asthma pathogenesis.

Material and method: 112 asthmatic patients and 94 healthy people who admitted to Cukurova University Chest Diseases Department were included. The age and gender of asthmatics and control group were similar. The demographic data were recorded. Both asthmatics and control group had vitamin D determination tests and their vitamin D levels are studied with liquid chromatography.
Conclusions: Levels of vitamin D is decreased in patients with asthma. It let us hypothesize that 1.25\(\text{OH}_2\)D may be important in the pathogenesis of asthma. In serum (\(r=0.54\), \(p<0.05\)) difference of 1.25\(\text{OH}_2\)D was not obtained. Level of 1.25\(\text{OH}_2\)D significantly associated with asthma pathogenesis especially in females and poor lung functions.

Conclusion: in asthmatic patients, a significant positive correlation is determined between the vitamin D level of female patients was significantly lower than the male patients (23.88±11.92 ng/ml in females and 29.52±11.48 ng/ml in males) (\(p=0.03\)). Again in asthmatic patients, a significant positive correlation is determined between the forced expiratory volume in first second and serum vitamin D level (\(p=0.004\)).

Conclusion: With these results, it is thought that vitamin D levels could be associated with asthma pathogenesis especially in females and poor lung functions.

P1956

Levels of vitamin D is decreased in asthmatic patients

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Background and aim: 1.25-Dihydroxy vitamin D (1.25\(\text{OH}_2\)D) has long been recognized as a critical mediator in bone health. Several studies of recent years have shown the relationship between chronic inflammatory lung diseases and Vitamin D level serum levels. The aim of this study was to elucidate Vitamin D levels in allergic asthma (AA) and non allergic asthma (NA) patients, and to compare these results with healthy subjects (HS).

Methods and material: Eighteen patients with AA, 14 with NA, as well as 10 HS were involved to the study. 1.25\(\text{OH}_2\)D levels in serum samples were analysed by ELISA. Eosinophil count was evaluated in induced sputum and peripheral blood samples.

Results: We found that vitamin D levels in asthmatic patients were lower compared with HS in asthmatic group 66.93±21.5 pmol/L vs HS 134.5±20.1 pmol/L, \(p<0.05\). However in AA (81.06±21.5 pmol/L) and NA (52.8±21.5 pmol/L) significant difference of 1.25\(\text{OH}_2\)D was not obtained. Level of 1.25\(\text{OH}_2\)D significantly negatively correlated with eosinophil count in induced sputum in patients (\(r=-0.72\), \(p<0.05\)) and in serum (\(r=-0.54\), \(p<0.10\)).

Conclusions: Levels of vitamin D is decreased in patients with asthma. It let us hypothesize that 1.25\(\text{OH}_2\)D may be important in the pathogenesis of asthma.

P1957

Complex treatment of allergic bronchopulmonary aspergillosis (ABPA) in asthmatic patients

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Background: ABPA is an immunologic pulmonary disorder caused by hypersensitive reaction to Aspergillus fumigatus colonizing patient’s bronchial tree. The prevalence in general population is between 1-2%, in patients with corticosteroid sensitive reactions to Aspergillus fumigatus colonizing patient’s bronchial tree. The presence is associated with unfavorable prognosis of this disease. The standard treatment includes systemic corticosteroids (SCS) and antifungal agents (AFA). The biological therapy in ABPA is discussed.

Methods: A case report of 56 year old woman with ABPA, manifested as uncon- trolled severe persistent asthma with frequent exacerbations. We compared effects of 1. standard inhaled CS treatment, 2. combination of SCS with AFA and 3. Anti-IgE therapy using lung function tests, FENO, total IgE level, spec IgE level to Aspergillus fumigatus, ACT questioner and clinical course assessment.

Results: We found significant improvement in all parameters after 4 weeks of SCS + AFA therapy. Significant improvement has been observed in all parameters after 16 weeks, 8 months, 1year and 2 years of anti-IgE, with no need of AFA and SCS. Only one exacerbation of ABPA was observed during 24months of anti-IgE treatment. No adverse effects from anti-IgE therapy were observed.

Conclusion: Anti-IgE therapy could prove to be an alternative targeted treatment options in patients with ABPA. Successful response to anti-IgE in severe asthma patients with ABPA could result in reduced need of AFA and SCS therapy, stable lung function and lower risk of exacerbations.

P1958

Phenotypes of adult-onset asthma by cluster analysis

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Rationale: Asthma phenotyping is of increasing importance to identify patients who could benefit from personalised therapeutic strategies. Several studies suggested that adult-onset asthma is a specific phenotype. In order to explore underlying mechanisms of adult-onset asthma, we aimed to identify subphenotypes by unsupervised clustering methods.

Methods: 200 patients with adult-onset (>18yr) asthma (60.5% female; age 54 (26-75) yr, 45% atopic) were characterized with respect to clinical, functional and inflammatory markers. Initial variable reduction was achieved by elimination of redundant data and factor analysis. K-means non-hierarchical cluster analysis was performed to identify clusters.

Results: We identified three clusters of adult-onset asthma. Cluster 1 (n=41) consisted of predominantly females, with higher BMI and more often of non-Caucasian descent. They showed higher symptom scores, higher health care utilization and frequent exacerbations. However, they had lower sputum eosinophils and normal exhaled nitric oxide (FeNO) levels. Cluster 2 (n=60) consisted of predominantly males with severe asthma. They showed high symptom scores and frequent exacerbations, with reduced lung function, elevated sputum eosinophils and relatively high FeNO levels. Cluster 3 (n=90) consisted of predominantly males with mild-moderate asthma, normal lung function, minimal symptoms and health care utilization.

Conclusions: Non-hierarchical cluster analysis identifies three subphenotypes of adult-onset asthma that can be distinguished by gender, symptom severity, BMI lung function and airway inflammation. Identifying these subphenotypes can help to investigate the associated pathobiology and provides new directions to personalized management.

P1960

Asthma phenotypes in Turkey: A multicenter study

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Conclusions: Non-hierarchical cluster analysis identifies three subphenotypes of adult-onset asthma that can be distinguished by gender, symptom severity, BMI lung function and airway inflammation. Identifying these subphenotypes can help to investigate the associated pathobiology and provides new directions to personalized management.
of different geographic locations were involved. A standard questionnaire was applied between February -December 2011. Results: The percentage of females was 75%. Severity of the disease was found as mild persistent in 10%, mild intermittent in 40%, moderate in 38% and severe in 12%. 12% of the patients had irreversible airway obstruction. Smoking/quitting patients were 34% of the study group, 42% of the patients had obesity (BMI> 30), 11% had allergic intolerance and 29% had psychological triggers. Smoking rate was found to be lower in females (p<0.01) whereas the rate of obesity, allergic intolerance and psychological triggers was higher in females (p<0.001) than males. Allergic attack phenotype consisted 21% of the study group. Total control rate was found as 22%; which was higher in males compared to females (29% vs 19%) (p<0.01). There was no difference between genders in term of partial control however uncontrolled asthma was more frequent in females than males (31% vs 22%) (p<0.01). Pulmonary function tests, total IgE values, skin prick test results and severity of disease were all comparable between males and females. The most frequent comorbidities were chronic rhinitis/rhinosinusitis (49%) and reflux(34%). It was found that the cases with lower asthma control levels had higher rates of allergic intolerance and multiple comorbidities (p<0.01). Conclusion: To our knowledge this is the first study on asthma phenotypes in our environment. We believed that it will have significant contribution in obtaining control in our asthma patients.

P1961 Asthma and atopy: How much is it really attributable? About a representative population of Tunisia Ines Saada, Joude Cherif, Sonia Toujani, Hafedh Zakhama, Yacine Ouazhchi, Nozha Ben Salah, Rechtir Louiz, Jalloul Daghfous, Nedia Mehai, Majed Beji. Pulmonology, La Rabta Hospital, Tunis, Tunisia

Introduction: In recent decades it has become routine to describe asthma as an atopic disease. We carried out this study to evaluate the prevalence of asthma and assess the association of atopy with asthma in individuals and in population.

Method: A cross-sectional survey, single pass, representative of the general population was carried out in subjects aged from 2 to 50 years. Informed consent was obtained. Prevalence was determined through questionnaires, validated and used in international surveys, corresponding to the screening asthma and lung function test. Definition of atopy was based on clinical symptoms of rhinitis and allergy skin.

Statistical analysis was performed using SPSS 18.0.

Results: The study included 4470 subjects. There was 40.2% male and 59.8% female. Current asthma prevalence was 6.8% in adults and 5.9% in children. Lung function test showed reversibility in 20%. The proportion of asthma cases that are “attributable” to atopy (defined as rhinitis and allergy skin) was estimated by the prevalence of atopy risk. About 53.5% of children’s asthma. The percentage of females was 75%. Severity of the disease was found as mild persistant in 10%, mild intermittent in 40%, moderate in 38% and severe in 12%. 12% of the patients had irreversible airway obstruction. Smoking/quitting patients were 34% of the study group, 42% of the patients had obesity (BMI> 30), 11% had allergic intolerance and 29% had psychological triggers. Smoking rate was found to be lower in females (p<0.01) whereas the rate of obesity, allergic intolerance and psychological triggers was higher in females (p<0.001) than males. Allergic attack phenotype consisted 21% of the study group. Total control rate was found as 22%; which was higher in males compared to females (29% vs 19%) (p<0.01). There was no difference between genders in term of partial control however uncontrolled asthma was more frequent in females than males (31% vs 22%) (p<0.01). Pulmonary function tests, total IgE values, skin prick test results and severity of disease were all comparable between males and females. The most frequent comorbidities were chronic rhinitis/rhinosinusitis (49%) and reflux(34%). It was found that the cases with lower asthma control levels had higher rates of allergic intolerance and multiple comorbidities (p<0.01). Conclusion: To our knowledge this is the first study on asthma phenotypes in our environment. We believed that it will have significant contribution in obtaining control in our asthma patients.

P1962 Asthma registry, a path to uncover pitfalls in asthma Syed Ali Reza Mahdaviani, Seyed Amir Mohajerani, Majid Malekmohammad, Seyeda Zadeh, Aftef Fakharian, Alireza Eslaminejad, Maryam Husazrad, Mohammad Reza Masjedi, Ali Akbar Velayati, Mazerah Ebrahimian. Pediatrics Respiratory Disease Research Center, Pediatrics Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Background: We performed a prospective study with a group of consecutive adult patients with allergic rhinitis and asthma from our outpatient clinic. The control of the disease was assessed using both ACT and CARAT tests. Results: Forty patients were evaluated (mean age 53, 70% female). 17% of the patients had ACT controlled asthma and 45% had ACT uncontrolled asthma. In both groups CARAT results were equivalent. Conclusion: A tool able to assess both asthma and allergic rhinitis control was lacking. In our patients, using the CARAT was useful mainly in the partially controlled asthma population by helping to differentiate those in whom uncontrolled rhinitis was the main cause of the uncontrolled asthma.

P1964 Correlation of changes of IgE with skin reactivity and clinical outcome during specific immunotherapy against home dust in asthmatic subjects Besim Prnjavorac1, Rafid Sejdnovic1, Enes Hondo1, Adlija Caulevic2, Sabina Szemza2, Maja Malenica2, Tamer Bego2, Tanja Dujc2.1Paludomology, General Hospital Tuzla, Bosnia and Herzegovina; 2Clinical Biochemistry, Faculty of Pharmacy, Sarajevo, Bosnia and Herzegovina

Background: Effectiveness of SIT was well documented in many cases and published data. Selection of patients for SIT should be very serious and must include skin test and total and specific IgE measurement. How outcome of SIT correlate with changes of IgE, skin reactivity and overall symptoms reduction is aim of this study.

Material and methods: Skin testing, total and specific IgE measurements were performed before and after each year of treatment. Skin test assessment was performed according to recommendation of Manual of Laboratory immunology. IgE was performed using ELISA method. Clinical outcome was assessed using AQLQ questionnaire.

Results: During five years period 58 asthmatic subjects with home dust and dermaphagoides allergy were treated by SIT. Baseline total IgE was 488.5 IU/ml (SD 78.9), mean specific IgE against dermaphagoides pteronissinus was 36.5 IU/ml (SD 15.2). Subcutaneous tests showed 15-20 mm weal in 43, and more than 21 mm in 15 cases. After 5 years mean total IgE was 227 IU/ml (SD 9.2) and mean specific IgE was 28.2 IU/ml (SD 8.9). Skin tests showed decrease diameter of weal. In 49 out of all patients clinical outcome were very well, and in 9 satisfied (according to AQLQ questionnaire). Using test of correlation, by linear regression, better correlation was shown between of skin testing and AQLQ than in total or specific IgE. So, in vivo skin tests were better predictor for success of SIT, than measurement of IgE.

Conclusion: Results of skin tests in diagnostic assessment of allergy in asthmatic patients were better predictor of successful outcome of SIT than laboratory measurement of total and specific IgE.

MONDAY, SEPTEMBER 3RD 2012
To date, the pharmacokinetics (PK) of salmeterol xinafate (SX) following oral inhalation are only sparsely described in the literature (Kirby, S. et al. Eur J Clin Pharmacol 2001; 56:781-791; Harrison, L. L. et al. 3rd Annual ERS/CPS Health Biomark. Drug Del 2011; 24:1-8). Now, improvements in bioanalytical method sensitivity allow full characterization of the pharmacokinetics of SX following administration of the marketed dose (50 mcg). In 2 studies, healthy adult subjects received 50 mcg salmeterol by oral inhalation as Advair Diskus® (100/50 (100 mcg fluticasone/50 mcg SX, Study 1, 23 subjects, 2 Advar bats) or Advair Disks® 500/500 (500 mcg fluticasone/50 mcg SX, Study 2, 20 subjects). Activated charcoal was not administered to block oral absorption. PK blood samples were collected pre-dose and 3, 4, 5, 7 min with additional serial timepoints to 48 hours (Study 1), or 2, 3, 4, 5, 6, 8 min with additional serial timepoints to 72 hours (Study 2) and processed in two ways: 1) MS/MS/MS assay with a 0.05 pg/mL LLOQ. Peak plasma concentration (Cmax) was 153.59 and 151.58 pg/mL (Advair Batches A and B, Study 1) or 185.49 pg/mL (Study 2). Time to Cmax was 4 and 3 min (Study 1) or 3 min (Study 2). By 12 hours postdose the plasma concentration was <5% Cmax. Elimination half-life was 12.9 and 15.4 h (Study 1) or 13.5 h (Study 2). These results illustrate the importance of early frequent sampling to capture SX Cmax followed by observation to 48 - 72 hours to capture 3 - 5 elimination half-lives.

238. Tobacco use and cessation

P1965

Salmeterol pharmacokinetics following a 50-mcg dose by dry powder oral inhalation to healthy volunteers

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NRT and without NRT was offered to intervention and control groups 2 prospective study to assess the impact of workplace health promotion programs (WHPP) on SC rates conducted in 348 health professionals at 4 outpatient clinics in 12-months period. Average age of patients was 49±12. At first visit 94.8% were diagnosed with COPD GOLD III/IV and 73%-6% with high blood cholesterol, of which 58.2% and 51% respectively were new findings (<p =0.05). By the end of treatment SC rates in intervention group were 46.7% compared to 3.3% of controls (<p =0.001). Increase of lung function was observed in intervention group compared with controls (p<0.01). Stress levels did not increase in 50% quitters and decreased in 35.7% cases. Among participants of WHPP after 12-months in intensive intervention settings (HE interventions+HP handouts) significant decrease of 17% of smoking rates was reached, in reference settings only handouts given no significant changes observed. Prevention of NCD requires systematic identification of smokers and provision of SC assistance at all levels of PHC. Workplaces are ideal settings for HP interventions. Intensive assisted SC interventions significantly increase success rates.

P1968

The INAsma study – Environmental tobacco smoke exposure at home and smoking prevalence in the Portuguese population

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Background: The data on the prevalence of tobacco smoke and environmental tobacco smoke (ETS) exposure in Portugal is scarce, especially after the 2008 smoking bans. Aims: We aimed to: 1) estimate the prevalence of exposure to ETS at home and of tobacco smoking in Portugal; 2) identify variables associated with smoking or exposure to ETS.

Methods: Nationwide, cross-sectional, population-based telephone survey; 6003 individuals participated. ETS exposure at home was defined as exposure to at least one current smoker (CS) at home. A smoker was someone with ≥15 years smoking at least 1 cigarette per day during a year; a CS smoked in the last month. Results: Exposure to ETS at home was reported by 26.6% (95%CI 25.5-27.7), Age <18 years old (OR=1.57, 95%CI (1.72-2.13)), current asthma (OR=1.69, 95%CI (1.26-2.46)), living in households with ≥3 persons (OR=34.31, 95%CI (26.54-59.597.07)), those living in households with ≥3 persons (OR=2.21, 95%CI (5.59-30.27)) and those exposed to ETS at home (OR=14.39 (10.14-20.41)). Conclusion: Exposure to ETS at home in Portugal was higher than previously reported. Children/adolescents and asthma patients had a higher risk of exposure. The prevalence of tobacco smoking was slightly lower than in previous reports.

P1969

Efficacy of smoking cessation assistance in Tunisian women

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Introduction: Smoking is the most preventable cause of death. Although, woman started smoking in greater numbers later than man, she seems to have more difficulties in quitting cigarette than he. Aim: Evaluate the smoking intoxication rate in Tunisian woman and the effectiveness of smoking cessation intervention.

Patients and methods: It’s a prospective study, including 100 women smokers treated for smoking cessation during the period from 2007 to 2010. We recorded data on smoking history, degree of nicotine dependence, strategies of smoking cessation and the most successful intervention after 3 and 6 months.

Results: Mean age of women smokers was 43.6±13.3 years. The mean age of onset of tobacco use was 19.7±6.4 years. The mean duration of exposition was 23.4±12 years, with a mean of cigarettes consumption of 22.1±11 cigarettes/day. Tobacco dependence level was important in 65% of women. A half of them, a low level of education attained, and most of them (71.4%) had unfavourable socioeconomic status. According to HAD test, 20 patients were anxious and 45 patients were depressed. The principal reason of quitting cigarette smoking was health problems associated with cigarette (83.2%). Nicotine replacement treatment was the most strategy prescribed (98%). After the first counselling, 40% were lost of side. Con-
Motivation to quit smoking among patients with atherosclerosis compared to asymptomatic smokers.

The predictors of success or failure in smoking cessation programme (SCP), specific for the Brazilian population have been low studied. We evaluated characteristics influencing the success in a SCP. This non-randomized, prospective and open clinical trial evaluated 172 smokers in a SCP based on cognitive behavioral treatment associated or not with medication therapy. Individuals were followed for 12 months. Statistical analysis was performed using the R statistical software. For quantitative variables (age, pack years index and cigarettes/day) were used t-tests and for qualitative variables (gender, education level, lived with others, smokers, medication therapy, nicotine dependence, socioeconomic, anxiety and depression level) were used χ² test. The influence of epidemiologic characteristics on smoking cessation (SC) in univariate and multivariate analyses was tested, calculating Relative Risks (RR) with confidence intervals of 95% (CI). Variables resulting in P>0.15 for univariate analysis were selected to enter into logistic regression model. Differences were considered significant at P<0.05.

Results: 172 individuals were included, 126 (73%) started treatment, of which 61 individuals (56.4%) quit smoking and according the logistic the individuals who used medication therapy had eight-fold more chances to start abstinence (P=0.002 RR=8.3 CI 3.2-29). Thirty-three percent of individuals remained abstinent for 12 months and smokers with lower socioeconomic level had nine-fold more chances to return to smoking (P=0.005 RR=9.0 CI 2.5-72).

Conclusions: The success rate of this program was 16% and medication, as well as socioeconomic status are predictors of success in SC.

Effectiveness of smoking cessation skills building workshops in educating smoking cessation techniques to Pakistani physicians.

Introduction: Physician advice to quit smoking is an effective component of a smoking cessation strategy. Published data indicates that teaching/training smoking cessation skills to physicians improves their smoking cessation practices and increases quit rates among their patients.

Objective: To determine the effectiveness of smoking cessation skills building workshops (SCW) among local physicians.

Methods: Five one-day SCW were arranged across Pakistani cities. A validated questionnaire assessing attitude and knowledge related to smoking was administered pre-workshops (PRW) and immediately post workshops (POW) attendance.

Results: 113 physicians completed the SCW. 90 were men. Age range was 22-61 years (mean ±SD 37±11 yrs). 72 were GPs, 11 chest physicians, 11 cardiologists, 8 consultant internist and 11 trainee physicians. Post workshop physicians felt 'very confident' about their knowledge to treat nicotine dependence-15.9% (PRW) vs. 64.6% (POW); they felt 'very confident' in discussing the smoking cessation issues with their patients- 52.2% (PRW) vs. 80.9% (POW); their knowledge regarding pharmacotherapy improved- 9.7% (PRW) vs. 49.1% (POW). The 5Ax approach was answered correctly by 17.7% (PRW) vs. 69.9% (POW). Appropriate prescribing of Nicotine Replacement Therapy improved - 38.8% (PRW) vs. 61.1% (POW). Awareness of possible adverse effects of medications enhanced - 46.9% (PRW) vs. 71.1% (POW).

Conclusion: After attending a one-full day smoking cessation skills building workshop, physician’s felt more confident in discussing anti-smoking issues with their patients and their smoking cessation knowledge improved significantly.

Sm score of patients with PAD is higher (8.8 points) than motivation of asymptomatic smokers (8.6 points) whereas the stage of addiction is lower (5.2) in contrast to the control group (5.7)-difference not significant. There is a significantly higher score of Sm and with an apparent association with better education and with poorer and less-educated people. Relapses were common after 6 months of smoking cessation assistance.

Predictors of success in smoking cessation among Brazilian subjects.

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Introduction: Inhaled therapies can only be effective if the patient uses the delivery device correctly and complies with treatment, which in turn may be influenced by their attitude towards the disease and its treatment. Patient education is fundamental to optimizing this, as is their perceived effectiveness of medication. This study explores patients’ attitudes towards inhaled therapy with a view to provide targeted education.

Methods: Forty eight respiratory clinic patients (60% male) completed a self-administered structured questionnaire evaluating attitudes towards their current inhaled therapy.

Results: All respondents considered Inhaler therapy important, and 61% had a good understanding of their lung condition. Although 70% had been given advice regarding inhaler use, 67% did not use these as prescribed (see table). Moreover, 63% had not discussed their concerns with a doctor or nurse but 80% would like more training (73% preferred pharmacists to do this).

Conclusion: This study has identified a need to further address education. A significant proportion of patients do not use their inhaler as prescribed and have some concerns about inhaled therapy, emphasizing the importance of providing patients with adequate information about their disease and treatment at every opportunity to enhance compliance. To aid this, targeted education and training sessions delivered by Pharmacists are being developed.

Pregnancy and smoking: cessation advice and health consequences of CO fetal exposure: An exploratory study.

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Introduction: Fetal exposure to second-hand smoke (SHS) is the most important avoidable cause of fetal morbidity and mortality. Health professionals’ (HPs) cessation advice is crucial, since women may be more prone to change.

Study aims: To evaluate – HPs’ cessation advice, – Fetus exposure to CO and association with anthropometric parameters of the newborn.

Methods: Prospective cohort study. Face-to-face structured interviews were applied to 94 pregnant, followed up at São Sebastião Hospital, mean age 31 years. Newborn parameters were collected from clinical files. We performed “baby CO”. We used chi squared, Mann-whitney, Kruskal Wallis tests, and Pearson’s correlation.

Results: 37% of the participants were smokers (average 6 cigarettes/day). 54% had a smoker partner. 80% reported SHS exposure. 67% were questioned about smoking. 93% of the smokers wanted to change their consumption, but only 7.4% did quit (cold turkey, on their own). The observed decrease in consumption was significantly associated with HP counseling (p<0.05), while cessation counseling was not associated with quitting. Neonates of the smokers were born, on average, 231,30g lighter and with less 0.76 cm of cephalic perimeter (p<0.05).

Conclusions: The majority of pregnant women were advised to change tobacco consumption and was exposed to SHS. Most of the smokers wanted to reduce smoking, but did not want to quit. Cessation counseling was not effective. Nevertheless, all the low consumption, smoking and CO levels were negatively associated with newborn parameters. There is a need to train HPs in cessation counseling, including SHS exposure and partners’ smoking.
Influence of smoking among residents doctors in a tertiary teaching hospital

Francisco Rius, 3, Manuel Garcia

Rationale: An appreciation of the high rate of tobacco use by those with mental illness is important. Although the practice guidelines suggest that intervention useful with the general population should be used, it remains unclear whether mentally ill smokers could benefit from smoking cessation program. The study aims were to determine the abstinence rate among people with or without mental illness, and to identify the factors influencing on it.

Methods: An observational study was conducted on all smokers who participated in the three-months smoking cessation program in our clinic between August 2007 and March 2011. Clinical and tobacco-related variables were assessed.

Results: Of the 370 participants, 105 (28.4%) had mental disorders (mean age: male=52.7 ± 12.8, female=52.5 ± 20). 49 (46.7%) mentally ill patients accomplished the program. The cessation rate at 12 weeks was 49.0% in those with mental illness and 70.4% in those without mental illness (P < 0.01), respectively. Among those with psychiatric conditions, quitters are older (57.7 ± 11.3 and 51.0 ± 10.1, P = 0.035), showed lower exhaled carbon monoxide level (31.8 ± 8.9 and 18.3 ± 11.7, P = 0.037), and lower FEV1 (70.1 ± 22.3 and 83.6 ± 15.9, P = 0.020), compared with smokers. No significant differences were found between quitters and smokers in the average nicotine addiction level, according to the tobacco dependence screen (TDS) test, the average pack-year, and the prescription rate of varenicline.

Conclusions: The quit rate in mentally ill people was lower than in general population. Further studies are needed to modify the cessation interventions that address mental illness.

A pharmacological intervention with varenicline among a lung cancer LDCT screening trial: The MILD experience

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Introduction: Low dose CT screening (LDCT) for lung cancer may be a teachable moment for smoking cessation. We aimed to determine the abstinence rate among people with or without mental illness and assess predictors of smoking cessation in a lung cancer screening trial: The MILD experience.

Methods: A total of 1298 patients (819 males and 479 females) were screened. The average age was 62.3 ± 11.0 years. The average pack-year was 21.9 pack/years, a Fagerström test of 7.5 ± 2.2 points and a slight increase in FEV1 (P < 0.001) was recorded.

Results: Pts with a FEV1 < 80% showed higher CO values than Ctrl at baseline and along the study. Side effects were longitudinally recorded. Pts with a CO ≥ 22.3 and 83.6% < 80% presented more side effects than Ctrl. A significant higher percentage of pts with a CO ≥ 22.3 and 83.6% < 80% (P < 0.001) had more than 50% of them wish to consult Anti-Smoking clinic.

Conclusions: Smoking prevention, in particular the practice of minimal advice, is still prevalent among patients who have acute coronary syndrome and with smoking cessation advice, in contrast with (87%) of non smokers doctors. The incidence of Smoking in the family’s smoker resident doctors was 64.6% in contrast with non smokers (41%).

Burden of smoking in acute coronary syndrome

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The purpose of this study was to evaluate the burden of smoking among patients who had acute coronary syndrome seen at Philippine Heart Center in terms of its outcomes and expenditures.

199 patients (138 males and 61 females) participated in the study. Smoking habits were recorded including their co-morbidities, GRACE and TIMI scores. Financial data were gathered, tabulated and evaluated. Outcomes of ACS were tabulated in relation to patients’ smoking history and were evaluated.

In this study, it shows that among those patients who have acute coronary syndromes, predominantly were smokers, both direct and passive smokers comprising 72% of the patients. In a developing country like ours, the mean amount expended for each patient admitted for acute coronary syndrome who smokes (direct and passive) was two hundred forty-seven thousand two hundred sixty pesos (Php 247,260.00:276,428.00 excluding physician’s professional fee) which is already a sumptuous that drains one’s finances. And of these, for every smoker patient who had acute coronary syndrome, the mean expenses for each person with each admission were Php 217,160.00:226,791.00 for those who survived and were discharged and Php 517,960.00:648,085.23 for those who died. Therefore, smoking is still prevalent among patients who have acute coronary syndrome and with each admission, each patient expend a sumptuous amount of money for the health resources.

Smoking tendencies in physicians and surgeons from Andalusia

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Aim: To obtain relevant information regarding smoking habits, intention of quitting and consumption in the workplace.

Methods and material: General survey on smoking was performed in 15 andalui- sian hospitals in the last quarter of 2010, a questionnaire (written and anonymous) for each person admitted for acute coronary syndrome who smokes (direct and passive) was used. Descriptive study was made using the statistical package SPSS for windows. Study population: medical.

Results: n=1098 (55% men, 45% women). Mean Age 42 years (range 20-66). Smoking Status: Current smoker (14%), occasional smoker (5%), non-smoker (59%), former smoker (22%). Mean Cigarettes 15 per day (1-50). 21% will try to quit in the next 6 months and 22% want to quit right now. 33% of smokers smoked during working hours.

Conclusions: Physicians and Surgeons show low prevalence of smoking, favorably disposed to quit and only one third of them smoke in the workplace.

How France has hijacked tobacco price increase, an effective tool of tobacco control, to increase the financial profits

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Association, OFF (Office Français de Prévention du Tabagisme), Paris, France

Increasing the tobacco products price is a tool to reduce tobacco consumption. The FTCCT announces a 4% decrease of tobacco consumption for a 10% price increase.

The last decade France has experienced two opposite periods with two opposite effects.

Method: We have compared tobacco price increase to sales of cigarettes in France during the presidency of J.Chirac 2002-2007 and the presidency of N.Sarkozy 2007-2012.

Results: In 2003 President Chirac implements the first cancer plan and, among 20 measures against tobacco, a 39% increase of tobacco taxes produce price of cigarettes within 18 months, just after a 12% increase in 2002 (total = 51% increase). The price of Marlboro 20 cigarettes pack has increased of 1.4€. The number of cigarettes sold by year has dropped down from 82 billion to 54 billion (34% decrease).

From 2007 to 2012 the influence of the tobacco industry has been strong in France,
and cigarettes prices have increased 4 times of 6% and a new increase of 7, 5% is anticipated in 2012. These 32% increase of prices has been managed by the tobacco industry. As a result, the sales of cigarettes remain 54 billion a year; nevertheless at the end of 2012 we will have a total increase of cigarettes pack of 1,6 €.

Conclusion: The elasticity of the increase of price on consumption has been very high (0.67) when increase of price is driven by taxes and supported by a strong engagement. The price elasticity is 0.0 when the increase of price is drive by tobacco industry and when tobacco lobbyists may be active anywhere. Article. 5.3 of PCTC on interaction between tobacco industries on politicians may prevent in France failure of tobacco control.

P1981
Is calprotectin a marker of tobacco smoke related inflammation? A pilot study in children
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Objectives: Environmental tobacco smoke (ETS) related inflammation has an anorexigenic effect through affecting the release of appetite-modulating mediators, leptin and ghrelin in two groups (p values are 0.85, 0.87 and 0.42 respectively), but serum calprotectin levels were statistically higher in Group 1 (p=0.003).

Material and methods: A cross-sectional study was performed by searching the smoking status of patients. After signing of questionnaires, parents were phoned and children were invited to supply fasting blood samples in order to measure serum levels of leptin, ghrelin and calprotectin, and to calculate their BMI.

Participants were divided into Group 1, those who are exposed to and Group 2, not exposed to indoor ETS.

Results: There were no statistical difference between BMI and serum levels of leptin and ghrelin in two groups (p values are 0.85, 0.87 and 0.42 respectively), but serum calprotectin levels were statistically higher in Group 1 (p=0.003).

Conclusions: In this study serum levels of calprotectin were found to be higher in children with indoor ETS exposure where no relation was detected with BMI and serum levels of leptin and ghrelin. Increased serum levels of calprotectin might be an indicator of inflammation related to ETS exposure.

P1982
Smoking and metabolic syndrome
Lízra Fontes1, Hanns Moshammer2, Ibrahim Elmadfa1, Institut für Ernährungswissenschaft, University of Vienna, Austria; 2Inst. Environmental Health, Medical University of Vienna, Austria

Background: Smoking causes inflammation and chronic systemic inflammation predisposes to a range of metabolic disorders usually described as metabolic syndrome. This might likely be one pathway leading to cardiovascular disease. Nicotine reduces appetite. Therefore exact control of caloric uptake (and physical activity) is necessary when studying the association between smoking and metabolic syndrome.

Methods: We used data collected during preventive check-ups among 987 employees of a large bank. Health data including routine laboratory parameters were enhanced by a detailed nutritional recall protocol and a standardised physical activity questionnaire. Physical activity and calories uptake were indeed significant predictors of several metabolic outcomes thus proving the data reliability. Associations were investigated using linear regression.

Results: Current smoking (number of cigarettes currently smoked) showed a non-linear association with most outcomes including waist circumference, high density lipids, fasting glucose, and triglycerides. While moderate smoking did not differ significantly from non-smoking the daily consumption of more than 20 cigarettes lead to significantly adverse effects on all these parameters. Adverse effects were more pronounced and roughly linear when cumulative smoking (pack years) was taken into consideration. Smoking also lead to an increase in white blood cell counts indicating an inflammatory response.

P1983
The association of smoking and blood viscosity
Gündüz Cakmak1, Fatma Ates Alkan2, Kazim Korkmaz3, Zuhal Aydan3, 1, 2, Ibrahim Elmadfa1, 1, Fatma Ates Alkan3, Kazim Korkmaz3, Zuhal Aydan3

Objectives: to determine the relationship between smoking and blood viscosity from this point of view. One hundred people were invited and three groups were formed: group 1 composed of ex-smokers, group 2 composed of individuals who had been smoking, group 3 composed of the individuals who never smoked. Measurements of blood viscosity were performed at different shear rates. Since the hematocrit levels can significantly effect viscosity, in order to avoid this, hematocrit levels were fixed at 40.

Table 1. Blood viscosity of groups at different shear rates

<table>
<thead>
<tr>
<th>Group</th>
<th>Hct</th>
<th>BV1</th>
<th>BV2</th>
<th>BV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1–Group 2</td>
<td>0.338</td>
<td>0.699</td>
<td>0.221</td>
<td>0.971</td>
</tr>
<tr>
<td>Group 1–Group 3</td>
<td>0.658</td>
<td>0.138</td>
<td>0.001***</td>
<td>0.642</td>
</tr>
<tr>
<td>Group 2–Group 3</td>
<td>0.459</td>
<td>0.188</td>
<td>0.004**</td>
<td>0.506</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.001.

We think that corrective measures for increased blood viscosity may be important for preventing and/or treatment of related diseases mainly cardiovascular ones.

239. Infections and sepsis in the ICU

P1984
Serum microRNA signatures identified by Solexa sequencing predict sepsis patients mortality: A prospective observational study
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Background: Sepsis is the leading cause of death in Intensive Care Unit. Novel biomarkers and targets of treatment were still needed to improve the mortality.

Our goal of the prospective study was to investigate if serum miRNAs identified in genome-wide scans could predict sepsis mortality.

Methodology/Principal findings: 214 sepsis patients participated in the study. Solexa sequencing followed by qRT-PCR were used to test for differences in the levels of miRNAs between survivors and non-survivors of sepsis patients. miR-223, miR-15a, miR-16, miR-122, miR-193* and miR-483-5p were significantly differentially expressed, and the area under curve of the six miRNAs predictive value ranged from 0.610 (95% CI, 0.523-0.697) to 0.790 (95% CI, 0.719-0.861). Logistic regression analysis showed that sepsis stage, APACHE II score, miR-15a, miR-16, miR-193* and miR-483-5p were correlated to the death of sepsis and area under curve of the six variables predictive value was 0.950 (95% Confident interval, 0.919-0.982), which was much higher than APACHE II score, SOFA score, and procalcitonin with area under curve of 0.782 (95% CI, 0.721-0.851), 0.752 (95% CI, 0.672-0.832) and 0.695 (95% CI, 0.611-0.784), respectively. When the cut off point set at 0.526, the predictive value of the six variables provided a 85.2% sensitivity and a 90.4% specificity. In addition, miR-15a* had highest odds ratio of 9.23 (95% CI, 1.20-71.16).

Conclusion/Significance: Six miRNA expression profiles could be used to predict septic mortality. The predictive value was better than the indicators that used in clinical.

P1985
The effect of peer-to-peer feedback on severe community acquired pneumonia
T.K. Lim1, 2, H.F. Lim1, Jason Phua1, 1, 2, Malcolm Mahadevan1, 1, 2, Medicine, National University Hospital, Singapore; 2Accidents & Emergencies, National University Hospital, Singapore

Delays in intensive care unit (ICU) admission are associated with higher mortality in community acquired pneumonia (CAP). (Phua J, Eur Respir J 2010;36:826.) In 2008 we employed minor severity criteria from the 2007 IDSA/ATS guidelines plus point of care lactate to identify high risk patients in the emergency department.
In July 2010 we implemented peer-to-peer feedback (p2p) on severe CAP in the "Marianthi Simou" Laboratory, 1st Dept. of Critical Care, "Evangelismos" Hospital, University of Athens Medical School, Athens, Greece. This was associated with reduced mortality in severe CAP, without increasing ICU admission rates. (Lim TK, Int. Forum on Quality & Safety in Healthcare 2012).

**Intervention:** In July 2010 we implemented peer-to-peer feedback (p2p) on severe CAP management between ED & ICU teams to improve teamwork and safety. (Haddon DW, et al Am J Med Qual. 2011 Dec 27)

**Results:** From Jul 2010-Dec 2011 we admitted 243 patients with severe CAP in our ICU. ICU admission were delayed in 36% and hospital deaths 22%. Delays in ICU admission increased from 31% in 2010 to 42% in 2011. Nevertheless, there was a small drop in overall mortality (25.5% to 20%) mostly in patients directly admitted to ICU which fell from 26.5% to 17.2%. Mortality in delayed ICU admission was stable (23.9% to 23%). Adherence to the resuscitation bundle was high in 2010: point of care lactate test 91%, antibiotics 97%, intravenous fluids 95% & vaso-pressors 100%. But it fell in 2011 to 84%, 80%, 98% & 86% respectively.

**Conclusion:** In the management of severe CAP p2p was associated with reduction in mortality without increasing early/direct ICU admission rates timely. And sustained p2p feedback may be required to maintain a high degree of adherence to resuscitation bundles and to further improve patient outcomes in severe CAP.

**P1986**

Determining the best diagnostic biomarker for sepsis and prognosis assessment

**Lorenzina Su**1,2, Linxie Xie1,2, Lin Feng1,2, Qing Song1, Hongjian Kang3, Xiangang Liang1, Yanhong Jia1, Dan Feng1. 1Department of Respiratory Medicine, Hainan Branch of Chinese PLA General Hospital, Sanya, Hainan Province, China; 2Department of Respiratory Medicine, Chinese PLA General Hospital, Beijing, China; 3Department of Medical Statistics, Chinese PLA General Hospital, Beijing, China

**Introduction:** Current clinical practice lacks reliable diagnostic indicators for sepsis and its prognosis. The objectives are to describe the value of sTREM-1, sCD163, PCT, CRP, WB and SOFA scores during the course of sepsis, as well as their value in prognosis.

**Methods:** 130 critically-ill patients suffering from medical, surgical and trauma-pneumonia. Aims: To investigate if sEPCR plasma levels of critically-ill subjects at ICU admission ≤24h post ICU admission; all patients were free of sepsis. Demographic data are shown in Table 1. sCD163 and SOFA were recorded on day 1, 3, 5, 7, 10, and 14. Results: On ICU admission day, the sepsis group display higher levels of sTREM-1, sCD163, PCT, CRP, WB and SOFA scores (Table 1, p=0.004, respectively). ICU mortality and PCT tended to be higher in the sepsis group as compared to the non sepsis group (5.1% vs. 0.8%, p=0.004, respectively). ICU mortality and PCT tended to be higher in the sepsis group.

**Conclusion:** Conclusions: High sEPCR, CRP plasma levels at ICU admission (i.e. ≤24h) predict sepsis development.

**P1988**

Role of gallium-67 scintigraphy in the evaluation of occult sepsis in the medical ICU

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Patients in intensive care units (ICUs) frequently have multiple infections or persistent fever despite management. This study was to evaluate the diagnostic contribution of gallium-67 scintigraphy in ICU patients with suspected occult sepsis. One hundred and seventeen patients who had undergone gallium-67 scintigraphy in the ICU of our medical center over a 3-year period were retrospectively reviewed and analyzed. Patients were categorized into Group 1 (n = 84), those with a known infectious source, but who still had persistent fever or sepsis despite antibiotic treatment or abscess drainage; or Group 2 (n = 33), those without an evident infectious source after clinical, physical, and imaging studies. Among these patients, 19 (16.2%) had a new diagnosis. In Group 1, 12 patients (14%) had a new infection, including pneumonia (4 patients), bed sore infection (2 patients), pulmonary tuberculosis (2 patients), leg cellulitis (1 patient), psoas muscle abscess (1 patient), osteomyelitis (1 patient), and infective endocarditis (1 patient). In Group 2, seven patients (21%) had a new infectious source, including septic arthritis (3 patients), osteomyelitis (2 patients), neck abscess (1 patient), and cholecystitis (1 patient).

**Summary:** Gallium-67 scintigraphy helped to detect new or additional infectious sites, particularly bone, joint, and soft tissues.

**P1989**

Peculiarities of an ARDS and respiratory support in patients with severe viral (H1N1) pneumonia

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**Background:** We aimed to evaluate clinical features of an ARDS and effectiveness of sequential differentiated respiratory support (SDRS) in patients with viral H1N1 pneumonia.

**Methods:** Retrospective analysis of 39 patients with severe H1N1 viral pneumonia treated at Respiratory Intensive Care Unit (RICU).

**Results:** Among these patients, 10 patients subsequently developed sepsis and 29 did not. SOFA score (mean±SD: 6.4±2.7) and sEPCR levels (median & IQR: 173.4 (104.5-223.5) ng/mL) were significantly higher in the subsequent sepsis group as compared to the non sepsis group (5.6±3, p=0.037, and 98.3 (69.8-147.7) p=0.004, respectively). ICU mortality and PCT tended to be higher in the sepsis group. Cox regression analysis identified sEPCR as the only parameter related to sepsis development with time (HR: 1.078 & 95% CI: 1.016–1.144, by 10 sEPCR units, p=0.013). When the whole cohort was dichotomized above (≥139.5) and below the sEPCR median (<139.5), the probability of developing sepsis with time was significantly elevated in the high-sEPCR group (Log-Rank test, p=0.028).

**Conclusions:** In our cohort, high sEPCR plasma levels at ICU admission (i.e. ≤24h) predict sepsis development.
undertaken in cases of refractory hypoxemia that lasted for 30-45 min. Mechanical ventilation was carried out in 28 (71.8%) patients in the regime of PCV with "aggressive" parameters: FiO2 - 0.8-1.0, PEEP - 15-20 cm H2O, PIP - 30-40 cm H2O, I:E - 1:1. Vt - 500-600 ml was achieved easily, indicating about preserved lung compliance. All patients required sedation at the beginning of mechanical ventilation in order to synchronize with the respirator. Muscle neuro muscular relaxants was not used. Duration of mechanical ventilation ranged from 7 to 81 days. NIV was excluded from the scheme of SDRS due to inefficiency.

Conclusion: A peculiar form of ARDS, without reducing elasticity of lung tissue, without sepsis, developed in patients with severe viral pneumonia. SDRS consisted of two phases: controlled oxygen therapy and invasive ventilation.

P1990
Overt disseminated intravascular coagulation in severe sepsis associated with specific organ dysfunction and poor survival
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Background: In sepsis, abnormal coagulation cascade cause disseminated intravascular coagulation (DIC). Little is known about the clinical characteristics in overt DIC in severe sepsis.

Objective: To investigate the clinical features and dysfunction of different organ systems in overt DIC in severe sepsis

Methods: This prospective observational study was conducted in the medical intensive care unit in a tertiary medical center in Taiwan. Adult patients admitted for severe sepsis would be enrolled. Patients with cirrhosis or advanced malignancies would be excluded. Baseline patient profiles were obtained, including APACHE II and SOFA scores. Overt DIC was defined according to the scoring system from the International Society on Thrombosis and Haemostasis.

Results: From Oct 2009 to Dec 2011, 248 consecutive patients admitted for severe sepsis were screened for the eligibility, and a total of 100 patients were enrolled. The APACHE II and SOFA scores were 25.9±6.4 and 9.9±3.4, respectively. Only 8 patients (8%) had overt DIC. The 28-day mortality was higher in patients with overt DIC than in those without (62.5% vs. 20.7%, P=0.001). Patients with overt DIC had higher SOFA scores than those without (14.1±4.8 vs. 9.5±4.0, P=0.001). Higher hepatic (P=0.003), cardiovascular (P=0.031) and coagulation (P=0.001) SOFA sub-scores were found in patients with overt DIC, while the respiration, central nervous system, and renal subscores were not significantly different without overt DIC.

Conclusions: In our patients with severe sepsis, overt DIC is uncommon, and is associated with organ dysfunction mainly involving hepatic, cardiovascular, and coagulation systems.

P1991
Remifentanil attenuates LPS-induced neutrophil activation
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Surgical trauma and anesthesia are associated with a complex dysregulation of the immune system with neutrophil activation involving activation of both pro-inflammatory and anti-inflammatory cytokines. Several studies demonstrate that opioids modulate the immune response via opioid receptors expressed directly in the immune cells themselves. Neutrophils play a pivotal role in the coordination and regulation of immune responses. However, the ability of opioid directly participating in LPS-induced neutrophil activation has not been fully examined. In the present experiments, the effects of various opioids including remifentanil, sufentanil, alfentanil and fentanyl were investigated. Remifentanil only could attenuate activation of neutrophils exposed to LPS. In particular, remifentanil decreased LPS-induced activation of intracellular signaling pathways, including p38 mitogen-activated protein kinase (MAPK) and ERK1/2, and expression of pro-inflammatory cytokines, including TNF-a, IL-6 and IL-8. There was no effect of remifentanil on LPS-induced activation of c-Jun N-terminal kinase (JNK) in neutrophils. These results demonstrate that remifentanil can attenuate LPS-induced neutrophil responses and also suggest that such effects are sufficiently important in vivo to play a major contributory role in neutrophil-mediated inflammatory responses by surgical and anesthetic trauma.

P1992
C-reactive protein (CRP) as a marker of disease severity in community acquired pneumonia patients with sepsis
Sanjay Dhawan1, Himayatullah Khan2, Dinesh Babu2, Vivek Gupta2, Ajith Raghavan3, Ajith Raghavan3, Ajith Raghavan3.
1Pulmonology, Ahaliya Hospital, Abu Dhabi, United Arab Emirates; 2Cardiology, Ahaliya Hospital, Abu Dhabi, United Arab Emirates; 3Intensive Care Unit, Dept. of Internal Medicine, Dr. Surat Seth Chest Diseases and Surgery Education and Training Hospital, Erim, Turkey; 4Intensive Care Unit, Surayyya Chest Diseases and Surgery Education and Training Hospital, Istanbul, Turkey

Introduction: C - Reactive Protein (CRP), an early sensitive marker of inflamm-

ation is studied extensively in various common medical disorders. Until recently CRP measurement was not studied widely in Pneumonia. We intended to study its usefulness for assessment of disease severity in patients of Community acquired pneumonia (CAP) with Sepsis.

Objective: To evaluate the utility of C - Reactive Protein as a marker of disease severity in patients of Community acquired pneumonia with Sepsis.

Methods: Study design: Prospective observational study

Setting: 12 bedded ICU of a multi specialty hospital in Abudhabi, UAE.

Subjects: 40 patients admitted during June 2010 - January 2012, fulfilled the study criteria.

Cap and Sepsis were defined based on the ATS and ACCP/SCCM 1992 criteria respectively.

Results: Patients were divided into two groups, Group A with CRP < 300 mg/L and Group B with ≥ 300 mg/L. Mean age being 36.5 and 42.6 years respectively. Characteristic of disease severity were compared in both the groups.

Table. Disease severity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Organ dysfunction ≥ 2 organs</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusion: CRP level of greater than 300 mg/L within first 48 hours of admission to ICU appears to be a good marker of disease severity in patients of Community acquired pneumonia with Sepsis and may be useful to identify high risk patients.

P1993
Impact of experience and education in treatment of adult respiratory distress syndrome (ARDS) using extracorporeal membrane oxygenation (ECMO)
So Wong Kim, Gun Hoon Hong, Yoomsack Koh, Chue Man Lim, Jin Won Huh.
Department of Pulmonology and Critical Care Medicine, Asan Medical Center, Seoul, Korea

Background: Extracorporeal membrane oxygenation (ECMO) is a form of long-term cardiopulmonary bypass and recently have been used to treat adults with respiratory or cardiac failure despite maximal medical therapy. ECMO is a high risk procedure with 25% of mortality rate.

The previous a few studies showed that improving equipment and increased experience to manage ECMO is important to patient survival and improving results. ECMO training program is important in solving significant, life-threatening problems that can occur during ECMO application.

Our aims in this study are to show our experience of ECMO management and reduction in mortality rate according to an accumulation of experience and knowledge.

Method: A nonrandomized retrospective study was performed.

Results: In 2009-2011, ECMO was applied to 82 patients. Veno-venous and veno-arterial ECMO was 63.4% and 36.6%, respectively ECMO was applied to 47 patients in 2009–2010 and 35 patients in 2011. The most common cause of ECMO application was pulmonary problem.

The most common complication of ECMO was bleeding and the most common cause of death was pneumonia. 41.5% of patients were weaned off the ECMO.

Intensive care unit mortality was higher on 2009–2010 than on 2011 (89.4% vs. 57.1%, OR 3.106, CI 1.235-7.812, p=0.014).

Conclusion: According to an accumulation of experience and knowledge, mortality was reduced in 2011 compared to 2009-2010.

P1994
Predictors of mortality in cancer patients requiring intensive care support: Two-centered cohort study
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Aim: Acute respiratory failure (ARF) can be developed in cancer patients due to disease progression or as a complication of treatment. In our study we aimed to identify the factors associated with mortality in cancer patients admitted to the intensive care unit (ICU) due to ARF.

Method: A retrospective-cohort study was planned in two ICUs of training hospital of chest diseases between January 2008 and December 2011 period. Demographic data, type of cancer, cause of ARF, comorbided disease, APACHE II value, type of
treatment, and mortality were recorded from the medical records of cancer patients followed in ICU.

Results: During the study period 463 (373 male) cancer patients were included in the study followed by two-centers in the ICU. The median age of the patients was 65 (57-72). 78% of the patients were lung cancer while 22% of the patients were extrapulmonary cancer and the mortality rates were similar. Cause of ARF in 48% (n=391) of the patients were due to cancer invasion and 12% was infections. APACHE II value was 24 (18-30) and on ICU day was 5 (2-10). Application of invasive and noninvasive mechanical ventilation was respectively 29% and 74%. The mortality rate of the cancer patients in ICU was 54%. APACHE II value was significantly higher in patients who died (p<0.001). The mortality of the female patients were higher (p=0.05).

Conclusion: The mortality is higher than the overall ICU mortality, in patients with advanced cancer who required ICU support. In our study; APACHE II value and female gender are the marker of high mortality in cancer patients developed ARF.

P1996
Extracorporeal membrane oxygenation as bridge in patients with non-iartrogenic massive hemoptysis
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Despite advanced technologies in intensive care, massive hemoptaxis can cause death in a small subset of patients. In special, extensive bleeding, hypoxia, decreased primary function and other comorbidities make it more difficult or impossible to perform bronchoscopy, arterial embolisation or resectional surgery. Extracorporeal membrane oxygenation (ECMO) is expected to provide adequate gas exchange, to reduce ventilator-induced lung injury and, eventually, to improve outcome in patients with respiratory and circulatory failure. However, it is not sure whether it is beneficial or not to perform ECMO in unstable patients with non-iartrogenic massive hemoptaxis. The case applying ECMO to patients with iatrogenic massive hemoptaxis is also very rare. A male with medical history of pulmonary tuberculosis received mechanically ventilator support because of severe community acquired pneumonia. As he abruptly showed severe hypoxemia and hypotension due to massive hemoptaxis, ECMO was instituted. We herein describe detailed course of our case, helping physicians make a decision to initiate ECMO in patients with non-iartrogenic massive hemoptaxis.

P1998
Clinical outcome and prognostic factors of acute respiratory failure due to pneumocystis pneumonia in non-HIV patients
Yousang Ko, Kyoungmon Jeem, Division of Pulmonary and Critical Care Medicine, Samsung Medical Center, Seoul, Republic of Korea

Pneumocystis pneumonia is a potentially life-threatening infection that occurs in immunocompromised individuals. While it is well known that the clinical course of PCP in non-HIV patients differs in HIV-positive patients. But, the ICU mortality of patients with acute respiratory failure requiring mechanical ventilation dose not well known.

The objective of this study was to examine the outcome and prognostic factors of ICU mortality in patients with acute respiratory failure caused by Pneumocystis pneumonia. We conducted a five-year retrospective review (from October 2005 to December 2010) of all patients who had histologic evidence in the non-HIV patients. Of the 44 adult patients investigated, 25 patients (56%) had solid or hematologic malignancies, 17 (33%) had received organ transplantation and 10 (22%) had received corticosteroid. Median P/F ratio on day 1 was 139 (IQR:116-187), SAPS 3 score on day 1 was 46 (IQR:36-58) and SOFA score on day 1 was 7 (IQR:5-9). The ICU mortality in patients with acute respiratory failure caused by pneumocystis pneumonia was high. Especially, the severity on ICU admission and newly developed shock after ICU admission was associated with higher ICU mortality.

P1999
Inhaled colistin on Acinetobacter baumannii treatment
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Introduction: Ventilator associated pneumonia and tracheobronchitis (VAP/VAT) due to multiresistant A. baumannii are preeminent causes of mortality and morbidity at ICU’s. High and/or prolonged duration of mechanical ventilation, mechanical ventilation, duration of hospital stay and the development of ventilator associated pneumonia (VAP) and ventilator associated tracheobronchitis (VAT) are independent predictors of adverse outcomes and mortality. A. baumannii was extensively resistant in almost all cases, being sensitive only to polymyxins in 20% (87%). Mean inhaled colistin dose was 3.5 µg / (1.6-0.6 µg), with a mean duration of 7.8±3.5 days. Systemic colistin was co-administered in 6pts, with 100% eradication rate and 2 of 3 successful cases (87%) were identified. At failure to eradicate or relapse no change in treatment was made. A. baumannii was extensively resistant in all cases, being sensitive only to polymyxins in 20% (87%). Mean inhaled colistin dose was 3.5 µg / (1.6-0.6 µg), with a mean duration of 7.8±3.5 days. Systemic colistin was co-administered in 6pts, with 100% eradication rate and only one relapse. ICU and hospital mortality was 5.3% and 10.6%.

Conclusions: On critical patients, inhaled colistin was effective treating VAP/VAT due to extensively resistant A. baumannii. No change on antibiotic resistance profile was observed after treatment.
P2000

Intensive care unit acquired pneumonia with or without etiologic diagnosis: A comparison of outcomes
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Background: The impact of intensive care unit acquired pneumonia (ICU-AP), without etiologic diagnosis, on patient outcomes is largely unknown.

Objective: To compare the clinical characteristics, inflammatory response and outcomes between patients with or without microbiologically confirmed ICU-AP.

Methods: We prospectively collected 270 patients with ICU-AP. Patients were clustered according to positive or negative microbiologic results. We compared the baseline characteristics and outcomes between groups.

Results: ICU-AP without etiologic diagnosis was found in 82 (38%) patients. In comparison with patients with microbiologically confirmed ICU-AP patients without etiologo confirmed more frequently chronic renal failure (15, 18% vs. 11, 6%, p=0.003), chronic heart diseases (35, 43% vs. 55, 29%, p=0.044), higher hypoxemia (PaO2/FiO2 165±73 vs. 199±79 mmHg, p=0.001) and shorter intensive care unit (ICU) stay before the onset of pneumonia (5.5± vs. 7.9± days, p=0.001). The systemic inflammatory response was similar between groups. Despite similar severity at the ICU admission and onset of pneumonia, in patients with microbiologically confirmed ICU-AP there was higher in-hospital (84, 45% vs. 25, 31%, p=0.043) and post ICU mortality (18.7, 51% vs. 28, 36%, p=0.043).

Conclusion: Microbiologically not confirmed ICU-AP develops earlier and it is associated with better outcomes and specific underlying comorbidities that increase the risk of severe sepsis. Ultimately suggesting a potential misdiagnosis.

Supported by: EC07/90390, SEPAR 2009, FUCAP, Ciberes (Ciberes is and initiative of Instituto Carlos III), IDIAPBS, Curesis AG.

P2001

Post-resuscitation central venous pressure and serum lactate associated with survival in severe sepsis and septic shock
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Background: The survival in severe sepsis and septic shock is improved by quanitative resuscitation, with goals as mean arterial pressure (MAP), central venous pressure (CVP), oxygen saturation of central venous blood (ScvO2), and lactate pressure (CVP), oxygen saturation of central venous blood (ScvO2), and lactate clearance.

Objectives: To investigate whether post-resuscitation MAP, CVP, ScvO2, and lactate level predict the survival in severe sepsis and septic shock.

Methods: A total of 124 patients were enrolled from Aug 2009 to Dec 2011. The APACHE II and SOFA scores were 25±3.0 and 9.9±0.3, respectively. The 28-day mortality was 26.6%. Multi-variates logistic regression analyses showed that CVP (P=0.010) and serum lactate (P=0.011) were associated with 28-day mortality.

Results: The survival in severe sepsis and septic shock, high post-resuscitation CVP and serum lactate were associated with organ dysfunction and high mortality.

P2002

Effect of antibiotic prophylaxis on pneumonia in cardiac arrest patients treated with therapeutic hypothermia
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Background: Infections complications are frequent after cardiac arrest and a few reports have demonstrated that infections may be even more frequent after therapeutic hypothermia. Pneumonia is the most frequent infectious complication in these patient.

Objectives: We investigated the effect of antibiotic prophylaxis on the development of pneumonia in cardiac arrest patients treated with therapeutic hypothermia.

Methods: We retrospectively reviewed medical records of patients who admitted for therapeutic hypothermia after resuscitation of out-of-hospital cardiac arrest between January 2010 and December 2011. Patients dying within the first 72 hours were excluded.

Results: Of the 46 patients admitted after cardiac arrest, 31 patients were analyzed. 24 patients (77%) were treated with prophylactic antibiotics within 24 hours.

P2003

Effectiveness of touchscreen device (iPad) as communication tool for intubated patients admitted at the University of Santo Tomas Hospital Apolonio Javier Jr.1, Patrick Gerard Moral2;1 Pulmonary and Critical Care Medicine, University of Santo Tomas Hospital, Manila, Philippines; 2Pulmonary and Critical Care Medicine, University of Santo Tomas Hospital, Manila, Philippines

Objectives: To improve the communication between intubated patients and health-care providers using iPad. Specifically, (a) we would like to determine if the level of frustration of intubated patients in the ICU while using touchscreen device (iPad) as a communication tool (b) determine the helpfulness of touchscreen device (iPad) as a communication tool between intubated patients in the ward/ICU and health care providers.

Subjects: (1) more than 18 years old, (2) able to read, speak and understand either English or Filipino, (3) oriented to person, place, time and situation at the time of interview, (4) Glasgow Coma Score 11 (Eyes 4, Verbal 1, Motor 5), (5) competent and able to sign an informed consent form; hemodynamically stable and (6) required intubation for at least 18 hours.

Design: A pilot observational descriptive study design.

Results: Patients level of frustration while intubated, eighty-eight percent (88.46%) of the sample reported extreme levels of frustration when communicating with other people while intubated. Seventy-seven percent (77.49%) reported their experience as very frustrating. Almost four percent (3.85%) reported their experience as frustrating. Almost four percent of the patients (3.85%) reported their experience to be somewhat helpful, fifteen percent (15.38%) reported their experience to be neither helpful, almost four percent (3.85%) reported their experience to be most helpful, and seventy-six percent (76.92%) reported their experience to be extremely helpful when iPad was used as a communication tool.

P2004

The usefulness of high resolution computed tomography in burned patients with inhalation injury
Cheol-Hong Kim, In-Gyu Hyun. Department of Internal Medicine, Hallym University College of Medicine, Seoul, Republic of Korea

Background: Smoke inhalation may affect both airway and lung parenchyma. Then, airway injury can be easily assessed by bronchoscopy, but lung parenchymal injury may be evaluated by other imaging modalities. The aim of this study is to assess lung parenchymal injury by high resolution computed tomography (HRCT) in burned patients who had been identified inhalation injury bronchoscopically.

Methods: The bronchoscopy with biopsy at carina or 2nd carina and HRCT were performed in burned patients with inhalation injury initially after admission. Positive HRCT findings include peribronchial ground glass appearance with or without consolidation, bronchial wall thickening, branching linear attenuation, atelectasis, interlobular septal thickening and bronchiectasis. We analyzed APACHE II scores, PF ratio, the need for mechanical ventilation care, pneumonia and degrees of airway injury according to HRCT findings.

Results: 22 burned patients were enrolled. Bronchoscopy was performed in all and HRCT in 19. Of those, 10 patients (52.6%) showed positive HRCT findings. Between positive and negative HRCT, age, burn size and initial COHb were not significant different (43±17 vs. 37±11.8, p = 0.08; 14±9/21.76 vs. 0.56±0.73%, p = 0.05; 6.2±6.76% vs. 11.5±8.64%, p = 0.05). Positive HRCT

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findings were closely associated with more frequencies of mechanical ventilation and pneumonia, and higher APACHE II scores and PF ratio, and more severe airway injury.

Conclusions: HRCT in burned patients with inhalation injury may be useful to assess lung parenchymal injury and to guide further therapy because radiographic evidence for lung parenchymal injury may predict the severity of inhalation injury.

P2005
Clinical analysis of patients treated with mechanical ventilation in an emergency respiratory ward
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Aim: To make analysis of indications, duration, complications and outcome of the mechanical ventilation in patients treated in the Emergency Respiratory Ward.

Data and methods: A retrospective analysis of the patients in the Emergency Respiratory Ward treated with mechanical ventilation during the last 5 years (2007-2011) has been made. 191 patients (10,33%) from the total number of patients (1848) needed mechanical ventilation.

Results: The percentage of patients, treated with mechanical ventilation, does not differ substantially during the studied years – from 10,81% in 2007 to 11,68% in 2011. The most common reason for heavy respiratory insufficiency, demanding mechanical ventilation, is pulmonary pathology (81,67%) as the greatest percentage belongs to those patients with diagnosis and its complications (pneumonia) – 134 patients (85,90%). The most common reasons from the non-pulmonary pathology are alveolar hypoxemia in case of extreme obesity, chest deformations, left-sided cardiogenic failure.

The usual duration of mechanical ventilation is 15 days as there are no significant differences in the studied years – from 77,14% to 87,10%. 7 of the patients (3,66%) have a verified diagnosis ventilator-associated pneumonia.

The total number of patients with lethal outcome is 66 (34,50%) as there are no significant differences in the studied years.

Conclusion: About 10% of the patients, treated in Emergency Respiratory Ward, need mechanical ventilation as the most common pulmonary pathology is COPD. Prognostic problematic flora, most often Gram-/ -strains are isolated in tube secrets, which significantly deteriorates the prognosis and leads to lethality in 34,50% of the cases.

P2006
BiPAP in advanced IPF: Hope for palliation?
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Introduction: IPF poses challenges in patient management due to limited treatment options particularly in countries without option of lung transplantation. BiPAP was offered to patients admitted with acute exacerbation of IPF worsening of disease as a final non invasive supportive measure. We report 7 such patients of advanced IPF treated in our hospital.

Methods: 7 patients with advanced IPF and optimal medical management were included. Pharmacotherapy included pirfenidone (1 did not tolerate), NAC, PPI and prednisolone. BiPAP was administered as final non invasive supportive measure. We report 7 such patients of advanced IPF treated in our hospital. In clinical courses, they showed ARDS and were moved to ICU and died and were autopse. The lungs and other organs were pathologically investigated what is the pathophysiological findings of clinical ARDS. Elastic stain, Al-PAS stain and immunohistochemistry for type I and IV collagen, a smooth muscle actin and Ki-67 were used. The periods of clinical ARDS and the estimated stages of DAD were compared and clinic-pathologically analyzed.

Results: A half of ARDS states were clinically diagnosed as ARDS while the other was aspergillosis with CMV pneumonia. Some cases also showed pathologically acute pneumonia, though the lesions of pneumonia are localized in the proximal portion of organized DAD. These findings mean the lesions of pneumonia appear after DAD.

Conclusion: It is confirmed that DAD itself mainly causes ARDS in the patients associated with chronic underlying diseases under the treatment in a hospital.

P2007
The impact of paramedics' education on controlled oxygen prescribing for patients with acute exacerbations of COPD during ambulance transfers on outcomes
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Introduction: Oxygen is a drug and should be administered with caution and only when indicated using the principle of target oxygen saturation (British Thoracic Society-BTS emergency oxygen guidelines, 2008) particularly in those at risk of Type 2 Respiratory Failure (T2 RF) like COPD patients.

Aims: To reduce complications of excessive use of oxygen during ambulance transfers in patients with acute exacerbation of COPD.

Methods: Ambulance paramedics within Salford, UK were offered education on the BTS acute oxygen therapy guidelines that included lectures and written material with supplementary access to on-line training. The education focused on the principle of using target O2 saturations and controlled oxygen delivery to guide oxygen therapy in patients transferred to hospital with suspected exacerbation of COPD.

Results: Total of 63 paramedics were trained. Over the 3 months evaluation period post training, 75 (21 males) patients with COPD exacerbations were transferred by ambulance to the local hospital, 10 of whom were transferred by trained paramedics. No differences were noted between the 2 groups of patients in relation to first blood gas results (pH, PCO2, PO2), length of stay and number of days readmissions. Fewer patients in the trained paramedics group needed NIV within 24 hours of admission, were admitted to ITU, or died in hospital.

P2008
Clinico-pathological analysis of acute respiratory distress syndrome (ARDS)
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Purpose: ARDS is a severe disease and the therapy is not completely established and the pathophysiology is still controversial. There is a report one third of clinically diagnosed ARDS in the Intensive Care Units (ICU) were pathologically not diagnosed alveolar damage (DAD), but were pneumonia, hemorrhage and so on. In this context, we clinicopathologically studied the autopsy cases with clinically diagnosed ARDS in our hospital.

Methods: The 20 patients had originally chronic diseases and were treated in our hospital. In clinical courses, they showed ARDS and were moved to ICU and died and were autopse. The lungs and other organs were pathologically investigated what is the pathophysiological findings of clinical ARDS. Elastic stain, Al-PAS stain and immunohistochemistry for type I and IV collagen, a smooth muscle actin and Ki-67 were used. The periods of clinical ARDS and the estimated stages of DAD were compared and clinic-pathologically analyzed.

Results: A half of ARDS states were clinically diagnosed as ARDS while the other was aspergillosis with CMV pneumonia. Some cases also showed pathologically acute pneumonia, though the lesions of pneumonia are localized in the proximal portion of organized DAD. These findings mean the lesions of pneumonia appear after DAD.

Conclusion: It is confirmed that DAD itself mainly causes ARDS in the patients associated with chronic underlying diseases under the treatment in a hospital.

P2009
Usefulness of noninvasive ventilation in patients with acute respiratory failure admitted in the intensive care unit (ICU) – Experience of a Portuguese ICU
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Introduction: Noninvasive ventilation(NIV) is a safe and effective mean of improving gas exchange in patients with many types of acute respiratory failure(ARF).

Study design and patient selection: Retrospective observational study to access the usefulness of NIV in patients with ARF submitted to mechanical invasive ventilation(MIV) admitted to the ICU(Santa Luzia Hospital Viana do Castelo, Portugal). We enrolled adults with ARF admitted to the ICU in 2011. Patients were analyzed globally and in two subgroups: patients that received MIV and NIV and patients that received only MIV,recording various parameters, namely, comorbidities, diagnosis, SAPS II, APACHE II, presence of hypercapnia, pH, pCO2, MIV duration, number of days in the ICU and release condition. The two groups were compared by the Chi-square and Mann-Whitney tests.

Results: 104 patients were included, mainly admitted for pneumonia (52%), other causes of ARF (23%) and COPD exacerbation/hypercapnic acidaemia (HA) (13%). 22 (21%) received MIV and NIV and 92 (97%) only MIV. When analyzed the differences between groups, was found statistical significant differences regarding the diagnosis (p=0,002), presence of hypercapnia (p=0,005), MIV time (p=0,015) and number days in the ICU (p=0,001), but no differences when compared co- morbidities, SAPS II, APACHE II, nutritional status, social dependence or release condition.

NIV was used in patients with HA (36%) and difficult weaning (63%).

Conclusion: NIV was effective in reducing the MIV time and number of days in the ICU probably because,in selected patients, it reduces the risk of ventilator-associated pneumonia,however no significant difference in mortality was observed.
P2010 Factors associated with the requirement of ventilatory support during an acute exacerbation of COPD
Rosalind Benson, Anne Pocock, Nosheen Kazmi, Syed Huaq, Sanjeev Agrawal. Respiratory Medicine, St. Helena and Knowsley Teaching Hospitals NHS Trust, Prescot, United Kingdom

Background: Identification of high-risk patients is important. Identifying high-risk patients based on age and sex on admission. They also had a relatively better PS. Admission glucose and lactate levels were also important factors. Identifying high-risk patients based on these factors can improve clinical outcomes.

Methods: A retrospective study of consecutive patients admitted with AECOPD in an acute teaching hospital.

Results: 67 patients (45% male) with a mean (SD) age of 72 (12), % predicted FEV1 of 55 (20) and baseline ECGOQ performance status (PS) of 2 (1.2) were studied. 10 (15%) required invasive or non-invasive ventilatory support at some point during their admission.

Baseline characteristics and admission parameters

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Admitted norm</th>
<th>Not ventilated norm</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 (11)</td>
<td>73 (13)</td>
<td>0.38</td>
</tr>
<tr>
<td>% predicted FEV1</td>
<td>67 (3)</td>
<td>54 (21)</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline PS</td>
<td>1 (2.25)</td>
<td>2.14 (1.14)</td>
<td>0.005</td>
</tr>
<tr>
<td>No. of admission in the preceding year</td>
<td>1.2 (1.7)</td>
<td>1.1 (1.4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Admission serum glucose, mmol/L</td>
<td>8.1 (3.9)</td>
<td>6.8 (1.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Admission SpO2</td>
<td>88 (9)</td>
<td>94 (3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Admission lactate, mmol/L</td>
<td>1.5 (0.8)</td>
<td>1.2 (0.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Admission respiratory rate</td>
<td>24 (10)</td>
<td>21 (5)</td>
<td>0.04</td>
</tr>
<tr>
<td>pH</td>
<td>7 (0.9)</td>
<td>7.42 (0.06)</td>
<td>0.21</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>6.85 (1.81)</td>
<td>5.51 (1.15)</td>
<td>0.004</td>
</tr>
<tr>
<td>PaO2, kPa</td>
<td>9 (2.6)</td>
<td>10.2 (3.8)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Values presented as mean (SD).

Conclusions: Patients with AECOPD who subsequently required ventilatory support had a significantly lower SpO2, higher PaCO2 and a higher respiratory rate compared with the Aerogen T-adapter (305.6±9.3 mg vs 142.4±1.9 mg, p<0.001) corresponding of an increasing of a factor 2 in term of output rate with Combihaler (7.1±0.2 mg/min vs 3.4±0.2 mg/min; p<0.001). The mass of salbutamol deposited on the filter was 2.3 fold higher with Combihaler chamber in comparison with the T-adapter (43.5±0.63 μg vs 18.8±1.9 μg, p<0.05).

P2013 Predictors of 1-year mortality at hospital admission for acute exacerbations of COPD – A real-life study
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Background: Acute exacerbations of COPD (AE-COPD) are related to high mortality, especially when hospitalization is needed. Predictors for severe outcomes are still not sufficiently defined which constrains optimal management.

Methods: A retrospective, observational cohort study including all consecutive patients admitted to the pulmonary ward of the University Hospital Maastricht between January 1, 2009 and April 1, 2010 for AE-COPD. Potential predictors were assessed at initial presentation and at the emergency room. Primary outcome was mortality at 1 year. Univariate and multivariate time-to-event analysis using Cox proportional hazard models were used for statistical analysis.

Results: 260 patients were enrolled. The mean age was 70.5±10.8 years, 50.0% were male and 63.4% had advanced COPD. In-hospital mortality rate was 5.8% and the 1-year mortality was 27.7%. Independent risk factors for mortality were age (Hazard Ratio [HR], 1.04; 95% confidence interval [CI], 1.01-1.07), male sex (HR, 2.00; 95% CI, 1.15-3.48), prior hospitalization for AE-COPD in the last 2 years (HR, 2.56; 95% CI, 1.52-4.30), prior recorded congestive heart failure (HR, 1.75; 95% CI, 1.03-2.97), PaCO2 >3.0 kPa (HR, 2.90; 95% CI, 1.65-5.09) and urea >8.0 mmol/L (HR, 2.38; 95% CI, 1.42-3.99) at admission.

Conclusions: Age, male sex, prior hospitalization for AE-COPD in the last 2 years, congestive heart failure, hypercapnia and elevated levels of urea at presentation are independent predictors of mortality within the first year after admission.

P2014 Airflow limitation in critical care patients with respiratory failure: Incidence and clinical effects
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Background: Airflow limitation (AF) is the most common arrhythmia in general population and among the critically ill patients. If not treated appropriately it might be an important cause of mortality and morbidity.

Aim: To determine the incidence of AF among critically ill patients and to evaluate its effect on ICU outcome.

Material and method: The ECGs of all the patients (both intubated and nonintubated) at admission were evaluated prospectively for the presence of AF. Patients were grouped into two as AF+ and AF- and compared for their ICU outcomes, cardiac and bronchodilator therapies.

Results: A total of 147 patients (76 male, 71 female) with the mean age of 68±15 years were included in the study. AF was found in 36 (25%) patients and among them 33 were diagnosed and received treatment before ICU admission. Although no significant difference was identified at admission APACHE II, length of MV and NIMV, length of ICU stay, mortality was higher in AF+ patients (36% vs 21%, p<0.05). Congestive heart failure, history of cerebrovascular event and acute renal failure development was significantly higher in AF+ patients (p<0.05). No significant difference was identified between the two groups when their pre and post admission bronchodilator therapies were compared. Among the 23 discharged patients with AF, 12 (52%) were discharged with warfarin and 11 (48%) with LMWH.

Conclusion: Airflow limitation must be given great importance and must be treated appropriately since it can be seen in 25% of critically ill patients and it must be treated in order to prevent the incidence of heart and renal failure and mortality is higher in those patients.
P2015 Attitudes to oxygen prescription
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Background: The BTS guidelines for emergency oxygen use in adults were published in 2008 to ensure the evidence-based safe usage of this commonly given drug. Four national BTS audits have repeatedly shown poor prescription and delivery of oxygen. This was reflected in our data at the Queen Elizabeth Hospital, Woolwich, a 500-bed district general hospital. We investigated the cause of poor oxygen use despite mandatory oxygen prescription (trust guidelines) and incorporation on the bedside prescription chart.

Methods & results: We distributed a survey to medical, nursing, and pharmacy staff. 113 responses were obtained. Assessment of oxygen knowledge was generally good among doctors, but 56% of nurses had not had any teaching on the subject. Amongst doctors 75% felt oxygen would be given no matter what the prescription stated and 60% felt that nurses did not look for the prescription on the drug chart. The majority did not believe that it was onerous to prescribe or that blanket provision of oxygen was harmless. Amongst nurses 47% felt that using oxygen prescription was onerous. 44% rarely or never signed for oxygen on ward rounds, and only 42% had changed the delivery device or flow rate independently despite prescription. 40% of pharmacists felt that it wasn’t a part of their role to check oxygen prescription and 50% thought that oxygen would be given regardless of a prescription.

Discussion: Despite recognizing its importance, there are significant attitude barriers to better oxygen prescription. As a result doctors don’t prescribe oxygen as they believe nurses will ignore the prescription and nurses don’t sign on the chart as oxygen isn’t prescribed. Attitudes towards oxygen prescription need to be radically changed to improve matters.

P2016 The noninvasive ventilation results of critical stable hypercapnic patients in an intensive care unit

Introduction: The application of noninvasive ventilation (NIV) in respiratory assistance (RA) has been defined. The data about use of NIV in patients without RA for treating hypercapnia is limited. Aim: We aimed to study the results of NIV application for critical hypercapnic patients with terminal disease in an intensive care unit (ICU).

Methods: Study design: single center, retrospective cohort study. Setting: 22 bed medical ICU in a research and training hospital. Study period: January 2010–December 2011. Patients: Hypercapnic (PaCO2 ≥ 55 mmHg) critical respiratory patients with RA (pH < 7.35) who had no contraindications for NIV. ICU severity score (APACHE II), demographics, duration of NIV, arterial blood gas (ABG) results at admission, during NIV, nasal O2 and on last ICU day. ICU days and mortality were recorded from patients’ records. Patient data were given as median and interquartile ratio (IQR, 25%-75%).

Results: Of 2103 patients admitted to ICU in study period, 582 (2.7%) patients with inclusion criteria were retrieved. PaCO2 value at admission, during NIV, nasal O2 and last day of ICU were 74 (69-82), 67 (61-79), 74 (63-80) and 50 (66-76) mm Hg, respectively (p < 0.001) and PaO2/FIO2 values at admission and discharge were 186 (143-235) and 240 (202-282), respectively. APACHE II score, duration of NIV as hours (h) on first and last day were 16 (12-18), 13 (9-14) and 6 (4-10), respectively. Days of ICU was 6 (4-9) and mortality in patient population was 4.3% (n=2).

Conclusion: The improvement of hypercapnia in critical patients without RA can be achieved by intense and regular application of NIV in ICU. Those patients should be considered for long term home NIV support.

P2017 Intensive care unit mortality of critically ill patients in first 24 hours: A single center 4-year cohort study
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Aim: There is limited number of studies examining the clinical features of patients who died within 24 hours of intensive care unit (ICU) admission. In our study we investigated whether these group of patients are in their terminal stage of disease or not.

Methods: Study design: Retrospective cohort study. Single center. Study place: 22 bed ICU of tertiary research and training hospital. Study period: January 2008–September 2011. Patients and data: All patients died within first 24 hours of ICU admission during mentioned period were included. Demographic data of patients, ICU severity scores (APACHE II), ICU time, data of ICU entry and death were recorded. Terminal stages of patients were identified by evaluating existence of advanced stage of chronic diseases (cancer, pulmonary parenchymal diseases, neurological diseases) and their functional life performance of last 3 months (Karnofsky performance scale). Statistics: Results are recorded as median and inter quartile ratio (IQR).

Results: Within the specified period 16 (n=447) of 2787 patients died 96% (21) of these patients who died within the first day of ICU admission were included in the study. Patients’ values were found as for age and APACHE II: 68 (56-76), 32 (26-36) respectively. Distribution of 48 (5%) patients who meet the definition of terminal illness from 2008 to 2011 were as follows: Group 1: 56% (n=26), 46% (n=24), 51% of patients died in first hour while 50% of them died in the first 9 hours.

Conclusion: Considering the presence of terminal disease in the half of the patients who died in the first day of ICU admission, we recommend to follow the group of patients in the special units outside the ICU as national health policy and planning.

P2018 Does severity of obesity effect intensive care outcome of patients with obesity hypoventilation syndrome?
Nalan Adığüzel, Zuhal Karakurut, Gökyü Güngör, Özlem Yazıcıoğlu Moçin, Merih Balci, Cüneyt Saltırık, Feyza Kargin, Hurye Berk Takir. Intensive Care Unit, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

Aim: Aim of study is to investigate the effect of severity of obesity on intensive care (IC) outcome of obesity hypoventilation syndrome (OHS) patients admitted to ICU with acute respiratory failure (ARF).

Method: Study is designed as retrospective cohort study between June 2009–2011 at ICU of teaching hospital. Patients with hypercapnia (PaCO2 ≥ 45 mmHg) and body mass index (BMI) ≥ 30 kg/m2 were grouped according to BMI ≥ 30 and group 1; and ≥ 40 as group 2 (morbid obesity). Demographic characteristics, comorbid diseases, blood gases (ABG), invasive and noninvasive mechanical ventilation, ICU length of stay (LOS), mortality of groups are compared. Results are recorded as median and inter quartile ratio (IQR, 25%-75%).

Results: 149 OHS patients were included, 86 patients in Group 1, 66 patients in group 2. Respectively, patients median age was 66 (55-71), 61 (55-70) years; admission APACHE II score 16 (15–20), 18 (16–23); admission PaCO2: 75 (69–86), 78 (67-85); PaO2/FIO2: 173 (149-216), 180 (155-230) were similar. IMV application was 93% and 89%, NIV application was 99% and 93%. The falling rate of PaCO2 below 45 mmHg was 55% and 75%, respectively and difference was significant (p<0.015). LOS and mortality rates were similar between groups. Device reporting for home ventilation was 40% for group 1 and 64% for group 2 (p<0.026). COPD/asthma coexistence was 40% at group 1 and 1.6% at group 2 (p<0.001).

Conclusion: Obesity and morbid obesity don’t alter ICU outcome of patients with OHS and ARF. COPD and asthma comorbidity cause persistent hypercapnia independent of BMI. Improvement in hypercapnia in morbid obesity without comorbidity is better.

P2019 Does technology matter? One intensive care unit’s experience
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Background: Pneumatic nebulizers (PN) can add significant flow to the circuit and can harbor harmful pathogens. Use of a portable mechanical ventilator (MV) often results in incomplete nebulization with retrograde contamination from the patient. Vibrating mesh nebulizers (VMN) have a physical barrier between the aerosol pathway and the medication reservoir, reducing risk of contamination. We hypothesized that VMN would provide more effective therapy and potentially reduce the risk of VAP.

Method: The Neuroscience ICU Respiratory Therapists initiated a PI project, trialing a VMN (Aerogen, Galway, Ireland), locating one controller in each room to avoid cross-contamination issues as part of a VAP reduction strategy. All medicated aerosol was permed by VMN. Cumulative data was compiled for the 12 months prior. The new method (VMN) was used for 9 months, resuming the old method for an additional 60 day period (to act as an additional control)

Results:

<table>
<thead>
<tr>
<th></th>
<th>12 Months Prior</th>
<th>9 Months</th>
<th>60 Days Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Old Method)</td>
<td>(New Method)</td>
<td>(Old Method - Control)</td>
</tr>
<tr>
<td>Average Ventilator Days</td>
<td>5.62</td>
<td>3.95</td>
<td>4.87</td>
</tr>
<tr>
<td>ICU Length of Stay</td>
<td>4.52</td>
<td>3.51&lt; (p&lt;0.05)</td>
<td>3.72</td>
</tr>
<tr>
<td>VAP Rate (1000 Vent Days)</td>
<td>4.05</td>
<td>3.87</td>
<td>3.83</td>
</tr>
</tbody>
</table>

Use of VMN resulted in a 15% drop in vent days, with a 19% increase during the 60 day return. LOS decreased by 28.7% during the study period. There was no statistically significant change in the VAP rate, possibly due to the change in weight value from the decreased vent days.

Conclusions: VMN was preferred by the therapists. In this instance, the advent of technology was felt to make a significant impact on patient care. Further study of the impact of choice of aerosol delivery device on patient outcome is indicated.

P2020 Determination of critical threshold value of SPO2/FIO2 ratio in the diagnosis of acute lung injury
Rhea Lorello Iani, Encarnita Limpin, Rommel Bayot, Teresita De Guia, Fernando Ayuyao. Division of Pulmonary and Critical Care Medicine, Philippine Heart Center, Quezon City, Metro Manila, Philippines

The determination of the critical threshold of S/F ratio for ALI/ARDS was conducted and evaluated. Corresponding measurements of PF and SF ratio was obtained from 106 intubated patients with the diagnosis of Respiratory Failure. Type I, non cardiogenic(ALI) admitted in the intensive care units of Philippine Heart Center from June 2008 to December 2011. A Linear Regression Model [S/F = 29.6 ± 1.09(F/P); p < 0.000] was obtained to determine the critical threshold of the SF ratio among Filipino patients. A correlation coefficient of 0.804 was obtained between the P/F and S/F ratio which yielded the critical threshold for SF ratio of 248 for P/F ratio < 200 and a critical threshold SF ratio of 357 for P/F ratio < 300. Analysis between ROC AUC of 0.645 and the inverse of FiO2 correlates with P/F and SF ratios. The SF ratio threshold of 248 (corresponding to P/F < 200) yielded a sensitivity of 100% and specificity value of 96.23% with a likelihood ratio of 26.5 (95%CI: 6.80 – 103.20) for ARDS, while SF ratio threshold of 357 (corresponding to P/F < 300) had a sensitivity and specificity of 100% and 98.19%, respectively with likelihood ratio of 66.23 (95%CI: 18.8 – 283.8) for ALI. The high correlation between the SF and PF ratio and critical as well as the consistent relationships between ROC AUC and inverse FiO2 vs. P/F ratio, excellent sensitivity and very satisfactory specificity for ARDS and ALI indicate that the threshold SF ratio of 248 and 357 for SF ratio of 200 and 300 can measure and discriminate ARDS and ALI among critically ill Filipino patients.

P2021 Influence of the pattern of admission on the outcome of patients admitted to a respiratory intensive care unit: Does the step-down pathway differ from the step-up one?
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The influence of the location prior to the admission in a Respiratory Intensive Care Unit (RICU) on the patients’ outcome has never been assessed. We have evaluated the clinical outcomes and prognostic indices, according to their provenance, in 175 consecutive patients admitted over 1 year period in our RICU. 37% of the patients were admitted directly from the Emergency Room (ER), 27% from one of the referring wards (RW), 18% from our Respiratory ward (RW) and 18% transferred from other medical wards (OWs). Patients transferred from our RW had a significantly higher SAPS II score (44±10 vs 34±13, 34±13 and 44±14, for ER-ICUs and OWs, respectively), a lower albumin (2.9±0.5 vs 3.2±0.6 and 3.6±0.5 for ICUs and ER, respectively). All the other clinical variables were similar except for CHF that was lower in those patients admitted from the ICUs. Mortality rate was significantly higher in the patients transferred from our RW and OWs (15%, 18%, 38% for ICUs and ER, respectively). A Cox multivariate analysis and the mortality risk (Hazard ratio) showed that an high SAPS II score (p<0.0154), low albumin levels (p<0.0024), non invasive mechanical ventilation (NIV) (p<0.004) and congestive heart failure (p<0.0481) were significantly associated with the mortality rate. In conclusion, when our RICU acts as “step-down” the mortality rate is lower than when it acts as “step-up”, probably because these latter patients are admitted in end-stage conditions. NIV was surprisingly correlated with a high mortality risk, because in a large subset of patients it was used as ceiling treatment.

241. Noninvasive ventilation for weaning and acute exacerbation management of airway obstruction

P2022 Invasive and noninvasive ventilation in adults hospitalized with asthma in Portugal - Nationwide data from 2000-2010
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Introduction: Few studies have addressed the use and outcomes of invasive (IV) and noninvasive positive pressure ventilation (NPPV) in severe asthma exacerbations.

Objective: To describe the use of IV and NPPV in patients hospitalized due to asthma in Portugal from 2000 to 2010.

Methods: Retrospective study of inpatient records with principal diagnosis of asthma, age ≥ 18 years, in acute care hospitals of the national healthcare system (N=85) in mainland Portugal, with discharges between 2000 and 2010 (N=17,446). Analysis of all episodes that included IV and NPPV that were identified using ICD-9-CM (codes 93.9x and 96.7x). The Charlson/Deyo index, a comorbidity risk adjustment measurement, was used.

Results: In 1,041 episodes (6%) ventilatory support was needed: NPPV 2.3% and IV 3.6%. NPPV use increased from 17 to 79 cases, mainly after 2007, while IV use decreased over the years. Length of stay (days) was similar in both ventilation procedures. Mortality for IV was significantly higher than for NPPV (15% vs. 2.2%).

Conclusion: NPPV is increasingly used in severe exacerbations. Patients treated with NPPV have a lower mortality rate despite of being older and having an increased comorbidity risk index. Prospective studies are strongly needed.

P2023 Non invasive proportional assist ventilation in management of severe asthma exacerbation
Khaleed Hasween, Mohamed Metwally. ICU Unit of Chest Diseases Department, Assiut University Hospital, Assiut, Egypt

Background: NIV could be beneficial in selected patients with severe asthma exacerbation (SAE). However, its role is still not well defined.

Objective: To evaluate the efficacy of NIV using proportional assist ventilation (PAV) in SAE after failure of conventional medical treatment (CMT).

Patients/Methods: Thirty patients with SAE were failed to respond on CMT. NIV was applied via face mask as a last resort before intubation.

Results: The mean age was 39 ± 9.7 with female predominance (19 females Vs 11 males). The successful outcome was achieved in 23/30 patients (76.6%). Follow up of respiratory distress and gasometric parameters after 1 hour NIV in successful group was shown in table 1.

Table 1. Follow up of respiratory distress and gasometric parameters after 1h NIV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional therapy</th>
<th>1h NIV</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Heart rate</td>
<td>125 ± 9.5</td>
<td>107 ± 6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>38 ± 3.3</td>
<td>25 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.04</td>
<td>7.36 ± 0.04</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PaCO2</td>
<td>55.3 ± 8.4 mmHg</td>
<td>42.5 ± 2.1 mmHg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaO2</td>
<td>58 ± 8.4 mmHg</td>
<td>87 ± 9.5 mmHg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 predicted</td>
<td>30 ± 7.4</td>
<td>64 ± 6.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: NIV can relieve respiratory distress and improve gas exchange in majority of patients with severe asthma exacerbation who are candidate for intubation after failure of CMT.

P2024 Mixed acid-base disorders, hydroelectrolyte imbalance and lactate production in hypercapnic respiratory failure: The role of noninvasive ventilation
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Hypercapnic COPD exacerbation in patients with comorbidities is complicated by
mixed acid-base, hydro-electrolyte and lactate disorders. Aim of this study was to determine the relationships of these disorders with the requirement for and duration of noninvasive ventilation (NIV).

Methods: Sixty-seven consecutive patients who were hospitalized for hypercapnic COPD exacerbation had their clinical condition, respiratory function, blood chemistry, arterial blood gases, blood lactate and volmetric state assessed. Heart and respiratory rates, pH, PaO₂, PaCO₂ and PaO₂ and blood lactate were checked at the 1st, 2nd, 6th and 24th hours after starting NIV.

Results: Nine patients were transferred to the intensive care unit. NIV was performed for 11/17 (64.7%) mixed respiratory acidosis–metabolic alkalosis, 10/16 (27.8%) respiratory acidosis and 3/5 (60%) mixed respiratory-metabolic acidosis patients (p=0.026), with durations of 45 ± 8.9, 36.2 ± 8.9 and 53.9 ± 4.1 hours, respectively (p = 0.016). The duration of ventilation was associated with higher blood lactate (p < 0.001), lower pH (p = 0.016), lower serum sodium (p = 0.014) and lower chloride (p = 0.038). Hypopituitarism without hypervolemic hypochloremia occurred in 11 respiratory acidosis patients. Hypovolemic hypopituitarism with hypochloremia and hypokalemia occurred in 10 mixed respiratory acidosis–metabolic alkalosis patients, and euvoletic hypochloremia occurred in the other 7 patients with this mixed acid-base disorder.

Conclusions: Mixed acid-base and lactate disorders during hypercapnic COPD exacerbations predict the need for and longer duration of NIV.

P2025
Noninvasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF): Is the helmet an effective interface? A pilot RCT
Chiara Mega, Paolo Nevadani, Alfredo Gross, Raffaele Scala, Vanessa Repetto, Corrado Zenesini, Luca Fasano, Manuela Del Forno, Stefano Nava.
Respiratory and Critical Care, Sant’Orsola Malpighi Hospital, Bologna, Italy; Università degli Studi, Università di Bologna, Italy; University of Bologna, Area Epidemiologia, Bologna, Italy

To date the helmet is rarely used in AHRF, despite its hypoxic respiratory failure, it is employed as a “rotating” strategy when the facial mask is poorly tolerated. In a multicenter RCT, we compared the clinical efficacy of a new helmet designed to specifically improve the performance in COPD vs a full face mask during an episode of AHRF. 17 COPD with AHRF were randomly assigned to receive NIV either with full face mask (Group A, n=9), pH = 7.26 ± 0.07, PaCO₂ = 73.7 ± 10.8mmHg, PaO₂/PaCO₂ = 97.3 ± 5.3, or the helmet (Group B, n=8, pH = 7.24 ± 0.05, PaCO₂ = 83.3 ± 14.2mmHg, PaO₂/PaCO₂ = 100.6 ± 6.4). In the former group the ventilator settings were adjusted according to the usual practice (i.e. the maximal inspiratory pressure tolerate and CPAP = 4cmH2O), while in latter group according to published data (Crit Care Med 2009; 37:1921). ABGs were evaluated at admission, 1 and 6 hour and then everyday until discharge. Vital parameters, comfort scale, dyspnea score and adverse events were recorded. Baseline characteristics did not differ significantly between the two groups. 2 and 1 patients for group A and B respectively required intubation. NIV improved gas exchange vs baseline (p < 0.05) both with mask and helmet (pH = 7.34 ± 0.08, PaCO₂A = 97.3 ± 12.3mmHg, pH = 7.30 ± 0.05, PaO₂A = 83.4 ± 13.2mmHg; PaCO₂B = 73.7 ± 10.8mmHg, pH = 7.21 ± 0.07, PaO₂B = 73.7 ± 10.8mmHg; PaCO₂B = 58.0 ± 6.9mmHg, pH = 6.6). No differences in vital signs, patients’ comfort and dyspnea score were observed between the two groups. In conclusion this pilot RCT we have shown that the helmet may be a valid alternative to the “classical” full face mask during an episode of AHRF, making the former interface possible alternative for “rotating” strategy.

P2026
Effects of non invasive ventilation on left and right hemodynamic parameters during acute respiratory failure secondary to COPD exacerbation
Balldassare Canino, Vincenzo Calandrino, Caterina Urso, Roaul Aiello, Rosalia Lo Presti, Gregorio Cairini. Internal Medicine and Specialist (DIMIS), University of Palermo, Italy

Non Invasive Ventilation (NIV) is a technique used in different forms of acute respiratory failure that allows the patient to provide a full or partial ventilatory support without intubation. NIV has obvious effects on lung mechanics, but the changes that brings to the pulmonary vascular circulation, and to the right and left ventricle are more less investigated. Based on this assumption, we studied 32 patients (18 male, 14 women, mean age 72 ± 7.5 years) with respiratory failure secondary to COPD exacerbation who required NIV and we submitted to transthoracic echocardiography at the admission and at the resolution of respiratory failure. We have therefore shown that NIV not only has positive outcomes on right ventricular function (reduction of Pulmonary Insufficiency, Tricuspid Regurgitation, and four-chambers Ventricle Systolic and Diastolic Areas and short-axis Diameters with secondary improving of Tricuspid Annular Plane Systolic Excursion), but it had a statistical positive effect also on left ventricular function (Ejection Fraction increase, p < 0.05). Minimizing the effect of ventricular interdependence and deflating the lung, NIV not only has positive results on right hemodynamic parameters but, increasing venous return to the left ventricle and recovering the stroke volume, also improves its performance.

P2027
Factors predicting outcome of non-invasive ventilation (NIV) for acidotic hypercapnic respiratory failure (AHRF) from lung diseases other than COPD
Sarah Elgarf, Alice Turner, Ben Beauchamp, Rahul Mukhtarjee.
1Department of Respiratory Medicine & Physiology, Heart of England NHS Foundation Trust, Birmingham, United Kingdom; 2Queen Elizabeth Hospital Research Laboratories, University of Birmingham, United Kingdom

Background: NIV is the treatment of choice for AHRF in acute exacerbation of COPD, neuromuscular and thoracic cage disorders, but its indications have widened in UK hospitals, particularly in patients with AHRF of any cause whose comorbidities preclude invasive ventilation - we sought to establish the predictors of outcome in non-COPD Lung and Airway patients with AHRF.

Methods: Cohort analysis of prospectively collected data on acute NIV for non-COPD Lung and Airway diseases with AHRF in a ward-based NIV unit over 5 years recording diagnoses, demographics, response to NIV at 4 hours and in-hospital mortality (univariate analyses as total numbers too low for logistic regression).

Results: NIV was used to treat 39 episodes of pneumonia, 25 of exacerbations of non-cystic fibrosis (CF) bronchiectasis, 15 of asthma and 3 of CF (in 38, 22, and 3 individuals respectively), comprising 5.67% of all acute NIV episodes. All subgroups among non-COPD Lung and Airway patients receiving NIV for AHRF had impaired lung function with mean FEV1 of 34%, 41%, 43% and 18% respectively, 2 from the pneumonia group were intubated and 12 died during the admission - significantly more than the other subgroups (p=0.049); initial pH significantly predicted death in non-CF bronchiectasis (p=0.007).

Conclusions: In conditions other than COPD exacerbations, neuromuscular and thoracic cage disorders, acute NIV is useful in little in our unit (5.67%); when used, the predictors of death are broadly similar to COPD in non-CF bronchiectasis, but less predictable in the other groups, pneumonias being associated with higher co-morbidity and in-hospital mortality.

P2028
Long-term survival of COPD patients after first hospital admission with respiratory insufficiency and treatment with non-invasive ventilation in a respiratory ward in Denmark
Niels Glüer Tilsted, Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark

Introduction: Implementation of non-invasive ventilation (NIV) as an add-on treatment has been used routinely since 2004 at a University Hospital in Denmark, and data on COPD patients admitted to hospitals in Denmark have been monitored the last three years (National Indicator Project on COPD) show 30-day mortality data that can be estimated to 10%. No data on long-term survival on COPD patients in Denmark have been reported.

Method: Data from medical journals were retrieved from all patients admitted with respiratory insufficiency (respiratory acidosis and hypercapnea) and known or suspected COPD in exacerbation receiving non-invasive ventilation from January 1st 2005 until December 31st 2007. Demographic data collected included age and gender when receiving treatment with NIV for the first time.

Results: In total 257 patients (147 female/110 male) received NIV for the first time. The median age was in all 72 (25-percentile: 65.2 years and 75-percentile: 79.2 years). The 30-day mortality rate was 29.3%. Survival grouped by gender is illustrated in Fig. 1. There was no statistical significant difference between the groups. The total observation time was between 5 and 7 years.

Conclusion: The mortality rate of patients receiving NIV is as expected high, but the 5 years survival rate was 23.7% and with a trend of more female than male long-term survivors.

P2029
Mortality gain from illness leading to prolonged weaning failure
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Objective: For some patients prolonged weaning from invasive ventilation comes...
P2030
Who benefits most from non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease
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Respiratory Unit, Aberdeen Royal Infirmary, Aberdeen, United Kingdom

Introduction: Non-invasive ventilation (NIV) has revolutionised the management of hypercapnic exacerbations of chronic obstructive pulmonary disease (COPD).
We wished to evaluate factors related to its overall success in the “real-life” setting.
Methods: A retrospective analysis of patients receiving NIV for a hypercapnic exacerbation of COPD was performed. Demographics, laboratory data, blood gases and outcomes (hospital discharge or in-patient death) were extracted and subsequently analysed to identify factors relating to its overall success or failure.
Results: Over 6 years, 240 patients (mean age 70 years), received NIV with mean pH and pCO2 prior to NIV 7.24 and 14.4kPa respectively; of these, 167 survived to hospital discharge with a median age (70 vs. 74; p=0.02) lower than non-survivors.
Absolute values of pH and pCO2 (higher and lower respectively) prior to NIV and at 1 hour were both associated with outcome. pH was (p=0.02) in pH within an hour of receiving NIV - but not pCO2 - was associated with surviving to hospital discharge. Of all laboratory data assessed, only baseline area was significantly (p=0.02) associated with a successful outcome.
Conclusion: Younger patients with a lower area, higher pH and lower pCO2 at baseline and who demonstrate an improvement in pH within 1 hour, are more likely to have a successful outcome when given NIV for a hypercapnic exacerbation of COPD on an unselected basis.

P2031
Efficacy of non invasive mechanical ventilation (NIV) for acute respiratory failure (ARF) in COPD patients with and without pneumonia
Giovanni Alessandrini1, Caterina Antonaglia, Alessia Steffania, Paolo Marinielli, Matteo Bonini, Michela Mordenti, Mattia Internullo, Tullia Villani, Stefano Schiavetto, Elena Angelici, Paolo Palange. Department of Public Health and Infectious Diseases, Lang Function Unit, "Sapienza" University, Rome, Italy

Background: NIV represents one of the major technical advances in the management of ARF. Several data in literature showed the efficacy of NIV in COPD hypercapnic patients and in immunodepressed pneumonia patients. By contrast, the role of NIV in the treatment of pneumonia in COPD patients is controversial. We compared the efficacy of NIV for treating ARF in a group of immunocompetent COPD patients with and without pneumonia.
Methods: Among patients referred to our ward, we studied 12 COPD patients with ARF-P (66.3±14.65 years) and 9 with ARF-NP (74.5±4.6 years). Diagnosis of COPD and pneumonia were made according to International Guidelines. All patients were treated with a standard NIV pressure-support protocol. The following parameters were chosen as endpoints and recorded at baseline (B) and at 48 hours of NIV treatment: arterial PO2, PCO2, pH, and respiratory rate (RR). Data were analyzed using SPSS 17 statistical software.
Results: No differences in respiratory variables between the two groups were observed at B (p=ns). At 48 hours of NIV treatment, ARF-P patients showed a significant improvement in PO2 (69.3±10.9 vs 56.9±6.9; p=0.003), a significant reduction in PCO2 (51.0±9.4 vs 627±11.4; p=0.0006) and RR (18.6±2.1 vs 27.6±3.7; p=0.01). No differences were observed in pH value (7.4±0.1 vs 7.4±0.1; p=ns). Similar results were observed in the ARF-NP group. Time to hospital discharge was not significantly different between groups.
Conclusions: In COPD patients, NIV treatment for ARF is effective independently of the presence of pneumonia. Results should be confirmed on a larger population.

P2032
Nasal non-invasive positive pressure ventilation for moderate exacerbation of chronic obstructive pulmonary disease (COPD) treated in a Tunisian medical ward
Ibtihel Khouaja, Habib Ghedira. Pavillon 1, Abderahmane Mami Hospital, Ariana, Tunisia

Nasal Non-Invasive Positive Pressure Ventilation (NNPPV) is a soft method with a low burden which can be used in medical ward and may improve the outcome of COPD exacerbation.
Aim: The aim of this study is to evaluate the effectiveness of the addition of NNPPV to usual medical care in improving the outcome of patients treated in a medical ward for an exacerbation of COPD with moderate hypercapnia.
Methods: Among 25 patients who were hospitalized for an exacerbation of COPD with moderate hypercapnia, 10 were randomly selected to receive NNPPV (NNPPV group) and then compared to the 15 patients who received only an optimal medical treatment without ventilation support (control group). However, the role of NIV as a palliative measure in dying patients with COPD remains unclear.
Aim: To investigate the usefulness of NIV as an end-of-life measure in patients with COPD.
Patients and methods: We retrospectively reviewed the medical records of COPD patients who died of respiratory failure and had been receiving NIV at the end of life in a university-affiliated medical center.
Results: In 683 COPD patients who died, only 47 (7%) was under NIV support as a palliative measure before death. Most patients (79%) died in general ward, while the minority of patients had a preexisting "do-not-inhabit" (DNI) will, 76% placed a DNI documentation after initiation of NIV. There was no significant increase of respiratory rate or worsening of other vital signs 24 hours after starting NIV, suggesting the usefulness of NIV to prevent progression of distress. The consciousness significantly deteriorated (p=0.001) after the starting of NIV, which prevented the use of opioids or sedative agents. The mean length of NIV was 8.7±7.3 days and most of the patients (79%) were maintaining the NIV until they died, suggesting the tolerability.
Conclusions: Our study results suggest that NIV might be useful for dying COPD patients, who might experience a comfortable dying process. For relieving distress caused by respiratory failure, NIV may be a useful alternative measure to alleviate the dyspnea or discomfort. Further prospective study might be required.

P2034
Acetazolamide for reversing metabolic alkalosis during NIV treatment for AECOPD
Laura Borroengoa, Mattia Internullo, Liborio Sardo, Paolo Marinielli, Caterina Antonaglia, Alessia Steffania, Giovanni Alessandri, Matteo Bonini, Elena Angelici, Francesca Vaccaro, Paolo Palange. Department of Public Health and Infectious Diseases, Lang Function Unit, "Sapienza" University, Rome, Italy

Background: COPD is a leading cause of morbidity and mortality. Hypercapnic respiratory failure during acute exacerbation of COPD (AECOPD) strongly influences the prognosis. Non invasive ventilation (NIV) is an effective treatment for AECOPD. NIV may be less successful in the presence of metabolic alkalosis (MAK), due to the associated reduced ventilator drive. This study aimed to assess the effect of acetazolamide (ACET) on the correction of MAK, as well as of hypercapnia, during NIV for AECOPD.
Methods: Among patients referred to our clinical ward and treated with NIV, seven subjects (78.7±8.3 years) with AECOPD hypercapnic (PaCO2 >45mmHg) respirator failure (PaO2 <60mmHg), and MAK (pH = 7.40 and HCO3- <30mmol/L).
were enrolled in the study. Twenty-four hours (Day 0) from starting NIV treatment, ACET 500mg p.o. daily for two consecutive days (Day 1 and 2) was adminis-

tered. The following parameters were measured: arterial PO2, PCO2, pH, HCO3–, chloride and urinary pH. Results are expressed as mean±SD. Student t-test with Bonferroni’s correction was used for statistical analysis.

Results: Both at Day 1 and 2, pH and PaCO2 were significantly reduced compared to Day 0: pH 7.42±0.04 vs 7.45±0.04, p= 0.02; PaCO2 58±4mmHg vs 68±10, p= 0.03. HCO3– decreased with ACET, being the reduction more pronounced at Day 2 compared to Day 0 (36.2±4.8mmol/L vs 45.9±6.2, p= 0.0006). Conversely, urinary pH significantly increased during ACET. No drug adverse events were observed.

Conclusions: ACET may be useful for the correction of MAalk during AECOPD that requires NIV. A reduction in both pH and PaCO2 can be obtained in the first 24-48 hours of treatment. Further studies are needed on its long term efficacy.

P2035
Arterial bicarbonate as a determinant of the length of non-invasive ventilation (NIV) in COPD patients with acute hypercapnic respiratory failure (AHRF)

Sushil Agarwal1, Vikas Punamiya1, Shiva Bikmalla1, Christopher Bond 1, Biman Chakraborty1, Harjevan Gill1, Ben Beauchamp1, Rahul Mukherjee1.

1Department of Respiratory Medicine & Physiology, Heart of England NHS Foundation Trust, Birmingham, United Kingdom; 2School of Mathematics, University of Birmingham, United Kingdom

Introduction: Factors related to length of stay are complex and related to many non-medical factors, however length (duration) of NIV treatment is not. Although the associations of mortality of patients requiring NIV are well-documented (Thomas A et al Thorax 2010; 65:4. A33.), the determinants of the length of NIV have not been clearly elucidated, which we decided to investigate.

Methods: A retrospective analysis of the initial arterial blood gas bicarbonate (HCO3–)values on 115 consecutive episodes of NIV for at a dedicated respiratory NIV unit from 01 Jan to 31 Oct 2011 was carried out. Analysis of blood gases and duration of use of NIV (in days) was documented and analyzed.

Results: There were 115 patients admitted with AHRF with COPD. Plotting a graph with HCO3– and length of NIV we see that it has a linear relationship.

The p-value for HCO3– as a determinant of length of NIV is 0.00084, which suggests that it is significant.

Conclusion: This scientific survey indicates that the length of NIV therapy in patients in AHRF increases with a higher HCO3–. Though outcome and mortality is closely linked to the pH, length of NIV is more closely linked to the HCO3–. This is explained by the fact that people with higher HCO3– are likely to have had chronic respiratory failure for longer and are likely to take longer to recover from the respiratory failure.

P2036
Acidotic hypercapnia: Beyond type 1 and type 2 respiratory failure

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Introduction: The indications of non-invasive ventilation (NIV) have widened in the recent years, which is now used in treating hypercapnia with acidosis in a variety of patients. However, in many of the patients treated with NIV, the acidosis may have preceded the hypercapnia. The current case series from our 11-bedded ward based NIV unit describes such acidotic hypercapnia: hypercapnic respiratory failure following metabolic acidosis.

Methods: Time series of Arterial Blood Gas (ABG) findings in 4 patients with acidotic hypercapnia with a background of COPD confirmed with spirometry.

Results: The ABGs for cases 1 and 2 showed a rising CO2 following the onset of a metabolic acidosis; a mixed metabolic and respiratory acidosis in patients 3 & 4 - with the acidosis preceding hypercapnia (Case 3) or being out of proportion to CO2 rise (Case 4). All four patients improved with initiation of NIV combined with active fluid/electrolyte management. A sample ABG time series (Case 3) showing initial eucapnia with acidosis leading to hypercapnia is shown:

<table>
<thead>
<tr>
<th>Time</th>
<th>pH</th>
<th>pCO2</th>
<th>HCO3–</th>
<th>Base Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>7.36</td>
<td>11.2</td>
<td>21.6</td>
<td>-3.2</td>
</tr>
<tr>
<td>Day 2</td>
<td>7.43</td>
<td>11.0</td>
<td>29.4</td>
<td>-4.0</td>
</tr>
<tr>
<td>1 hour post NIV</td>
<td>7.56</td>
<td>5.55</td>
<td>3.0</td>
<td>+6.2</td>
</tr>
<tr>
<td>4 hours post NIV</td>
<td>7.46</td>
<td>7.91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The classic Acidotic Hypercapnic picture:

Discussion: Acidotic hypercapnia could be a further subtype of respiratory fail-
ure (akin to previously described Type 4 or shock-muscle hypoperfusion related respiratory failure) for which larger confirmatory studies and prospective trials to establish the efficacy and timing of NIV are required.

P2037
A cohort study for improvement of asthma attack by noninvasive positive pressure ventilation (NPPV)

Tomoya Katsuta1, Toshimitsu Suwaki2, Takayuki Kamo2, Shuzi Okahara3.

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Objective: A few study of efficacy of NPPV therapy in asthmatic patients have been reported. We studied efficacy and incidence rate of NPPV therapy.

Method: This prospective cohort study was performed in two hospitals in Okayama prefecture, Japan. All of the patients admitted because of asthma attack between January 2005 and June 2010 had to fulfill the following criteria before hospitalization. 1. The patients’ peak flow is less than 200L/min or 30% of his or her best peak flow 2. Borg scale is nine or ten. Hospitalization patients had to fulfill the following criteria for NPPV therapy. 1. Patients received PaCO2 >45mmHg and pH<7.351. 2. His or her Borg scale is ten.

Results: 94 patients were included in the study. Fourteen patients were received NPPV therapy. All patients avoided receiving mechanical ventilation.

Figure 1 shows profile of pH in the patients receiving NPPV. Figure 2 shows profile of Borg scale in the patients receiving NPPV.

Conclusion: The proportion of patients need NPPV therapy is 15%. In asth-
matic patients NPPV therapy appears highly effective in correcting gas exchange abnormalities and severe dyspnea.
P2038 Should teaching about non-invasive ventilation be made mandatory to all grades of general medical doctors? An audit of junior doctor knowledge regarding the management of patients on NIV before and after teaching sessions

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Introduction: Patients on non-invasive ventilation (NIV) are usually looked after out of normal working hours by general medical doctors.

Aims and objectives: We sought to determine the level of knowledge about NIV amongst general medical foundation (F1) doctors, core medical trainees (CMT) and specialist registrars (SpRs) before and after teaching.

Methods: Junior doctors were asked to complete a questionnaire covering knowledge about the criteria for commencing NIV, initial settings and appropriate manipulation of NIV machines according to patient response before and after mandatory teaching for F1 and CMT trainees and a voluntary attendance session for SpRs.

Results: Forty-nine doctors completed the questionnaire pre-teaching and all F1 and CMT doctors attended training but only 5/16 SpRs attended teaching.

Some of the most concerning findings were that all grades were poor at defining type II respiratory failure pre- and post-teaching. Knowledge about initial ventilator settings, alteration of pressure settings and target oxygen saturations on NIV were poor before teaching (although better in SpR group than more junior doctors).

Majority would have aimed for pressure settings too low to be effective. However, knowledge improved substantially after teaching amongst those who attended.

Conclusion: Baseline knowledge of all grades of junior doctors about practical NIV care is poor risking ineffective treatment but this can be improved by teaching. However, sessions need to be mandatory to ensure attendance.

P2039 Short and long-term outcomes after the first episode of non-invasive ventilation (NIV) for an acute exacerbation of COPD (AECOPD) on a general ward

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Background: NIV is an evidence based treatment for acute respiratory acidosis due to AECOPD. However, less data exist on long-term prognosis after the first episode of NIV.

Aim: To investigate the short and long-term outcomes after the first episode of NIV for AECOPD.

Method: A retrospective, observational, cohort study of 183 patients admitted to the hospital between 2008-2011 for an acute respiratory acidosis due to AECOPD treated with NIV on a general ward. Potential prognostic factors were recorded.

Results: During a 3-year period 275 admissions involving 183 patients were analysed. Included were 72 (39%) men and 111 (61%) women, with a mean age of 70 years (range 45-93y) and a mean FEVI of 33% (range 12-74%). 34 (19%) patients were readmitted for NIV with an average of 3 admissions (range 1-9).

Success rate of NIV was 76% (211 of 275 episodes). In 24% (64 episodes) NIV failed: 32 patients died during NIV (all prior Do-Not-Intubate patients), 7 did not tolerate NIV and died (all prior DNI patients), 16 needed invasive ventilation at the ICU (2 died), 9 died because of a non-respiratory cause.

In-hospital mortality during the first admission was 21%. The mortality rate at 1 hour and 5.12±3.42h: 0/22/78, p<0.001.

Conclusion: Success rate of NIV on a general ward is high (76%), but survival after 1 year is poor.

P2040 Outcome of respiratory critical care patients treated with noninvasive ventilation as a maximal intervention strategy

Elsa Fragoso, Filipe Monteiro, Carlos Lopes, Pilar Azvedo, Jorge Monteiro, Gabriela Brun, António Bugalho de Almeida. Pulmonology, Hospital de Santa Maria, Lisboa, Portugal

Background: End-of-life decisions are an important part of day-to-day medical practice in Respiratory Intensive Care Units (RICU), reflecting the need to prevent unreasonable therapeutic interventions. Noninvasive ventilation (NIV) can be used in the do-not-intubate patient and in palliative care setting.

Aim: To determine the outcome of patients with respiratory failure (RF) in whom NIV was suggested as a maximal intervention strategy. Noninvasive ventilation (NIV) can be used in the do-not-intubate patient and in palliative care setting.

Methods: Prospective study of 369 patients admitted to our RICU for 18 months. Age, gender, APACHE II, diagnosis, comorbidities, inpatient days, NIV duration, type of respiratory failure, PaCO2 on admission, NIV dependence (quantified in hours/day as follows: ≤15, 16-23 and 24) and ICU mortality were evaluated. Patients were divided in 2 groups based on outcome (alive/dead) and variables were compared between groups.

Results: Among patients in need of ventilatory assistance (n=242), 60 had a decision to forego tracheal intubation (24,8%). Age (y): 70±16. Males: 60%. APACHE II: 16±8. Inpatient days: 14±10. Diagnosis, %: chronic respiratory disease 50, heart failure 11, cancer 10, pneumonia 10, neuromuscular disorders 7, others 12. Thirty percent had at least two comorbidities (considering chronic heart failure, chronic renal failure, pulmonary hypertension and dementia). ICU mortality 73%. Mortality, % (hypoxemic RF/hypercapnic RF): 100/64, p=0,007. PaCO2, mmHg (alive/dead): 62±15/5±1,7, p=0,03. Mortality, % (NIV<15/16-23/24h): 0/22/78, p=0,001.

Discussion: The presence of hypercapnic RF had better prognosis, as opposed to hypoxemic RF. Greater NIV dependence was correlated with higher mortality. The mortality rate observed was high, as expected in this subset of patients.

P2041 Elective early noninvasive ventilation as a weaning method of COPD patients

Ahmed Sh. Mohamed 1, Ibrahim Ibrahim 1, 2. Chest Department, Tanta University Hospital, Faculty of Medicine, Tanta, Qalubia, Egypt; 1 Chest Department, Tanta University Hospital, Faculty of Medicine, Tanta, Qalubia, Egypt

Patients with acute exacerbations of COPD represent a large portion of critically ill patients that mechanically ventilated. The rate of weaning failure is high in these patients. Prolonged mechanical ventilation (MV) increases intubation associated complications.

Objective: To determine the efficacy of early non-invasive mechanical ventilation as a weaning method in COPD patients with acute hypercapnic respiratory failure compared with the conventional-weaning approach.

Methods: Study was conducted on a 30 mechanically ventilated COPD patients who had infective exacerbations. Patients were randomly extubated, receiving non-invasive ventilation (n=15), or weaned following a conventional-weaning approach (n=15).

Results: Compared with the conventional-weaning group, the noninvasive-ventilation group had shorter periods of invasive MV, total ventilator support, ICU stay, less incidence of ventilator associated pneumonia and less mortality.

Outcome parameters in both studied groups

<table>
<thead>
<tr>
<th>Character</th>
<th>Noninvasive ventilation Group</th>
<th>Standard Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Duration of invasive MV (days)</td>
<td>6.8±3.1</td>
<td>18.9±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of total MV (days)</td>
<td>13±6±2</td>
<td>18.9±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of ICU stay (days)</td>
<td>14±6±2</td>
<td>15±12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of VAP</td>
<td>1</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weaning failure</td>
<td>2</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Numbers of death in the hospital</td>
<td>1</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P value less than 0.001 was considered significant.

Conclusion: Patients with chronic obstructive pulmonary disease who had respiratory failure and were starting to breathe spontaneously, showed that noninvasive ventilation could decrease pneumonia, length of stay in the intensive care and the duration of ventilatory support.


242. Application of noninvasive ventilation in non-obstructive patients

P2042 Results of noninvasive ventilation in patients with acute hypercapnic ventilatory failure and obesity hypventilation syndrome (OHS)

Jesus Fernando Sanchez Gomez, Virginia Almadana Pacheco, Ana Gomez Bastero Fernandez, Patricia Guerrero Zamora, Jose Maria Benitez Moya, Agustin Valido Morales, Teodoro Montemayor Rubio. Clinical Unit of Pneumology, Hospital Universitario Virgen Macarena, Seville, Spain

Background: The NIV is used in patients with OHS presenting with hypercapnic respiratory failure. Few studies examine the evolution and impact after starting this therapy in this patient group.

Objective: To determine the efficacy of NIV in obtuse patients with acute hypercapnic respiratory failure and its prognosis consequences.

Methods: A prospective study with consecutive inclusion of obtuse patients with acute hypercapnic respiratory failure treated with NIV from Feb 08 to Jun 11.

Results: See Tables 1 and 2.

At the moment of discharge no differences were observed in comorbiddities, clinical data an blood gases between patients with or without NIV treatment. Patients discharged with NIV had tolerated better and had more total hours of use with BiPAP than those discharged without it.

Compliance measured at 3 months of onset and the last recorded was 4.5±1.3, 30 hours and 5.1±3.42 hours daily.

359s
Introduction: Patients with amyotrophic lateral sclerosis (ALS) and severe bulbar muscle impairment may be at respiratory failure risk during percutaneous endoscopic gastrostomy (PEG). Noninvasive ventilation (NIV) might reduce the risk of respiratory complications in patients with severe ventilatory impairment (SVI).

Objective: To report the outcomes of PEG placement with NIV in ALS patients with SVI.

Methods: Retrospective study including ALS patients with severe bulbar muscle impairment and indication for PEG placement. Pre-PEG pulmonary data was analyzed. Procedure was performed under nasal NIV using patients home bi-level ventilator. Vital signs, estimated tidal volumes and air-leaks were monitored. Due to increases in mouth air-leaks during the procedure ventilator parameters were readjusted. Low flow oxygen was only for SpO2 ≥ 95% despite NIV optimization. If SpO2 < 95% could not be reached the procedure was cancelled. NIV was maintained for 3h after.

Results: Ten patients (mean age 68.2 years) were included. Six patients didn’t require hospital admission. Patient’s pre-PEG pulmonary assessment is in Table 1.

Table 1

<table>
<thead>
<tr>
<th>VC (ml) (% predicted)</th>
<th>PEF (l/s)</th>
<th>SNIP (cmH2O)</th>
<th>SpO2 (%)</th>
<th>EtCO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>776 ± 455.9 (25.0 ± 14.9)</td>
<td>64.0 ± 69.9</td>
<td>33.4 ± 4.8</td>
<td>96.2 ± 1.0</td>
<td>38.4 ± 3.9</td>
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All patients used home NIV for 5.9 ± 10 months (mean daily use 14 ± 32h). Patients started the procedure with mean IPAP 19.2 ± 3 and EPAP 6.7 ± 1.5 mmH2O. All patients successfully underwent PEG placement with no complications, tolerated the ventilator adjustments maintaining SpO2 > 95% in 1month survival was 100%

Table 2

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mortality outside</th>
<th>Hospital p&lt;0.005</th>
<th>Survival Days</th>
<th>Readmissions</th>
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<tr>
<td>Discharged with BiPAP 122 (68.5%)</td>
<td>32 (26%)</td>
<td>1084 (92–1176)</td>
<td>55%</td>
<td></td>
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<tr>
<td>Discharged without BiPAP 56 (35.5%)</td>
<td>30 (54%)</td>
<td>562 (428–996)</td>
<td>48%</td>
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</tr>
</tbody>
</table>

Conclusion: NIV allows successful PEG placement in ALS patients with severe ventilatory impairment.

P3043
Noninvasive ventilation during percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis patients with severe ventilatory impairment
Malakia van Zeller, Rosa Ramilo, Susana Rodrigues, Miguel R. Gonçalves, João Carlos Winck, Guilherme Macedo, Department of Pulmonology, Centro Hospitalar de São João, Porto, Portugal; Department of Gastronenterology, Centro Hospitalar de São João, Porto, Portugal; Faculty of Medicine, University of Porto, Portugal

Introduction: Patients with amyotrophic lateral sclerosis (ALS) and severe bulbar muscle impairment may be at respiratory failure risk during percutaneous endoscopic gastrostomy (PEG). Noninvasive ventilation (NIV) might reduce the risk of respiratory complications in patients with severe ventilatory impairment (SVI).

Objective: To report the outcomes of PEG placement with NIV in ALS patients with SVI.

Methods: Retrospective study including ALS patients with severe bulbar muscle impairment and indication for PEG placement. Pre-PEG pulmonary data was analyzed. Procedure was performed under nasal NIV using patients home bi-level ventilator. Vital signs, estimated tidal volumes and air-leaks were monitored. Due to increases in mouth air-leaks during the procedure ventilator parameters were readjusted. Low flow oxygen was only for SpO2 ≥ 95% despite NIV optimization. If SpO2 < 95% could not be reached the procedure was cancelled. NIV was maintained for 3h after.

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Conclusion: NIV allows successful PEG placement in ALS patients with severe ventilatory impairment.

P3044
Training and confidence in the use of NIV/BiPAP amongst front-line medical staff in a teaching hospital setting
Imran Mahmud, Azhar Hussain, Ahmad Moinie, Ari Manuel, Hossam Fayed, Najib Rahman, Oxford Centre for Respiratory Medicine, Oxford University Hospitals, Oxford, Oxfordshire, United Kingdom

Background: Non-invasive ventilation is an evidence-based and validated treatment for patients with type II respiratory failure, and is widely used in acute and chronic settings. Poor training/preparedness have been linked with poor patient outcomes.

Aims and objectives: Staff confidence in managing patients on NIV is poorly described in the literature. Medical interns (with basic medical training) frequently care for patients on NIV during and outside normal working hours. We aimed to assess the preparedness and confidence of year 1 interns in managing patients on NIV within a teaching hospital in the UK. A structured questionnaire probed doctors’ understanding, confidence and practical skills in administering NIV.

Methods: 30 interns completed the questionnaire at a weekly mandatory teaching session. Answers were collated and analysed.

Results: 43% of interns did not know what “BiPAP” stands for; 33% described their knowledge of NIV indications as inadequate; 87% had no formal teaching in the use of NIV; 87% described their practical knowledge of NIV as inadequate, and 70% felt their confidence in managing patients on NIV was inadequate. The overwhelming majority (90%) of respondents felt they needed formal training in the use of NIV to ensure patient safety.

Conclusion: Our study illustrates worrying shortfalls in the training and confidence of front-line medical staff in the use of a medical intervention frequently found on hospital wards. This suggests a role for formal training at either the undergraduate or early postgraduate stage.

P2045
Introduction of a non invasive ventilation (NIV) care bundle in a district general hospital
Huw Ellis, Reham Nasser, Alan Hart-Thomson, Annika Graham. Respiratory Medicine, Huddersfield Royal Infirmary, Huddersfield, West Yorkshire, United Kingdom

Introduction: A care bundle is a group of evidence based actions needed to deliver optimal care in a clinical setting. It takes the form of a simple checklist, placed in the notes, which serves as a reminder to clinicians. It aims to ensure consistent delivery of care leading to safe and reliable care. Compliance with all elements is needed for optimum benefit.

Method: A 7 item bundle was created for acute NIV. It was introduced to coincide with the 2011 British Thoracic Society (BTS) NIV audit so that the impact could be assessed by comparison with the 2010 audit. The bundle was provided in the form of a sticker to be inserted in the case notes when NIV was commenced. Bundle elements not included in the table below were (1) NIV only to be delivered in areas where nursing staff are trained (2) arterial blood gases checked at 1 hour (3) at 4 and 4 hours review by a physician within 24 hours (4) Mon – Fri.

Results: 13 of 19 patients (67%) had a bundle in the notes. 11 of 13 (85%) had all 7 elements completed. The impact of the bundle on key measurements are summarised in the table (bundle items highlighted).

Conclusion: Implementation of an NIV bundle is possible in a DGH and coincided with improved audit outcomes, patient safety documentation of ventilation plans and increased pressures. Numbers are small but it may have contributed to reduced mortality and length of stay.

P2046
Efficacy and safety of continuous sedation for agitated patients under noninvasive ventilation
Takashi Matsumoto, Takahisa Kawamura, Koji Taimai, Junpei Takeshita, Kosuke Tanaka, Kazuya Monden, Kazuma Nagar, Kyoko Ootuka, Ashoki Nakagawa, Ryo Tachikawa, Kojuro Ootuka, Keisuke Tomi, Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan

Introduction: Sedation is often required for agitated patients under noninvasive ventilation (NIV). However, there have been few reports on use of continuous sedation in these patients. Aim: To evaluate the efficacy and safety of continuous sedation for agitated patients under NIV.

Methods: We retrospectively reviewed 110 patients receiving NIV for acute respiratory failure from May 2007 to December 2011, who needed sedation for treatment of agitation. Difference in clinical outcomes was compared between continuous use group and intermittent use group, according to do-not-intubate (DNI) status (n=73) or non-DNI status (n=37).

Results: In non-DNI patients, the severity assessed by baseline PaO2/FiO2 and mortality were similar between continuous use group (n=10) and intermittent use group (n=27) (117±66 mmHg vs. 116±50 mmHg, p=0.95 and 10% vs. 22%, p=0.40). No patient in continuous use group required intubation due to agitation, while three patients in intermittent use group required intubation due to failure of sedation (0% vs. 11%, p=0.54). In DNI patients, baseline PaO2/FiO2 ratio was lower and the mortality was higher in continuous use group (n=53) compared with intermittent use group (n=40) (131±51 mmHg vs. 151±42 mmHg, p=0.017, and 85% vs. 58%, p=0.011). Only one patient in continuous use group failed to continue NIV due to agitation. Patients with continuous sedation were safely managed under NIV with the level of sedation assessed by Richmond Agitation Sedation Scale, except only one adverse event of hypotension caused by midazolam.

Conclusions: Continuous sedation could be safely administered, and potentially prevent undesirable intubation due to persisting agitation under NIV.
**P2047**

Effects of a high-flow nasal cannula system (nHF) on ventilation in healthy volunteers and patients with IPF

Jens Brandmuller, Marcus Keckler, Hans-Jurgen Seyfarth, Stefan Hammerschmidt, Hubert Wenz. Department Pneumology, University of Leipzig, Germany

**Introduction:** Treatment with a nHF-system is able to improve symptoms of acute and chronic respiratory insufficiency. The method uses a warmed and humidified high flow of air/oxygen with 10-50 liter per minute (lpm). By using these devices an increase in mean pressure, pressure amplitude and a decrease in pCO2 is observable.

**Method:** Healthy volunteers and patients with IPF were included in this study. For detection of volume changes, frequency variations and I/E-ratios we used impedance measure bands. The bands were placed 10 cm below jugulum and 10 cm below xiphoid. The signal was relayed to a polysomnography device. Flows from 10 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 14/6 mbar. We compared the results with values measured during spontaneous breathing.

**Results:** Results were compared with the standard deviation (SD) and with the t-test.

- **Discussion:** HFNC led to no changes in tidal volume in patients with IPF and a decrease in healthy volunteers. The breathing rates in healthy volunteers and patients with IPF in comparison with spontaneous breathing were decreased. The I/E-ratio results in no significant changes in healthy volunteers and patients with IPF. In both groups, the minute volume was decreased. In comparison with CPAP and BiPAP, the measuring results showed different effects like HFNC.

**Conclusion:** HFNC led to no significant changes in respiratory parameters of healthy volunteers and in patients with restrictive pulmonary diseases. The changes in healthy volunteers and IPF will support respiratory efforts and will finally result in a reduction of breathing-related work.

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**P2048**

Acute repercussions of noninvasive ventilation in patient with severe heart failure

Andrea da Nobrega Céron Nogueira, Francisco Delano Campos Macedo, Vaso Pinheiro Diógenes Bastos, Leiana Silveira Marinho, Nathalia Parente de Sousa, Soraya Maria do Nascimento Rebonças Viana, Luz Henrique de Paula Melo, Raimundas Herzminda Maia Macedo, Maria do Socorro Quintino Farias, Juniora Maria de Oliveira Lima, Roberto Martins Rodrigues Sobrino, Marcelo Alcantara Holanda. Laboratory Respiration, Department of Medicine, Federal University of Ceará, Fortaleza, Brazil

**Objective:** To analyze the acute effects of noninvasive ventilation (NIV) on cardiac function in patients with severe heart failure (HF).

**Methods:** The study involved 10 patients with HF functional class III and IV (NYHA), ejection fraction (EF) ≤ 40%. Shan CPAP was used and CPAP 10 cm H2O for 60 minutes with an interval of 20 minutes. We analyzed Simpson ejection fraction (EF SIMP), cardiac output (CO), pulmonary artery pressure (PAP), heart rate (HR) and mean arterial pressure (MAP) by echocardiography and oxygen saturation (SaO2) monitored every 30 minutes.

**Results:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After NIV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF SIMP</td>
<td>30±10</td>
<td>40±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR</td>
<td>80±10</td>
<td>70±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CO</td>
<td>5±1</td>
<td>7±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAP</td>
<td>15±5</td>
<td>10±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MAP</td>
<td>70±10</td>
<td>60±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SaO2</td>
<td>90±2</td>
<td>95±2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Conclusion:** CPAP significantly alters HR, MAP and SaO2. The NIV had no significant changes on the FE SIMP, DC and PAP.

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**P2049**

Predictors of failure of non-invasive ventilation in patients with respiratory failure

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**Introduction:** In patients with respiratory failure, randomized studies have shown noninvasive ventilation (NIV) to be associated with lower rates of intubation. In these patients, predictors of NIV failure are not well characterized. We conducted this study to investigate variables predictive of NIV failure in patients with respiratory failure.

**Materials and methods:** This prospective study was conducted at a tertiary care hospital in India. Fifty patients were included in the study, and were then followed up to discharge/expiry.

**Result:** Patients matched on baseline characteristics. Most of the patients (68%) did not have any pre-existing lung disease while 8 out of 50 (16%) had COPD. 4 patients (8%) had bronchial asthma; 2 patients had malignancy and 2 patients (4%) had history of previous Tuberculosis. In associated co-morbidities, 17 patients (34%) had Diabetes and 24 patients (48%) had hypertension.

**Conclusion:** With prudent case selection, NIV is successful in more than 60% of cases. Failure of NIV may be related to the primary diagnosis. Association of co-morbidities as independent predictor of NIV failure needs further study.

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**P2050**

The use of non-invasive ventilation in paediatric lung transplantation

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**Introduction:** Progressive deterioration in paediatric patients (pts) with end-stage lung disease may result in diurnal hyperventilation. There are paucity of data describing polysomnography (PSG) & the benefits of Bilevel Positive Airway Pressure (BiPAP) therapy in these children.

**Aim:** To evaluate cardiorespiratory data & gas exchange using PSG in children awaiting lung transplantation (LTx) prior to & after BiPAP therapy.

**Methods:** Retrospective review of PSGs on these patients between 2005 & 2012 was performed. Change in cardiorespiratory parameters during PSG following BiPAP initiation was assessed & analysed using a paired t-test.

**Results:** Of the 31 pts identified, 24 underwent LTx & 7 were on a wait list (WL). 13 were male pts with mean age of 12 years (9 to 15). 9 LTX & 3 WL pts had PSGs; 10 pts were on supplemental oxygen. 9 pts had cystic fibrosis, 2 had interstitial lung disease & 1 had pulmonary venous occlusive disease (PVOD). 10 pts had evidence of nocturnal hyperventilation in the absence of obstructive or central apneas & were initiated on BiPAP. After titration of BiPAP to optimal settings, there was a significant increase in mean SaO2 [91% (SD 2.4) to 96% (SD 0.9); p=0.0001], decrease in heart rate [111 (SD 18.3) to 96 (SD 15) beats per minute, p=0.02]; respiratory rate [35 (SD 5) to 28 (SD 6) breaths per minute, p=0.03] and transcutaneous carbon dioxide recordings [74 (SD 17) to 67 (SD 14) mmHg, p=0.006] from baseline.

**Conclusion:** All pts had significant nocturnal hyperventilation with improved clinical parameters & gas exchange abnormalities following BiPAP. Further research is needed to assess the role of PSG & BiPAP therapy as a bridge to transplant in children with severe chronic lung disease.

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**P2051**

Ventilatory management in patients after intestinal transplantation

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Intestinal transplantation (IT) is a life-saving therapy for the patients with intestinal failure. However, ventilatory management of intestinal transplant recipients in the immediate post-operative period is difficult and challenging. Therefore, our aim was to establish the criteria for postoperative extubation, identify risk factors for prolonged ventilator needs.

We conducted an observational, prospective clinical trial and performed retrospective chart reviews of 7 patients receiving IT between 2007 and 2012 at the Far Eastern Memorial Hospital. The patients were divided into two groups; 3 patients were not successfully extubated within 72 hours of the IT operation (ventilated, V) and 4 were (extubated, E). The median age and weight in the V group were significantly lower than the E group, 9.67 yrs vs. 28.25 yrs and 23.33 kg vs. 36.75 kg respectively. When compared to the E group, congenital Hirschprung’s disease was cause of intestinal failure, preexisting respiratory disease, severe acute rejection, immunosuppressive level and longer operation time were more common in the V group. The consequences of not being extubated within 72 hours were increased.
Correspondence between clinical prediction and outcome in patients with AHRF due to RLD - further prospective studies are needed to establish this in detail. As NIV is increasingly used acutely on critically ill patients beyond the originally supposed indication of AHRF in selected patients (and even in palliative care), the use of NIV as the “ceiling of care” needs consistent monitoring.

High-flow nasal cannulae oxygen in acute respiratory failure: effectiveness and predictors of failure

Introduction: To determine the effectiveness of high flow nasal cannula (HFNC), and the factors predicting from failure of HFNC in acute respiratory failure.

Method: We retrospectively evaluated acute respiratory failure patients who received HFNC at Chungcheon Sacred Hospital, between August 2011 and January 2012.

Result: In all, 33 patients were included in the study. Their median age was 73 years (49-89). Majority of the patients were male(22 patients, 67%). The most common cause of acute respiratory failure was pneumonia followed by COPD acute exacerbation, acute pulmonary edema due to congestive heart failure, cancer progression, and lung fibrosis. The hospital mortality was 24%. In the unadjusted model, (P=0.03), APACHE II score (P=0.04), BNP (P=0.03) and higher respiratory rate (P=0.04) were associated with HFNC failure. However, in the adjusted model, higher respiratory rate (P=0.04) were associated with HFNC failure (P=0.04, OR 3.36).

Conclusion: HFNC has beneficial effect on clinical sign and oxygenation in ICU patients with acute respiratory failure. Predictors of high flow nasal cannula failure might be used to guide decisions regarding intubation.

Treatment of preterm infants with high-flow nasal cannulae: A review of the evidence

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Background: High-flow nasal cannulae (HFNC) are gaining popularity as a form of non-invasive respiratory support for preterm infants, and are proposed as an alternative to nasal continuous positive airway pressure (NCPAP) in a variety of clinical situations.

Objectives: We critically examined the published evidence for the mechanism of action, efficacy and safety of HFNC as a treatment for preterm infants.

Methods: Internet-based literature search for relevant, original research articles on use of HFNC in preterm infants. PubMed, Medline, and the Cochrane Library were searched, search terms [high flow OR high-flow] AND nasal cannula(e), without language restriction.

Results: The search produced a total of 73 articles; 15 studies were included in the review. Distending pressure generation from HFNC increases with increasing flow rate and decreasing infant size, and varies according to the amount of leak around the prongs. HFNC may be as effective as NCPAP at improving respiratory parameters such as tidal volume and work of breathing in preterm infants, but perhaps only at flow rates above 2 Litres/minute. Only four published randomized controlled trials (RCTs) of HFNC use in preterm infants were found; only two of these compare HFNC to NCPAP, and all are small. Based on the current, limited evidence, HFNC appears to be inferior to NCPAP as post-extubation support, and ineffective when used to wean from NCPAP. There are no RCTs of HFNC as a treatment for early respiratory distress.

Conclusions: The efficacy and safety of HFNC in preterm infants remain to be determined, and further RCTs in the settings of primary support from birth, post-extubation support, and weaning from NCPAP are required.
P2057
Respiratory depressants among patients undergoing noninvasive ventilation for hypoxemic-hypercapnic acidosis: Prevalence and impact on prognosis
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Medical records show frequent psychoactive drug treatments among the elderly with respiratory depression as a potential side effect. We evaluate their impact in patients undergoing noninvasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) with acidosis.
Methods: Prospective study in 103 consecutive admissions (71 M, age 74.9±9.9 yrs) starting NIV for AHRF with acidosis in a Monitoring Unit (Oct 08-Jan 12). Two groups based on previous therapy with psychoactive drugs and significant sedative effect. Variables: pH, PaO2, PaCO2, PaO2/PaCO2 at admission (1), of NIV (2) and 24h of NIV (3); in-hospital mortality and combined in-hospital and 30-day post-discharge mortality, length of stay (LOS) and intubation %. We recorded main diagnosis and thoracic comorbidities. Stat. analysis: = 7.02MW.
Results: 39 pts (37,9%) received sedatives: M 22,5%.F 77.5%; BZD 89.9%. Main diagnosis (% sedatives): COPD 48 (25%), OHS 20 (55%).Acute heart failure 16 (56,2%), Pneumonia 7 (28,6%). Acute pulmonary edema 6 (66,7%). Chest wall deformities 4 (25%).Comorbidity 55,3%. Group analysis (sedatives vs no sedatives): Sex (M) 41% vs 85,9% (p <0,001); age 77,4±8,1 vs 73,5±4,3 (p <0,05). In-hospital mortality 17,9% vs 10,9% (NS), In-hospital 30-day mortality 23,1% vs 14,1% (NS), COPD prevalence 30,8% vs 56,2% (p <0,05). NS differences in LOS, intubation %, pH and PaCO2; evolution between groups: pH 7,27±0,08 vs 7,29±0,58; PaCO2 37,3±10,09 vs 73,2±2,07; pH <7.3±3.5 (both groups).
Conclusions: We found a high prevalence of respiratory depressants in patients with AHRF. Sedatives may worsen prognosis and early response to NIV, especially in elderly female patients without COPD.

P2058
Effect of non-invasive ventilation on pH, carbon dioxide and bicarbonate, in acute, hypercapnic, respiratory failure
Diana Dolgova1, 1Cardiac Surgery, Kiev City Heart Centre, Kiev, Ukraine
Acute, hypercapnic, respiratory failure is defined by the presence of PaCO2>6.6 kPa and pH <7.35. Non-invasive ventilation is an established treatment for this condition. The improvement in alveolar ventilation leads to a lowering of the PaCO2 with normalisation of the pH. The role of renal buffering in the treatment of acute respiratory failure using NIV has not been reported in the literature. We undertook an audit of patients admitted to a high dependency unit in a large teaching hospital setting. The patients were in acute type II respiratory failure as defined above. They had an arterial blood gas (ABG) recorded before initiation of NIV, after 1-2 hours, after a further 4 hours and at discharge from NIV. We have shown the data for pre NIV and at the end of NIV treatment. The data is therefore for patients who successfully completed NIV therapy. The study was carried out over a twelve month period. The data was entered into the database by the ward junior doctor at the time of the patient’s admission and subsequent discharge.
Changes in Arterial Blood Gases
<table>
<thead>
<tr>
<th></th>
<th>Pre NIV</th>
<th>Discharge</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.26</td>
<td>7.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>10.13</td>
<td>7.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>11.26</td>
<td>9.2</td>
<td>0.23</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>32.11</td>
<td>32.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

We had complete data for 44 patients. The p value was derived from the t-test for paired data. This study confirms the findings of previous studies that the successful use of NIV in acute, hypercapnic, respiratory failure leads to significant improvements in both the pH and PaCO2. This improvement appears to be directly due to improved alveolar ventilation leading to a reduction in PaCO2; from this data there does not appear to be a significant contribution from renal buffering.

P2059
Noninvasive ventilation in acute cardiogenic pulmonary edema with haemodynamic instability
Irina Martyniuk1, 1Intensive Care, Kiev City Heart Centre, Kiev, Ukraine; 2Cardiac Surgery, Kiev City Heart Centre, Kiev, Ukraine
Background: Although noninvasive ventilation (NIV) in acute cardiogenic pulmonary edema (ACPE) is widely used, its use in patients with unstable hemodynamics is contradictory. Aims: To evaluate NIV use in ACPE with low systolic blood pressure (SBP) and search for the correlates of its success.
Methods: Prospective interventional trial of all 22 patients with ACPE with SBP 75-90 mm Hg, with no acute arhythmia, SaO2 90% on spontaneous breathing with 10 l per minute oxygen, cooperative, not hypercapnic, with low cardiac output due to acute myocardial infarction, mitral regurgitation or congestive heart failure, was done from July 1, 2010 through December 31, 2011. All patients were immediately started on conventional therapy (dobutamine and/or dopamine, morphine, furosemide, nitroglycerin) and NIV through a face mask with FiO2=1.0, initial PEEP 5 cm H2O and pressure support (PS) 5 cm H2O. Hemodynamic parameters, SaO2, central venous saturation (ScvO2), respiratory rate (RR) and end tidal volume (Vt) were documented every 3 minutes. If no relief in 3 minutes, PEEP was enhanced to 7 cm H2O and after next 3 minutes PS added to 7 cm H2O. Results: All patients had SaO2 90% and SBP>90 mm Hg after 10 minutes. If at this moment RR was 30 and Vt 5 ml/kg of body weight, or more than low doses of cardiotonics were needed, the patient was intubated (4 patients). After 30 minutes, those who needed FiO2 60% on NIV, were oliguric and failed to rise ScvO2 above initial, were intubated (2 patients). No intubation was needed in 16 patients. No factors correlated with NIV failure. Conclusion: In selected hemodynamically unstable patients with ACPE NIV helps avoid intubation.

P2060
Effects of use of Boussignac CPAP on development of post-operative atelectasis
Serife Savas Bozdogan1, 1Balam Er Dedekargioglu1, Serap Cakir2, Feza Yarbug 1, Karakaya1, Fuusan Onur Eyuboglu1, 1Pulmonary Medicine, Baskent University Faculty of Medicine, Ankara, Turkey; 2Pulmonary Disease, Corlu Public Hospital, Tekirdag, Turkey; 3General Surgery, Baskent University Faculty of Medicine, Ankara, Turkey
Background: Boussignac CPAP is a method to apply CPAP through a special valve system. Aims: Patients who had a high likelihood of postoperative atelectasis undergoing abdominal surgery were included in the study. It was aimed to evaluate the development of atelectasis and its effects on PFT parameters through utilisation of Boussignac CPAP system.
Patients and method: A total of 28 patients were included in our study and were randomized into two groups. Conventional methods (incentive spirometry, respiratory physiotherapy) were scheduled for the first group and Boussignac CPAP treatment in addition to conventional methods was scheduled for the second group. Boussignac CPAP system was applied to patients with spontaneous respiration for 3 days as 6 times and 15 minutes on each session. Pre and post application pulmonary function tests(PFT) parameters, chest X-ray findings and radiological atelectasis scores were evaluated.
Findings: Mean age was 65.4 years and 57.1% were male. There was not any significant differences in the Boussignac CPAP group and control group between location of incision, operation time and presence of pulmonary disease. Preoperative chest X-ray findings were similar(=0.05). In the Boussignac CPAP group, postoperative radiological atelectasis score was significantly lower than control group(p<0.05). In CPAP group, no decline in oxygen saturation and oxygen partial pressure was observed unlike control group. Significant decrease was observed in FVC that is one of PFT parameters in postoperative period.
Conclusion: Our findings suggest that development of post-operative atelectasis might be decreased, thus oxygenation might be improved by use of Boussignac CPAP.

P2061
Noninvasive ventilation in the emergency department: Early predictors of outcome in acute cardiogenic pulmonary oedema
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Introduction: The application of early continuous noninvasive ventilation (NIV) is well established in the Emergency Department (ED) for the treatment of acute respiratory failure (ARF) due to Acute Cardiogenic Pulmonary Oedema (ACPO). Aims and methods: To critically analyse the impact of NIV in ACPO, about ARF presentation and the treatment efficacy or failure (defined as hospital mortality or need for invasive mechanical ventilation). Observational clinical study in the real life practice of the ED of a University teaching Hospital, during 5 months, including every patient emergently admitted and treated for ACPO according to inclusion criteria referring to an institutional protocol. Results: 214 patients (media 1.42/day). Failure rate 15.5%. Failure versus success groups were similar in many characteristics and parameters. They were mainly different in: comorbid diseases, neurologic status, arterial blood pressure, rates of paliative or “ceiling” NIV, leukocytosis, AST, CPKMB, troponinI, LDH, PCR, changes in blood gas analysis parameters after 120 minutes. Conclusion: We identified early predictors of outcome in the ED: clinical parameters, biomarkers and arterial blood gas analysis data to recognize severe conditions and the response to treatment. Unnecessary delaying tracheal intubation remains
the major hazard of NIV in ARF; the overutilization of NIV is also a concern. A pivotal unresolved question is about selection criteria and early choices for patients having preset therapeutic and prognostic limits and acutely reversible processes. RCTs in the ED are necessary to define the subgroups of patients who are most likely to benefit for the early application of NIV.

### 243. Advanced experience with long-term noninvasive ventilation and late-breaking abstracts

#### P2062
A randomised controlled trial comparing stepwise versus immediate withdrawal from non-invasive ventilation in chronic obstructive pulmonary disease patients recovering from acute hypercapnic respiratory failure

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**Background:** COPD patients who suffer from exacerbation with acute hypercapnic respiratory failure (AcHRF) benefit from non-invasive ventilation (NIV). The best withdrawal method of NIV is not known.

**Aim and objectives:** To compare the success rate of withdrawal in NIV between stepwise withdrawal and immediate withdrawal in COPD patients with AcHRF.

**Method:** This was a prospective, single-centre, open-labelled randomised study comparing stepwise and immediate withdrawal of NIV. The primary end-point was the success rate of NIV withdrawal. The secondary end-points were hospital length of stay and duration of NIV use.

**Results:** Sixty patients were randomised: 35 patients to the stepwise withdrawal group and 25 patients to the immediate withdrawal group. There was no statistically significant difference in the success rate of withdrawal of NIV and length of stay after randomisation, with the success rate of 74.3% and 50% in stepwise and immediate withdrawal group respectively (p = 0.139). There was statistically significant difference in the duration of NIV with median duration of 5 days and 3 days in stepwise and immediate withdrawal group respectively (p = 0.001). The post-hoc analysis showed the use of LAMA, higher inhaled steroid dosage and higher arterial pH value on randomisation were the factors associated with success in withdrawal in the immediate group.

**Conclusion:** Our study showed no significant difference in the success rate and length of stay between stepwise withdrawal and immediate withdrawal of NIV. Duration of NIV was significantly shorter in the immediate withdrawal group.

#### P2063
Automatic tailoring of positive end-expiratory pressure (PEEP) by forced oscillation technique (FOT) during non-invasive ventilation: Effects of posture and exertion in COPD

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**Expiratory Flow Limitation (EFL) promotes the development of intrinsic PEEP (PEEPi) which can lead to hypercapnia and respiratory failure.** In mild to severe COPD, the development of EFL is greatly affected by posture and exertion and this results in major adjustments in the PEEP required to counteract intrinsic PEEP within the same patient.

Eleven COPD patients (GOLD stage 2-4, BMI 30±10, FEV1/FVC 56±8) were initiated to nasal BiPAP with automatic PEEP adjustment. After adaptation, ventilation was applied for 10 minutes in the seated and supine positions and during a 6MWT. Data were recorded in the last minute for each condition.

At PEEP=2cmH2O, 8 patients showed EFL in the seated position, 10 in the supine and 9 in the last minute of the 6MWT. The average PEEPopt is reported in figure. In mild to severe COPD, the development of EFL is greatly affected by posture and exertion and this results in major adjustments in the PEEP required to counteract EEPi within the same patient.

**Conclusion:** PEEPopt is adaptive and should be modified to posture and exertion in severe COPD.
P2066

Respiratory events during long term noninvasive positive pressure ventilation in children: Clinical implications and detection of events

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Objective: The aims of the study were (1) to describe the respiratory events during noninvasive positive pressure ventilation (NPPV) and, (2) to analyze the clinical consequences.

Method: Nocturnal polygraphic (PG) recordings were performed in stable patients. Respiratory events were scored using the SomnoNIV Group definitions [1]. The consequences of an event i.e. a fall of ≥ 3% of pulse oximetry (SpO2) and/or a ≥ 30% decrease in pulse rate amplitude (respiratory auto-micro-arousals) were described.

Results: PG tracings of 27 patients (13 boys, age range 1-18) were analyzed: neuromuscular disease (n=7), obstructive sleep apnea (n=8) and lung disease (n=12). Unintentional leaks, partial or total upper airway obstruction without reduction of ventilatory drive, a decrease in ventilatory drive, mixed events, and patient ventulator asynchronies were observed in 61%; 37%; 28%; 7%; 55% of the patients, respectively. These events were associated with a decrease of SpO2 in 21%; 37%; 18%; 12% of the patients and with a RAM in 38%; 27%; 8%; 3%; 32% of the patients respectively. The mean number of type of events per patient was 1.8±1.1. For a given patient, there was a predominant event representing 87±10% of total time with respiratory events. The median duration spend in respiratory event was 39% (range 0.7 to 92%) of total recording time. Of the patients, respectively. These events were associated with a decrease of SpO2 ≥ 3% of pulse oximetry (SpO2) and/or a ≥ 30% decrease in pulse rate amplitude (respiratory auto-micro-arousals) were described.

Conclusion: Respiratory events are common in stable children treated with long term NPPV and can be associated with desaturations and/or RAM. 1. Gonzalez J et al. Thorax 2011.

P2067

Polysonomographic criteria to assess the efficacy of noninvasive ventilation in chronic respiratory failure

Roozma Naeck1, Adriana Portmann2, Ubistan Freitas1, Donnia Boumonaire1, Florence Portier2, Christophe Letellier1, Jean-François Muir2, Antoine Cuvelier3,1, COPRA UMR CNRS 6614, Rouen University, St Etienne du Rouvray, France; 2Pulmonary & Respiratory Intensive Care Department, Rouen University, Rouen, France

Aim: We performed successive polysomnographies (PSG) under spontaneous breathing (SB) and under noninvasive ventilation (NIV) in order to assess the improvements of ventilation and sleep in patients with severe chronic respiratory failure.

Methods: 12 patients indicated to domiciliary NIV because of chronic respiratory failure (neuromuscular disease (n=4), obesity-hypventilation syndrome (n=6) or thoracic deformation (n=2)) have performed a PSG under SB at day 1, another PSG with the newly implemented NIV at day 2 and therefore a third PSG under NIV two weeks after (day 15). NIV titration was performed according to local protocols, based on nocturnal oximetries and morning arterial blood gas assessments.

Results: As compared to SB, the oximetric parameters significantly improved during the first night under NIV. Pco2 values, early-morning and diurnal arterial blood gases slightly improved during the first night under NIV but the differences were statistically significant only at day 15. We observed a rapid increase of time spent in REM sleep (9.1±2.1 vs 15.2±4.2% of total sleep time, p=0.0148), a reduction of obstructive apnea index (28.4±8.6 vs 9.7±4.2, p=0.0175) and the micro-arousal index (40.1±8.5 vs 25.7±1.9, p=0.0258). Heart rate and cardiac variability were significantly reduced under NIV. Patient-ventilator asynchronies were less in all patients except two and did not significantly vary between day 2 and day 15.

Conclusion: NIV efficacy is associated with a rapid and objective improvement of sleep quality, in parallel with a slower improvement of diurnal and nocturnal hypercapnia. Cardiac variability may be also a pertinent parameter to evaluate these patients.

Mean hours of use between VAPS and PCV were not significantly different (6.0 (±2.7) vs 5.9 (±2.4) hours respectively). There was a trend towards shorter time to initiate VAPS compared to PCV (3.4 vs 4.7 days respectively, p=0.071). During the trial period 2 patients from each arm died.

Conclusion: In patients with COPD and chronic ventilatory failure, VAPS achieves similar improvements in overnight oximetry and daytime PaCO2 compared to PCV. VAPS is a well tolerated and effective treatment for chronic ventilatory failure in this patient group. A longitudinal trial investigating survival may now be warranted.

P2069

Effect of transnasal “high-flow oxygen insufflation” in patients with severe COPD

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Introduction: Long-term oxygen therapy is one of the established treatment strategies. Nasal insufflation of warm, humidified air at a high flow rate is a new and simplified method in non-invasive ventilation.

Until now, no data on the safety, effects and efficacy of in COPD patients are available. Our multicenter, controlled study has been approved by the national ethic committees.

Aim: It was designed to examine the safety and effects of high flow therapy in patients with COPD IV and to explore possible changes in efficiency in ventilation and parameters of the lung function.

Method: Patients with COPD IV with indication for LTOT are enrolled. The following inclusion criteria have to be met: age 30-80, stable disease for 14 days, Hb>100g/l, and no current participation in another study.

Results: So far 38 subjects were recruited: 32 males, 6 females, age 67.5±6.64 yr; FEV1 14-49% predicted. Oxygen supplementation was performed in 10 min intervals each with an augmentation of 0.5-1 L/min until a pO2 >60mmHg was achieved. Using [TNI], oxygen was mixed with warm and humidified air at a constant flow rate of 15 L/min. Concerning safety high flow delivery was well tolerated in all patients and no significant differences were found for several spirometric parameters tested. Furthermore a highly significant decrease of CO2 in arterial blood after short-term treatment could be measured (-2.87 mmHg; p<0.0001) compared to conventional oxygen administration.

Conclusion: In conclusion, we can postulate that short-term treatment with high flow [TNI] seems to be safe in patients with COPD IV with a reduced oxygen saturation.

P2070

Uptake of NIV treatment in MND is dependent upon caregiver variables

Rosanna Cousins1, Hikari Ando1, Carolyn Young2, Biswajit Chakrabarti1, Robert Angus3, 1Health Sciences, Liverpool Hope University, Liverpool, United Kingdom; 2The Walton Centre, NHS Foundation Trust, Liverpool, United Kingdom; 3Attendance Chest Centre, Attendance University Hospitals NHS Foundation Trust, Liverpool, United Kingdom

There is robust evidence that NIV relieves respiratory symptoms and improves quality of life in MND. Nevertheless, about a third of those who would benefit

MONDAY, SEPTEMBER 3RD 2012

3658
from NIV decline the treatment. It is important to understand why the most effective treatment available for MND patients [1] is refused. To investigate this phenomenon, we undertook a cross-sectional quantitative analysis of 27 patient and caregiver dyads offered ventilatory support based on physiological markers, including forced vital capacity and nocturnal pulse oximetry. The analyses indicated that there were no differences between the patients who went on to accept NIV treatment (n=17) and those who declined (n=10) in terms of age, sex, MND symptomatology (ALS-FRS-R, ALSAQ-40, MND Dyspnoea Rating Scale, daytime sleepiness) and psychological measures (hopelessness, anxiety and depression). The similarity of the scores in the two groups is such that we are confident that we do not simply have a power issue. In view of assertions that uptake of NIV treatment increases caregiver burden, which suggests caregiver input in NIV treatment, we also analysed caregiving variables. There were no differences in general physical or mental health but caregivers who supported NIV treatment were significantly more emotionally stable and less anxious, and in terms of coping style more resilient, more committed and more in control. A regression analysis focusing MND symptoms to enter before caregiving variables still indicated that resilience: commitment alone explained 24% of the variance.

We will discuss these findings, and implications for clinicians.

Reference:

P2070
Triple O – A new respiratory syndrome?
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Introduction: There is a growing number of patients needing nocturnal ventilatory support, presenting with Obesity-Hyperventilation Syndrome (OHS). Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA). As these three entities seem to coexist we are using them to propose the Triple O Syndrome (TOS).

Objective: To characterize TOS patients and compare their demographic characteristics and ventilatory needs with OHS patients.

Materials and methods: Forty-four patients with obesity (BMI >30 kg/m²), COPD (FEV1/FVC ratio <70%), and OSA (AHI>5/h) were included. Exclusion criteria were pulmonary diseases others than COPD, OSA, data entry delay, bronchiectasis, Cheyne-Stokes Breathing, Complex OSA and Central Sleep Apnea. These patients were compared to 46 OHS patients. Both groups started ventilatory support between 2009 and 2011.

Results: TOS patients: mean age 69.4±9.1 years, 84% were male, BMI mean 35.8±4.4 kg/m², mean Epworth 11.4±4.8, mean FEV1 57.9%±19.5% predicted, median AHI 36.3h, median PaCO2 47.2 mmHg, median PaO2 18.0 cmH2O, median PaCO2 10.0 cmH2O, median RR 14 cycles per minute, 23% needed oxygen complement.

Conclusion: Compared to OHS patients, TOS patients were older, leaner, the percentage of male gender was higher, had less severe OSA and lower RR when adapted to ventilatory support.

Conclusions: Triple O patients seem to be an individualized group, with different demographic characteristics when compared to OHS patients. The ventilatory needs were similar between both groups, but the RR and the mask used, mainly nasal, in TOS patients.

P2071
Thoracoabdominal contribution to tidal volume after an inpatient cardiac rehabilitation program associated to continuous positive airway pressure (CPAP)
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Background: Continuous positive airway pressure (CPAP) is an important strategy for improvement of gas exchange and breathing work in post operative of coronary artery bypass grafting surgery (CABG). However, it's unknown the breathing pattern (BP) behaviour after inpatient cardiac rehabilitation (CR) program associated to noninvasive ventilation (NIV) during exercises.

Aim: To evaluate the BP of post-CABG patients engaged in CR associated to NIV.

Methods: Nineteen patients submitted to twice-daily supervised postoperative CR program. The criteria to include the patients in the CPAP group were: (a) no history of respiratory and cardiology maladies; (b) no history of COPD; (c) no history of thoracoabdominal contributions to tidal volume. The measurements were recorded with a flexible fiberoptic bronchoscope, with volume analysis and pressure measurement software, with special app. The patients were divided in 2 groups: patients in the CPAP group and patients in the control group. The objective was to compare both groups through a noninvasive ventilator, electronically controlled, with fixed pressure of 10 cmH2O. The cotton masks were used to avoid desaturation in the CPAP group.

Results:
- In the CPAP group: observed a respiratory rate of 15, mean arterial pressure of 114/73 mmHg. The patients were able to perform the ventilatory recruitment manoeuvre with tidal volume of 600 ml and BBUs of 15, in 15 min.
- The ratio of inspiratory to expiratory times was 1:1, with a tidal volume of 1500 ml. The mean arterial pressure was 114/73 mmHg, with a respiratory rate of 15. The patients were able to perform the ventilatory recruitment manoeuvre with tidal volume of 600 ml and BBUs of 15, in 15 min.

Conclusion: The results showed that the ventilatory pattern (BP) was improved in the CPAP group compared to the control group, with a significant reduction of respiratory work.

P2072
Adherence and tolerance of an auto-CPAP (APAP) device specially designed for occidental way of life and bedroom: Beyond technology, medical appearance is obsolete
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Observance up than 3hr/night, only is required in France to allocate reimbursement of CPAP treatment for Sleep Apnoea Syndrome. But control of hypertension requires up than 4hr/night. Breat-sleep, or Fisher&Pakell ICON are clearly designed to look as a clock or a radio-alarm-clock without external electric transformer.

Aim: Define if such CPAP device is associated with a mean sleep use up than 4hr/30, achieving 3 sleep’s cycles. Data collection [comfort, residual AHI, respiratory pressure, etc.]

Methods: Two HomeCare HealthCareProviders (no financial or material conflict of interest), Noncomparative observational study. We collect use’s duration of a month from 25 consecutive OSA patients, all ventilated by ICON. APAP mode, 4/16 cmH2O, no ramp with optimal subjective comfort humidification setting.

Results: 108 consecutive symptomatic OSA patients (IAH > 30/hr), evaluation time of 4 months delay treatment, 6% 65±4.6 y/o; residual AHI = 4.8±3.9/hr and P95% = 9.3±3.7 cmH2O

Observance: 34±2.4 min, comfort’s evaluation through a modified Analogic Visual Scale (AVS) 7.4±1.2, Design’s evaluation through a modified AVS 8.7±4.3.

Conclusions: A pretty bedroom designed CPAP device is associated with a therapeutic duration up than 2hr/30. An affective-based customer societal approach of such treatment seems relevant to enhance patient adherence. Comparative studies are required to confirm this monocentric and limited non comparative descriptive study.


P2073
Our experience in home mechanical ventilation
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Home mechanical ventilation (HMV) increases survival of patients with chronic respiratory failure. National center in Serbia for HMV in neuromuscular patients was established in 2007.

Aim: We aimed to evaluate our practice

Method: We retrospectively analyzed clinical history of patients receiving HMV in our center from 2007-2012.

Results: 146 patients were started on HMV (71 M/55 F) mean age 46±20 years. Most of the patients were treated with non invasive ventilation. Twelve percent of patients were ventilated invasively via tracheostomy. Three patients were converted from invasive to noninvasive ventilation. Most frequent diagnosis was motor neuron disease (MND) 78, mean FCV% 33±8,7 and spinal muscular atrophy (SMA) 15. Overall survival was 59% of patients. In MND group, mean survival was10 months, and all dystrophin patients are still in follow up.

Conclusion: In our country HMV in last years is increasingly used but its prevalence is still low compared with other countries.

P2074
Multidisciplinary MND clinics – Should every hospital have one?
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Motor neuron disease (MND) is best managed by a multi-disciplinary team, including a respiratory physician to assess for respiratory failure, for which non-invasive ventilation (NIV) is indicated. East Kent Hospitals University Foundation Trust has recently developed a regional neurology centre and has well established domiciliary ventilation services. The multi-disciplinary MND team was developed in 2008.
Aim: To review the management of MND in East Kent and the changes since the establishment of a multi-disciplinary MND team.

Methods: A retrospective analysis of the clinical notes of all patients diagnosed with MND over the last 10 years.

Results: Total number of patients with a diagnosis of MND was 65. 3 had familial disease (4.6%).

Methods: We prospectively studied a group of tracheotomized and chronically ventilated patients admitted to a weaning centre who could be suitable for decannulation and conversion to NIV because of absence of airway stenosis, normal swallowing function, preserved cough mechanism but unable to sustain a spontaneous breathing for more than 16 hours without increasing PaCO₂. Data collected for follow-up were: demographic, functional, severity score (SAPSII), need to re-trachecotomy, survival, hospital admissions/year, maintenance of adequate gas exchange. The Fisher exact test and the log-rank test have been employed for statistical analysis.

Results: 176 patients with tracheotomy and prolonged IV were evaluated: 26 patients (14 men) met the criteria and were decannulated and converted to NIV (16 obstr. 10 restr.). Mean age was 67.46 years, mean SAPSII score was 26.8, mean follow-up time was 24.8 months; 12 patients had at least 1 new episode of exacerbation, in 5 cases requiring ICU admission, and 2 patients needed re-tracheotomy. Two-years-mortality rate was 26%. Age and severity score turned out to be statistically significant predictors of survival.

Conclusions: Long-term maintenance of tracheotomy and invasive ventilation makes the patient more fragile and difficult to manage in the domiciliary setting. Decannulation and conversion from IV to NIV is a safe and feasible technique and should be attempted in selected hypercapnic patients.

P2078

Use of home non-invasive ventilation (NIV) in patients with ankylosing spondylitis (AS)

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Background: Ventilatory impairment is a recognised extra-articular manifestation of AS. To our knowledge there are no published data describing home NIV in this condition.

Aims and objectives: Retrospective assessment of home NIV in AS patients at a tertiary UK ventilatory support centre to determine i) indications for NIV, ii) physiological response to treatment and iii) compliance and survival.

Methods: Case records of patients referred for consideration of NIV between 1993 and 2011 were retrospectively reviewed and information regarding the indication for NIV, demographics, co-morbidities, arterial blood gas analysis, pulmonary function, mean overnight oxygen saturation (SpO₂), compliance and survival recorded.

Results: The case notes of 18 patients (15 male, 64±9.2 yrs) were reviewed. Most commenced NIV in the context of acute respiratory decompensation (n=11; 61%). The most frequent indication for NIV was hypercapnia (PaCO₂ ≥ 6.5, n=14; 78%). NIV led to a sustained decrease in PaCO₂ from the baseline (p<0.05) and rise in the mean overnight oxygen saturation (p<0.05). Twelve patients have died (68%) with the median time to death from starting NIV of 31 months (range 1-98). The mean duration of treatment was 33 months (range 1-99).

Physiological response | Baseline | Follow up | Most recent review
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<td>±SD</td>
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<td>(range 0.1-3 years) ±SD</td>
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<tr>
<td>Mean PaCO₂ (kPa)</td>
<td>7.8±1.0 (n=18)</td>
<td>3.8±0.2 (n=14)</td>
<td>8.0±1.4 (n=14)</td>
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<tr>
<td>Mean PaO₂ (kPa)</td>
<td>8.1±1.8 (n=16)</td>
<td>6.7±0.7 (n=14)</td>
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<td>Mean nocturnal SpO₂ (%)</td>
<td>85±8.6 (n=18)</td>
<td>93±3.2 (n=15)</td>
<td>92±3.5 (n=14)</td>
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<td>Mean compliance (hours)</td>
<td>6.8±3.0 (n=15)</td>
<td>6.0±2.9 (n=13)</td>
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Conclusion: AS patients demonstrated good compliance with NIV, which was associated with a sustained improvement in physiological parameters.

P2079

Home mechanical ventilation the Netherlands; an overview

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Background: Home Mechanical Ventilation (HMV) is well known as a cost-effective treatment which significantly improves quality of life. In this abstract we give an overview of the development of HMV in the Netherlands.

Methods: Since 1991 we have been collecting data regarding all patients treated with HMV the Netherlands.

Results: Over the last 20 years, the number of Dutch patients treated with HMV increased from 200 to 2000. There is a significant growth in number of patients treated with non-invasive ventilation. Mask and mouth-piece ventilation in combination with the progress in technical abilities of the equipment, allows patients to use the non-invasive ventilation up to 24 hours a day. Patients were divided in four categories: neuromuscular disease (NMD), thoracic cage restriction (TCR), lung disease and obstructive or central sleep apnea syndrome. Patients with NMD have been always and still remain the largest category in the Netherlands. The rise in NMD is especially due to patients with ALS; almost 100 patients with ALS started HMV last year. The 2nd largest group includes patients with TCR. Patients with
Obesity hypoventilation syndrome (OHS) are primarily responsible for the growth in this group. Patients with obstructive lung disease are a fairly stable group. Of all patients, 68.3% lives at home.

**Conclusion:** Most patients on HMV are currently treated non-invasively. The growth of these patients is specifically seen in patients with ALS or OHS. Despite this enormous rise of patients treated with HMV, 83% of the patients still live at home.

P2080
Home NIV for patients with stable COPD
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**Background:** Non invasive ventilation (NIV) is shown to be effective in the treat-ament of acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD) and as treatment at home in patients with chronic respiratory failure due to e.g. neuromuscular disease. Previous studies in patients with COPD have shown conflicting results of home NIV.

**Aim:** Audit of home NIV treatment initiated due to repeated admissions with NIV treated acute hypercapnic respiratory failure (AHRF).

**Method:** Retrospective study of acutely NIV treated patients in our dept. of lung medicine. Frequency and duration of hospital admissions respectively 12 and 6 months before and 6 months after the initiation of home NIV were compared.

**Results:** Figure shows a significant reduction in number of admissions 6 months after initiation of home NIV compared to 12 (avg 2.4 to 0.75 (p=0.05)) and 6 months before initiation (avg 4 to 0.75 (p=0.046)).

**Conclusion:** The study shows that home NIV is effective to reduce admissions with respiratory problems in a highly selected group of COPD patients with previous repeated AHRF and need of acute NIV treatment.

P2081
The evaluation of the efficacy and safety of phospholipids’ inhalation in patients with bronchial asthma (BA): A prospective randomized placebo-controlled study
Alexander Lisitsin1, Igor Kilmanov2, Svetlana Soodaeva3.

**Background:** The aim of the study was to evaluate the efficacy and safety of phospholipid’s inhalation (PhLi) in BA patients during the 24-week course of treatment.

**Materials and methods:** The prospective, single-blind, randomized, placebo-controlled, parallel-group study was performed. 38 patients (age 67.5±6.13, male 68.5%) with partly controlled and uncontrolled BA were enrolled (FEV1<50%). Group1 contains 30 patients who received a PhLi by compressor nebulizer once a day in addition to traditional therapy; group2 - 28 patients who received a traditional therapy only (control). The lung function test was performed in each clinical visit, as well as PEF measurements were performed twice daily by the patient itself. Usage of short-acting β-agonists and the asthma symptoms score were also determined.

**Results:** It was shown the statistically significant increase of FEV1 level in group1 compared with control (78.3±7.7 vs 72.9±9.2; p=0.01). The PEF increase was also determined in group 1 (570.1±206. vs 486.3±98.3 l/min; p=0.03). The strong correlation between these two parameters was observed (r=0.94; p<0.005).

**Conclusion:** The number of inhalations of bronchodilator reliever medication was significantly lower in group 1 (1.7±0.8 vs 2.9±1.6; p=0.027) as well as asthma symptoms score (4.2±1.1 vs 6.3±1.0; p=0.01).

**Conclusion:** The results obtained demonstrate that a phospholipids’ inhalation in addition to traditional therapy of BA has a significant positive effect both in clinical status and lung function test in patients with BA.

P2082
Onset of bronchodilation with fluticasone/formoterol versus fluticasone/salmeterol
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**Background:** Rapid bronchodilation has been identified as a key attribute of ICS/LABA combination therapy for asthma. This post-hoc analysis assessed the onset of bronchodilation with fluticasone propionate/formoterol fumarate (FLUT/FORM) and fluticasone propionate/salmeterol xinafoate (FLUT/SAL).

**Methods:** 202 adults with asthma (forced expiratory volume in 1 sec [FEV1] reversibility of ≥15%) were randomized to 12 weeks’ treatment with either FLUT/FORM (pMDI, 100/10 or 250/15 g b.i.d. [treatment doses]; n=101) or FLUT/SAL (pMDI; 100/50 or 250/50 g b.i.d. [treatment doses]; n=101) in a double-blind, parallel-group study. The percentage of patients with onset of bronchodilation within 5 min and 120 min post-dose was assessed on days 0 and 84. Onset of bronchodilation was defined as the first time point post-dose with ≥12% increase in FEV1 versus pre-dose.

**Results:** Baseline mean FEV1 was 2.1±0.6 L (reversibility 27.6±12.8%) and 2.1±0.5 L (reversibility 24.9±9.9%) in the FLUT/FORM and FLUT/SAL groups, respectively. On day 0, a significantly greater proportion of patients had an onset of bronchodilation with FLUT/FORM than FLUT/SAL within 5 min (38.6% vs 14.0%; odds ratio [OR] 1.0; 95% CI 2.0, 8.0) and within 120 min post-dose (78.0% vs 64.0%; OR 2.0; 95% CI 1.1, 3.9). This was sustained over 12 weeks; on day 84, the percentage of patients with an onset of bronchodilation was greater with FLUT/FORM than FLUT/SAL within 5 min (16.3% vs 2.0%; OR 9.6; 95% CI 2.1, 42.9) and within 120 min post-dose (51.0% vs 35.1%; OR 1.9; 95% CI 1.1, 3.4).

**Conclusion:** FLUT/FORM consistently provided more rapid bronchodilation than FLUT/SAL in patients with asthma over 12 weeks of therapy.

P2083
Intermittent versus daily inhaled corticosteroids (ICS) in children and adults with mild persistent asthma: A Cochrane review
Francisco Dieguez1, 2, Blureen Essawi2.

**Introduction:** Although guidelines recommend daily ICS in mild persistent asthma, most patients use, and many physicians prescribe, intermittent ICS.

**Objectives:** To compare the safety and efficacy of intermittent versus daily ICS in mild persistent asthma.

**Methods:** Randomised trials comparing intermittent vs. daily ICS in children and adults were eligible. Outcomes included: patients requiring rescue oral steroids (primary efficacy), serious adverse health events (primary safety), hospitalisations, lung function, asthma control, adverse effects, and withdrawals.

**Results:** Six (4 children; 2 adults) parallel-group trials using beclomethasone or budesonide, were included. There was no significant group difference in patients requiring rescue oral steroids (RR=1.07, 95%CI 0.87, 1.32) and serious adverse events (RR=0.82, 95%CI 0.33, 2.03). Compared to daily ICS, intermittent ICS was associated with lower change in FEV1, fewer control days, more PEF-agonists use, and higher exhaled nitric oxide. There was no group difference in acute care visits, hospitalisations, FEV1, adverse effects, and withdrawals. Compared to intermittent, daily budesonide was associated with lower growth in children (MD0.41cm, 95%CI 0.13, 0.69).

**Conclusions:** Intermittent and daily ICS strategies did not significantly differ in the use of rescue oral steroids, nor did they reach equivalence. Daily ICS was superior to intermittent ICS in several indicators of lung function, airway inflammation, control, and reliever use. The findings would support the greater efficacy of daily ICS in children and adults with mild persistent asthma, while using the safest, and lowest effective dose of, ICS in children.

P2084
Oral polyunsaturated fatty acid supplementation as adjuvant therapy for asthmatic children
Malak Shaheen1, Magdy Mahmoud2, 3, Eman Elshinawy2, 3.

**Introduction:** The feeding of long-chain polyunsaturated fatty acids (PUFA) competitively inhibit the formation of leukotrienes and prostaglandins produced from omega-6 fatty acids and thus provide anti-inflammatory effect. However, the precise impact of
omega-3 fatty acid oral supplements for asthmatic children has not been established. The aim of this study was to assess safety and efficacy of omega-3 PUFA supplementation for asthmatic children.

Method: In a prospective study, 44 known asthmatic children and 15 matched healthy children received oral supplementation with omega-3 PUFA for 5 weeks during all children underwent; history taking, clinical examinations, pulmonary function testing and assessment of omega-3 PUFA serum levels, total IgE (TiGE) levels and interleukin 4 (IL4) levels before and after the supplementation. Result: Basal omega-3 PUFA serum levels were significantly lower in asthmatic children compared to controls (p = 0.03) and much lower with severe grades of asthma (r = 0.25, p = 0.03). Three folds rise was documented in the mean omega-3 PUFA level of asthmatic children compared to eight folds increase in healthy children after PUFA supplementation (p = 0.0004). Clinical asthma scores showed one step down improvement only in 13.5% of asthmatic children (6:44). Mean values of TiGE serum levels in asthmatic children showed a significant reduction after supplementation (p = 0.04) while IL4 serum levels showed a rise after supplementation.

Conclusion: Significant difference exists between healthy children and asthmatic children regarding the impact of oral PUFA supplementation. However; it showed some positive effects for asthmatics, its safety is questionable in children.

P2085

Does a formal prednisolone absorption test lead to improved control in difficult-to-treat asthma?
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Patients with disabling asthma may have poor concordance with prescribed therapy and admit this only when confronted with firm evidence. Control may then improve through greater concordance with agreed management. Hypothesis: In individuals prescribed long term prednisolone, an absorption test may provide formal evidence of poor concordance and thus lead to improved clinical outcomes.

Design: Observational cohort

Population: 27 patients (22 female) with asthma and poor control despite specialist review, regular prednisolone, and reported concordance.

Intervention: 0.5mg/kg prednisolone orally. Prednisolone, prednisone, cortisol and cortisone levels every hour for 3 hours.

Assessment: First visit to the asthma service, appointment at which test requested, test day, and 6 months thereafter.

Outcomes: ACQ, FEV1% predicted, FeNO, peripheral blood eosinophil count, and reported prednisolone dose.

Analysis: Paired t tests. Results = mean ± SEM (2df).

Results: Patients had impaired lung function (FEV1 65% predicted ±6.0) and poor control (4.4±0.5) at time of test request despite prednisolone (30mg ±3.9).

12 (44%) patients had suppressed cortisol attest baseline. All tests showed adequate absorption of prednisolone.

FEV1, FeNO, prednisolone dose and ACQ did not change significantly across the four time points. Eosinophil count fell by a mean of 0.30 (CI 0.02-0.58, p=0.037) between request and test. This improvement was sustained from request to follow up (mean ±0.50, CI 0.11-0.90, p=0.016).

Conclusion: In this small study a prednisolone absorption test was associated with a sustained fall in eosinophil count. This was not reflected in improved exhaled, spirometric or clinical markers.

P2086

Patient characteristics that can predict response to omalizumab (an anti-IgE antibody) for achieving better control of asthmatic patients
Nancy Abdelaty, Chest, Sue: Canad University, Imsailia, Egypt

Background: Omalizumab is a monoclonal anti-immunoglobulin E (IgE) antibody indicated for the treatment of inadequately controlled severe persistent asthma despite optimal controller therapy. It is an expensive medication so there is a need to identify those patients most likely to benefit.

Aim of the study: To investigate characteristics associated with response to omalizumab in difficult asthma.

Patients and methods: The study enrolled 42 patients (15 female, 27 male) with age range (20y-52y) with severe asthma that was inadequately controlled despite step-4treatment as described in (GINA) guidelines. Omalizumab was given as add-on therapy to concomitant asthma treatment and administered subcutaneously every 2 or 4 weeks according to patients’ pretreatment bodyweight and baseline IgE levels, for at least 16 weeks, those who showed better asthma control, were analyzed to investigate whether pre-treatment patient baseline clinical characteristics could be reliably identified and to be predictive of a superior response to omalizumab.

Results: 12/42 (28.6%) of enrolled patients showed better asthma control. Using univariate and multivariate regression analysis, many variables showed significant effect on response to omalizumab including; age, duration of asthma, history of allergic Rhinitis, history of allergic dermatitis, bronchial reversibility, no of positive results to common allergen, in immediate skin-prick, sputum eosinophilia and baseline total (IgE).

Conclusion: Omalizumab is an expensive medication so it is recommended to target its use to patients most likely to benefit rather than recommend widespread use. Further studies are needed to confirm these data.

P2087

Physician assessment of asthma control in patients receiving omalizumab in a real-world setting
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1 Severe and Brittle Asthma Unit, Heart and Lung Tract, Birmingham, United Kingdom; 2 Pulmonary Medicine, Koch Robert Hospital, Edeby, Hungary; 3 Critical Care, Novartis Pharma AG, Basel, Switzerland; 4 Critical Care, Novartis Pharmaceuticals Corporation, East Hanover, United States.

GINA guidelines define controlled, partly controlled and uncontrolled asthma based on a number of individual components (symptoms, activity limitation, rescue medication use, lung function and exacerbations).

The 2-year, global, single-arm, observational eXpErience registry evaluated the efficacy and safety of omalizumab (OMA) in patients with allergic asthma in a ‘real-world’ setting. Investigators were instructed to assess asthma control using the GINA 2006 definitions. A post-hoc analysis compiled the individual components of control recorded by physicians and applied these to the GINA definitions. The intent-to-treat population consisted of 916 patients. Investigators’ assessment (IA) of control increased from 1.4% at baseline to 41.1% after 2 years of treatment (Table). Asthma control by strict GINA definitions increased from 0.8% at baseline to 21.0% over the 2 year treatment period (Table).

These data show differences between physician’s assessment of asthma control and control as determined by strict application of GINA 2006 definitions. This study did not explore what determined the differences in assessment, which may be of interest for future study. Regardless of method, asthma control improved over time in patients receiving OMA in this real-world study.

P2088

Effects of inhaled corticosteroids on asthmatic inflammation: The FeNoType trial
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Background: Personalised treatment for inflammatory asthma phenotypes confers superior benefits. The elevated exhaled nitric oxide (FeNO) inflammatory phenotype requires evaluation of dose-response to inhaled corticosteroids (ICS).

Methods: Randomised, crossover trial in mild-to-moderate asthmatics receiving ICS with elevated FeNO—40ppb after ICS washout. Patients received 2 weeks of: fluticasone propionate 50ug twice-daily (FP100) or 250ug twice-daily (FP500). Primary outcome: response in diurnal domiciliary FeNO levels. Secondary outcomes included: mannitol challenge; serum eosinophilic cationic protein (ECP); blood eosinophil count; and asthma control questionnaire (ACQ).

Results: 21 patients completed. We found significant dose-related reductions of diurnal FeNO compared to baseline: am: FeNO: baseline=71ppb, FP100=34ppb, p<0.001, FP500=27ppb, p<0.001; and significant dose separation for am, p<0.05, and pm, p<0.001. Time series FeNO displayed exponential decay:

\[ \text{FeNO} = \text{FeNO}_0 \times (1 - e^{-kt}) \]

where k is the decay constant, and FeNO0 is the initial concentration.

ACQ significantly improved exceeding the minimal important difference (>0.75) with values in keeping with controlled asthma (>0.75) after each dose: FP100=0.48, p=0.004; FP500=0.37, p=0.001. All other secondary inflammatory related outcomes showed significant improvements from baseline but no dose separation.
Conclusion: There is significant, dose-response of diurnal FeNO to FeNO in patients with a high FeNO phenotype, also associated with well controlled asthma.

P2089
Effects of Arg16Gly polymorphism in ADRB2 gene on responses to salmeterol: a multi-centre study added to inhaled corticosteroids in Japanese asthmatic subjects
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Methods: The primary endpoint was the difference of the change in morning PEF at 16 weeks [(APEF (Sal) – APEF (Mon)] between the two genotypes. Results: The mean difference in [(APEF (Sal) – APEF (Mon)] was 162mL (p=0.006), but no other significant differences were observed. The least significant differences were 36mL (p=0.05). Conclusion: It is likely that the Arg16Gly polymorphism does not influence the preferential bronchodilator effect of Sal or Mon in mild to moderate persistent asthma patients, at least, in 16 weeks follow-up.

P2090
The efficacy of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in asthma is comparable when administered in the morning or evening
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Methods: Single centre, randomised, double-blind, placebo-controlled, three-way crossover study. Subjects with persistent asthma (N=26; 24-64 years) received FF/VI (AM or PM) or matching placebo (P) once daily for 14±2 days. FEV1 (0-24h weighted mean and pre-treatment [AM and PM]) was determined after the Day 14 PM dose together with pre-treatment [AM and PM] PEF on Days 1–12. Results: FF/VI administered AM or PM produced clinically significant increases in weighted mean FEV1; the differences [95% CI] from P were 37mL [293, 462] and 422mL [337, 507], respectively; the difference between AM and PM dosing was 44mL [−135, 36]. Pre-treatment AM FF/VI differences [95% CI] from P were 403mL [272, 533] and 496mL [369, 624] after AM and PM dosing, respectively; the treatment difference was −94mL [−221, 34]. Pre-treatment PM FEV1 differences [95% CI] from P were 275mL [169, 380] and 309mL [205, 413] after AM and PM dosing, respectively; the treatment difference was −34mL [−138, 70]. FF/VI (AM or PM) produced rapid increases in PEF with the full effect apparent after the first dose and maintained throughout the 14 day treatment period. Conclusion: The efficacy of FF/VI (100/25mcg) was comparable when dosed in the morning or evening in subjects with persistent asthma. Funded by GSK (HZA114624, NCT01287005).

P2091
Efficacy of fluticasone furoate (FF) as a monotherapy and in combination with vilanterol (VI) over 12 weeks in patients with persistent asthma
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Introduction: The inhaled corticosteroid FF in combination with the long-acting beta2 agonist VI is under development for the treatment of asthma and COPD. Objectives: To compare the efficacy and safety of FF/VI and FF in patients (aged ≥12 years) with persistent asthma. Methods: In a randomised, double-blind, parallel-group study, patients (N=460; ITT) received FF/VI 100/25mcg, FF 100mcg or placebo once daily in the evening via a new dry powder inhaler. Co-primary endpoints: change from baseline in trough FEV1, and weighted mean (w) 0-24h FEV1. Rescue-free 24-h periods and safety were also assessed. Results: Placebo increased trough FEV1 (196mcL and wFEV1; [212mL vs baseline. FF/VI and FF, respectively, significantly improved compared with placebo trough FEV1 (172mL [p<0.001] and 136mL [p=0.002] and wFEV1 (302mL [p<0.001] and 186mL [p=0.003]), Treatment differences between FF/VI and FF approached significance for wFEV1 (160mL [p=0.06], but not for FEV1 (160mL, p=0.060), but not for FEV1 (302mL, p=0.405). Percent of rescue-free 24-h periods with FF/VI was 10.6% greater than FF and 19.3% greater than placebo. Statistically significant (p=0.032) urinary cortisol suppression was seen with FF/VI (ratio=0.82) relative to placebo, but not for FF Adverse event and safety profiles were similar across treatment groups. Conclusions: Significant improvement in lung function was observed with FF/VI and FF in patients with persistent asthma. Addition of VI to FF did not significantly improve FEV1, but a numerical increase was seen. The high placebo response in evening trough FEV1 may have influenced the assessment of efficacy in this study. Funded by GSK (HZA108627, NCT01165138).

Introducing the novel corticosteroid FF in combination with the long-acting beta2 agonist VI

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Introduction: The FF in combination with the LABA VI is in development for asthma and COPD. Objectives: To assess the safety and tolerability of the novel inhaled corticosteroid (ICS) fluticasone furoate (FF) in combination with the long-acting beta2 agonist (LABA) vilanterol (VI) administered once daily (OD) in patients with asthma William W. Busse1, Paul M. O’Byrne2, Eugene R. Bleeker1, Jan Lowitt1, Ashley Woodcock4, Leslie Andersen, Jody West3, Loretta Jacques4, Ludovic Apoux5, Eric D. Bateman6, 1Department of Medicine, University of Wisconsin, Madison, United States; 2Krefting Research Centre, University of Gothenburg, Sweden; 3Michael G DeGroote School of Medicine, McMaster University, Hamilton, Canada; 4School for Genomics and Personalized Medicine, Wake Forest School of Medicine, Winston-Salem, United States; 5Krefting Research Centre, University of Gothenburg, Sweden; 6School of Translational Medicine, University of Manchester, United Kingdom; 7Respiratory Medicines Development Center, GlaxoSmithKline, Research Triangle Park, United States; 8Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom; 9Respiratory Medicines Development Centre, GlaxoSmithKline, Uxbridge, United Kingdom; 10Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Uxbridge, United Kingdom; 11Department of Medicine, University of Cape Town, South Africa

Methods: Patients (N=503) were randomised (2:2:1) to FF/VI 100/25mcg or FF/VI 200/25mcg OD in the evening, or fluticasone propionate (FP) 500mcg twice daily. Safety evaluations included adverse events (AEs), non-fasting glucose and potassium, urinary cortisol (UC), heart rate (HR), pulse rate and ophthalmic assessments. Results: Statistically significant UC suppression was seen with FP compared with both FF/VI groups at Weeks 12 and 28 (p<0.006), but not at Week 52. Potassium and glucose values were similar across groups. Increases in pulse rate (10min post dose: Week 25) were reported with FF/VI vs FP (100/25mcg: 3.4bpm, p=0.002; FF/VI 200/25mcg: 3.3bpm, p=0.003). No significant differences with FF vs FP were observed on QTc(F) outputs or HR with Holter monitoring. AEs were reported by 66-69% of patients on FF/VI and by 73% on FP. Oral/oropharyngeal candidiasis (AEs: FF/VI 6.7%, FP 9%). Twelve SAEs were reported; one (worsening hepatitis on FP) was considered drug related. Low number of ‘special interest’ AEs (including ocular effects and pneumonia). Conclusions: FF/VI (100/25mcg or 200/25mcg) administered once daily over 52 weeks was well tolerated by patients aged ≥12 years with asthma. The overall safety profile observed for FF/VI did not reveal any findings of significant clinical concern and was similar to FP. Funded by GSK (HZA108639, NCT01018186).
QMFiS is an investigational once-daily (QD), fixed-dose combination of indacaterol (IND) and mometasone furoate (MF). This study assessed the long-term safety of QMFiS in patients (pts) with persistent asthma.

In this randomized, double-blind, multi-centre, Phase II study, pts (12–70 y) received QMFiS (IND maleate 500 μg/MF 400 μg) or MF (400 μg), both administered QD via the Twiskhaler® for 6–21 months. Systemic exposure data show that this QMFiS dose is comparable to 150 μg IND/160 μg MF in the Concept® (Breezhaler®) inhalation device, the delivery device that will be used in future studies. The primary endpoint was time to first serious exacerbation (resulting in hospitalisation, intubation or death). A key secondary endpoint was the cumulative incidence of serious exacerbations. AEs and SAEs were recorded.

Of 8 of 1519 randomised pts (QMF, 756; MF, 763) were hospitalised for a serious exacerbation (QMFiS, 2; MF, 6); none required intubation or resulted in death. QMFiS reduced the risk of a serious exacerbation vs MF by 69% (hazard ratio=0.31; 90% CI 0.21, 0.46; p=0.0076). The difference in cumulative incidence was 0.52 percentage points (90% CI 0.14, 1.14, 0.09) in favor of QMFiS, meeting the pre-specified, non-inferiority margin of difference of 1 percentage point. Similar proportions of pts experienced AEs and SAEs in both groups (QMFiS, 74.0% and 4.0%; MF, 73.4% and 5.8%). Most frequent AEs with QMFiS and MF were cough and asthma, respectively. There was one death (MF group), which was not treatment or asthma related. Mean plasma MF concentrations were similar in both groups.

QMFiS QD was not associated with additional safety concerns vs MF monotherapy in pts with persistent asthma.

Asthma control remains suboptimal in many patients as indicated by exacerbations and deteriorating symptoms. This pooled analysis of up to 5 randomized double-blind studies assessed the effects of fluticasone propionate (FP) and formoterol fumarate (FORM) in a single aerosol inhaler (FLUT/FORM) in asthma exacerbations.

Methods: Adults and adolescents with asthma (all severities) were randomized to FLUT/FORM (100/5, 250/5 or 500/20 μg bid), or equivalent nominal doses of FLUT (100, 200 or 500 μg bid; 5 studies) or FORM (10 μg bid; 3 studies) for 8 or 12 weeks. The proportion of patients with an exacerbation was assessed. Mild-to-moderate exacerbation was defined as peak expiratory flow rate >30% below baseline, awakening at night due to asthma symptoms, ≥4 times/day (each on ≥2 consecutive days); severe exacerbation was need for additional therapy, or emergency visit/hospitalization due to asthma.

Results: Significantly fewer patients reported exacerbations with FLUT/FORM than FLUT (27% [172/641] vs 33% [211/643]; odds ratio [OR] 0.75; 95% CI 0.59, 0.96) or FORM (18% [62/341] vs 31% [108/345]; OR 0.49; 95% CI 0.34, 0.70). The annualised exacerbation rate was significantly lower with FLUT/FORM than FLUT (ratio 0.66; 95% CI 0.61, 0.79; p<0.001) or FORM (0.55; 95% CI 0.44, 0.68; p<0.001). The risk of severe exacerbation was similar for FLUT/FORM and FLUT (2% [18/1264] vs 3% [18/643]; OR 0.66; 95% CI 0.32, 1.39), but lower with FLUT/FORM than FORM (2% [8/341] vs 10% [33/345]; OR 0.23; 0.10, 0.50).

Conclusion: FLUT/FORM significantly reduces the risk of reported asthma exacerbations (any severity) compared with its individual components.
P2098

Efficacy and safety of ciclesonide in the treatment of patients with persistent allergic or non-allergic asthma

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Aim: To evaluate the efficacy and safety profile of ciclesonide (CIC) in the treatment of persistent allergic or non-allergic asthma in a real-life setting in Austria.

Methods: 307 patients suffering from persistent asthma of any severity grade (42% treatment-naive) were enrolled in this non-interventional study (NIS). All patients used CIC for at least 3 months. Of the patients, 43.4% were prescribed concomitant medication, primarily short-acting β2-agonists. Efficacy was evaluated by FEV1, Asthma Control Questionnaire (ACQ), Asthma Quality of Life (AQLQ/S), asthma symptoms, physical activity limitations and use of rescue medication.

Results: Mean FEV1 % predicted increased from 75.1 ± 15.4% to 83.7 ± 14.9%. At the end of the observation period, the percentage of patients with daily symptoms that had declined from 33.2% to 3.9%, nighttime symptoms from 21.8% to 5.2%, physical activity limitations from 73.9% to 24.4%, and rescue medication usage from 70% to 29.3%. The mean total ACQ score was 2.32 ± 1.14 at baseline and 1.08 ± 0.88 at study end. The number of patients with well-controlled asthma (ACQ-score <1) increased considerably from 11.0% to 52.2%. Accordingly, clinically important mean improvements were observed in the total self-assessed AQLQ/S score. A low incidence of adverse drug reactions (ADR) was observed (4 ADRs in 3/307 patients).

Conclusion: This NIS in patients with persistent asthma confirmed the efficacy and safety of CIC in routine clinical care showing improvements in symptom control, lung function, and quality of life. CIC was well tolerated in this heterogeneous patient population.

P2099

Safety of formoterol in asthma clinical trials

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Background: We have previously reported safety data through 2006 from all AstraZeneca-sponsored, randomised, controlled, parallel-group trials with 3-12 months duration with formoterol. Data from 2007-2011 trials have now been added.

Methods: Risks associated with formoterol relative to non-LABA-treatments (ICS, SABA, placebo, salmeterol treatments, and conventional best practice, were assessed using rate and ratio measures for multiple safety endpoints.

Results: The 2007-2011 data added 15 trials and 22,599 patients including 17,447 treated with formoterol (with all concomitant ICS), increasing the combined dataset to 79 trials and 94,683 patients, of whom 67,380 received formoterol (94% using ICS). There were no asthma-related deaths in the new trials. In total, there were 8 asthma-related deaths among the formoterol-treated patients (exposure 33,700 years). No increased risk was observed for formoterol vs. non-LABA treatments for all-cause mortality (RR 0.94; 95% CI: 0.52-1.80), cardiac mortality (RR 0.47; 95% CI: 0.19-1.22), or cardiac-related SAEs (RR 0.94; 95% CI: 0.32-1.80). Asthma-related SAEs were significantly reduced for formoterol vs. non-LABA treatment (RR 0.63; 95% CI: 0.53-0.75). The new trials added a substantial number of black patients to the dataset, but no increased risk for asthma-related SAEs was observed for this subgroup in the combined dataset.

Conclusion: Use of formoterol in asthma patients, most using ICS, is not associated with any increased risk of asthma- or cardiac-related deaths or SAEs.

P2100

Prospective follow-up of novel bone turnover markers in asthmatics exposed to low or high doses of inhaled ciclesonide over 1 year

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Background: There is concern that asthmatics receiving long-term inhaled corticosteroids could develop systemic adverse effects on bone metabolism. We investigated if exposure to inhaled ciclesonide at high vs low doses over 1 year caused any adverse effects on sensitive biomarkers of bone turnover in asthmatics.

Methods: Post hoc analysis of stored bone marker samples in a subgroup from a prospective, randomised parallel group trial (Lipworth et al. Chest DOI:10.1378/chest.11-1748) where ciclesonide was titrated to control asthma against either mannitol airway hyper-responsiveness (AHR strategy) or control (based on symptoms, reliever use and lung function) over 1 year. 100 mild-moderate asthmatics, 18-65 years, with AHR to mannitol challenge had been bone marker samples available for analysis. Outcome measures: bone formation (PINP, PIIINP), resorption (ICTP, CTX) and adrenal suppression (overnight urinary corticosteroids). We divided patients into two groups at baseline based on their inhaled corticosteroid exposure (AHR strategy vs control group).

Results: There were 100 mild-moderate asthmatics, 18-65 years, with AHR to mannitol challenge. Bone formation (PINP, PIIINP) was significantly higher in the AHR strategy group compared to the control group. Bone resorption (ICTP, CTX) was significantly lower in the AHR strategy group compared to the control group. Adrenal suppression was not significantly different between the two groups.

Conclusion: Exposure to inhaled ciclesonide at high vs low doses over 1 year caused significant differences in bone turnover markers in asthmatics exposed to high doses of inhaled corticosteroids.
Results: In pts with mMRC ≤2 (respectively COPD 1425/1752), mean age was 63.1/63.9 years, FEV1 57.6/51.8% predicted, FEV1/FVC 53.9/51.6%. Differences of the GLOW1 and GLOW2 studies of notable pulse rate (FVC) at Day 1 and Wks 12, 26 and 52, 24-hr serial spirometry in a subset of patients for NV A237 and TIO, respectively, with no deaths. There were no reports of notable pulse rate (>130 bpm, or >120 and >90 bpm from baseline) and QTc interval (Flickerca) >500ms over 52 wks. Dry mouth incidence was less frequent with NV A237 (1.6%) vs TIO (5%). A clinically significant increase from baseline in pre-dose FEV1 was observed for NVA (101 mL) and TIO (173 mL) at Wk 12. The event-free rate for moderate or severe COPD exacerbation was 78.9% for NV A237 and 76.6% for TIO at Wk 52.

Conclusion: NV A237 once daily had a safety and tolerability and efficacy profile similar to tiotropium in Japanese patients with moderate-to-severe COPD over 52 weeks.

P2104

Sputum neutrophil monitoring is useful for long-term oxygen therapy in patients with COPD

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Long-term oxygen therapy (LTOT) is the treatment proven to improve survival in chronic respiratory failure patients, especially chronic obstructive pulmonary disease (COPD). Participation of airway neutrophil inflammation is suggested to be a part of illness, such as COPD. The aim of this study is to evaluate whether sputum neutrophil monitoring is useful for LTOT in patients with COPD exacerbations.

Twenty two patients, mean age were 72 years, were participated in this study. Twenty patients survived to the follow-up after 14 months of this study. Before receiving LTOT, mean sputum neutrophil was 8%. However, after LTOT administrations, sputum neutrophil was decreased to approximately 3% and reduced the number of hospitalizations including outpatient service. Also St George's Respiratory Questionnaire score (SGRQ) was significantly improved. In peripheral blood, downward tendency was seen, but not so significant. Before outpatient service in COPD patients, average neutrophil percentage in the sputum was gradually raised up to 19%±6%. So we could respond for COPD exacerbations at an early stage using corticosteroid and antibiotic drugs. While this neutrophil partciapate mechanism is still unknown, further study should be needed including cytokine evaluation. However, this study indicates that in patients with COPD, long-term oxygen therapy is associated with airway sputum neutrophil reduction.

P2105

The effect of high dose N-acetylcysteine (1200mg daily) on airway function and airway trapping in COPD patients – A double blinded randomized placebo controlled trial

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Introduction: High dose N-acetylcysteine (NAC) has both antioxidant and mucoytic effect. However, there was a lack of study to demonstrate its beneficial use in COPD patients.

Aims: To investigate the effect of high dose NAC (1200mg daily) on airway function in stable COPD patients

Methods: This is a 16-week double-blinded randomized placebo-controlled trial conducted in a government hospital in Hong Kong. Spirometry confirmed COPD patients (FEV1/FVC <70%) were recruited and randomized into treatment (NAC 1200mg daily) and placebo groups. Both patients and doctors were blinded for

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the group allocation. Lung function tests were measured at the beginning and at the end of the treatment period. Primary outcome variable: change from baseline over the treatment period in predose FEV1; secondary outcome variables included lung function time to first exacerbation, tolerability.

Results: 1293 patients were randomized. Both BUD/FORM and FORM improved predose FEV1 (improvements of 4.6% and 1.5%, respectively), the change from baseline was significantly greater with BUD/FORM vs FORM for 12-week period (p=0.001). Both treatments were well tolerated. The incidence and type of adverse events were similar in both groups; most commonly reported adverse events (BUD/FORM vs FORM) were COPD exacerbation 7.9% vs 4.6%, nasopharyngitis 5.1% vs 4.9% and bronchitis 2.0% vs 2.3%.

Conclusions: BUD/FORM 160/45 μg two inhalations daily was more effective than FORM 4.5 μg two inhalations daily in patients with moderate to severe COPD. Both treatments were well tolerated. Funding: AstraZeneca.

P2108
Budesonide/formoterol vs formoterol, both via Turbuhaler®, in patients with moderate to severe COPD: Phase III study results
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Background: This study evaluated the efficacy and tolerability of budesonide/formoterol (BUD/FORM) vs formoterol (FORM) in patients with moderate to severe COPD.

Methods: In this randomised, double-blind, parallel-group, phase III study (NCT01069289) patients with moderate to severe COPD for ≥2 years received either BUD/FORM 160/4 μg 2 inhalations twice daily via Turbuhaler® or FORM 4.5 μg 2 inhalations twice daily via Turbuhaler® for 12 weeks. Primary endpoint: salbutamol 100 μg via pMDI. Primary outcome variable: change from baseline over the treatment period in predose FEV1; secondary outcome variables included lung function time to first exacerbation, tolerability.

Results: 1293 patients were randomized. Both BUD/FORM and FORM improved predose FEV1 (improvements of 4.6% and 1.5%, respectively), the change from baseline was significantly greater with BUD/FORM vs FORM for 12-week period (p=0.001). Both treatments were well tolerated. The incidence and type of adverse events were similar in both groups; most commonly reported adverse events (BUD/FORM vs FORM) were COPD exacerbation 7.9% vs 4.6%, nasopharyngitis 5.1% vs 4.9% and bronchitis 2.0% vs 2.3%.

Conclusions: BUD/FORM 160/45 μg two inhalations daily was more effective than FORM 4.5 μg two inhalations daily in patients with moderate to severe COPD. Both treatments were well tolerated. Funding: AstraZeneca.

P2107
Effect of once-daily indacaterol in a predominantly Chinese COPD population: A 26-week Asia-Pacific study
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Background: Severe exacerbations of COPD require hospitalization and have serious long-term consequences for patients. Roflumilast (ROF) is a PDE4 inhibitor that significantly reduced moderate-to-severe exacerbations in clinical studies. Its effects on severe exacerbations and any adverse events leading to hospitalization have not been described previously.

Aim: To investigate the effects of ROF on the rate of hospitalizations resulting from severe exacerbations or any other adverse events in two 1-year studies (M2-124 and M2-125).

Methods: In a post-hoc pooled analysis of the pivotal studies of ROF 500 μg (n=1537) vs placebo (n=1554), statistical analyses were performed on the overall population and in patient subgroups with: A) severe/very severe COPD; B) frequent COPD exacerbations; and C) severe/very severe COPD and frequent COPD exacerbations. Negative binomial regression analyses were used to investigate the rate reduction for hospitalizations.

Results: In the overall population, ROF decreased the rate of hospitalizations resulting from severe exacerbations vs placebo by 21.6% (rate ratio 0.784; 95% CI 0.619, 0.993, p=0.0439), and overall there were trends towards extended times-to-onset of severe exacerbations leading to hospitalization. Although not statistically significant, ROF reduced hospitalizations resulting from any adverse event compared with placebo. In all subgroups analyzed, ROF had a positive numerical but not statistically significant effect on rate reduction of all-cause hospitalizations, time to hospitalization and risk of hospitalizations.

Conclusions: Roflumilast significantly reduced the rate of severe exacerbations leading to hospitalization vs placebo.
P2110

The effect of tiotropium on lung dynamic hyperinflation and treadmill exercise capacity in mild to moderate COPD

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Rationale: In previous studies tiotropium improved cycle exercise duration in GOLD II-IV COPD patients. This double-blind crossover study (NCT01072396) compared tiotropium with placebo in GOLD I and II COPD using treadmill exercise testing.

Methods: Patients were current or ex-smokers aged >40y with post-bronchodilator FEV1/FVC <70%, FEV1 ≥50% predicted, and dynamic hyperinflation (>100 mL inspiratory capacity [IC] decrease during incremental treadmill exercise). Patients received tiotropium 18 μg bid and placebo for 6 weeks each (random order, 4-week washout). Patients performed constant work rate treadmill exercise at 80% of peak incremental work rate before and after each treatment period. The primary endpoint was the difference in exercise isotime IC change from baseline to Week 6 between tiotropium and placebo. Secondary endpoints included change in exercise duration.

Results: Patients (n=126, 52% male) had mean age 61 y, post-bronchodilator FEV1/FVC 59% and FEV1 77% predicted. Baseline IC was 2.27 L and exercise duration 447 s. The difference in change in exercise duration between tiotropium and placebo was statistically significant (65 mL, P<0.009). The difference in change from baseline in exercise duration between tiotropium and placebo was a non-inferiority in the combined GOLD II+III (29.3 s, P=0.109) and GOLD I (23.5 s, P=0.415) groups, but was statistically significant for GOLD II (65.0 s, P=0.007).

Conclusions: Tiotropium was associated with reduced lung hyperinflation at rest and during exercise in GOLD I and II COPD patients. Significantly improved exercise duration was observed in GOLD II patients but not the combined or GOLD I groups.

P2113

Safety of fluticasone furoate (FF), an inhaled corticosteroid in combination with vilanterol (VI), a long-acting beta agonist in management of COPD exacerbations

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INTRODUCTION: FF and VI are in development as combined once-daily (OD) therapy for COPD.

Objectives: Assess the safety of FF/VI (3 strengths) and VI in COPD.

METHODS: In two replicate 1 year studies, after a 28 day run-in with ADVAIR DISKUS® 250/500mcg, subjects received FF/VI 50/25, 100/25, 200/25mcg or VI 25mcg OD. Primary endpoint: annual rate of moderate/severe exacerbations (described separately). Safety endpoints included all, serious and fatal Adverse Events (AEs), Local Steroid Effects (LSE, including candidiasis), bone disorders (BD, including fractures) and pneumonia.

RESULTS: Pooled safety findings are shown in the table.

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<th>VI</th>
<th>FF/VI</th>
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<tbody>
<tr>
<td>ITT: n (%)</td>
<td>25 (N=818)</td>
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<tr>
<td>AE*</td>
<td>575 (70)</td>
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<tr>
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<td>126 (15)</td>
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<tr>
<td>Fatal AE*</td>
<td>13 (2)</td>
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<tr>
<td>LSE*</td>
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<tr>
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<tr>
<td>Pneumonia*</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Pneumonia HR (95%CI) vs VI</td>
<td>1.7 (1.1, 2.8)</td>
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</tbody>
</table>

Pooled safety findings are shown in the table.

P2112

The impact of treatment of chronic obstructive pulmonary disease (COPD) on function, health status quality of life of patients

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INTRODUCTION: FF and VI are in development as combined once-daily (OD) therapy for COPD.

Objectives: Assess the safety of FF/VI (3 strengths) and VI in COPD.

METHODS: In two replicate 1 year studies, after a 28 day run-in with ADVAIR DISKUS® 250/500mcg, subjects received FF/VI 50/25, 100/25, 200/25mcg or VI 25mcg OD. Primary endpoint: annual rate of moderate/severe exacerbations (described separately). Safety endpoints included all, serious and fatal Adverse Events (AEs), Local Steroid Effects (LSE, including candidiasis), bone disorders (BD, including fractures) and pneumonia.

RESULTS: Pooled safety findings are shown in the table.

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HR, Hazard Ratio. "On-treatment." *On-/Post-treatment. HR for LSE and BD were significantly higher for FF/VI vs VI in all comparisons except LSE at 0.025 (p=0.065).

Conclusions: In COPD patients FF/VI exhibited similar rates of serious and fatal AEs to VI, although rates of AE, BD, LSE and pneumonia were greater with FF/VI than VI alone. The efficacy of the combination is currently being funded by GSK. HZC102871:NCT01009463, HZC102970:NCT01017952.
P2114 Inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) combination can decrease mortality of COPD patients, a nationwide population-based cohort study in Taiwan

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Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan

Background: Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. Current treatments, including pharmacological and non-pharmacological, can only alleviate symptoms, prevent exacerbation and improve quality of life. Previous large-scale studies failed to demonstrate benefit of mortality reduction which is also important for a chronic illness.

Objective: The aim of this study is to determine whether ICS/LABA combination can reduce mortality of COPD by using Taiwan National Health Insurance Database.

Method: This was a nationwide population-based cohort study. A total of 1989 COPD patients were identified from one million sampling cohort dataset between January to December in 2005. Patients with diagnosed in 2005 as COPD were grouped as non-controller user (n=638), ICS/LABA (n=265) and LAMA (n=86). Cox regression model was used to evaluate the incidence of mortality and pneumonia in the following 3 years to December 2008.

Result: The incidence of pneumonia was not different among three groups. However, COPD patients with older age (H.R. 1.398 for every increase of 10 years, p < 0.0001) and male gender (H.R. 1.414, p < 0.001) had higher incidence to have pneumonia. The mortality rate was lower in patients who used ICS/LABA combination as compared with non-controller group (H.R. 0.694, p = 0.0165)

Conclusion: In the selected Taiwanese population, COPD mortality was lower among patients who used ICS/LABA. Incidence of pneumonia was not increased with ICS/LABA, but significantly related increased age and male gender.

P2116 Effect of formoterol alone and in combination with aclidinium on electrocardiograms in dogs

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Introduction: Co-administration of a long-acting β-agonist with an anticholinergic is common clinical practice for the management of COPD, but there are concerns that systemic exposure to both drugs could cause undesirable pharmacodynamic effects on the heart.

Aims: To evaluate the cardiovascular safety of formoterol alone and in combination with aclidinium in conscious dogs.

Methods: Formoterol (1, 3, 10 μg/kg iv), aclidinium (50, 167 μg/kg iv) and formoterol/aclidinium (1+17, 3+50, 10+167 μg/kg iv) were administered to fasted male Beagle dogs (n=4; 13–16 kg) in a 3-min perfusion. Each dog received each dose with >6-day washout. Electrocardiograms were recorded at baseline (for 1 h) and 24 h post-administration (for 90 min) and assessed for ventricular tachycardia (VT) and premature ventricular complexes (PVC).

Results: Formoterol alone showed a dose-dependent trend to induce VT. VT was observed in 0, 1 and 4 animals treated with formoterol 1, 3 and 10 μg/kg, respectively. Aclidinium alone (both doses) did not induce VT. The combination of formoterol/aclidinium resulted in VT in a similar number of animals as formoterol alone (2 and 3 animals with 3±50 and 10±167 μg/kg, respectively). Similar results were observed for PVC. At the highest doses of formoterol and aclidinium, plasma concentrations corresponded to 32 and 4000 times those reported in human plasma after clinically relevant doses.

Conclusions: Addition of aclidinium does not alter the incidence or rate of formoterol-induced VT or PVC in dogs. These results suggest that aclidinium has no synergistic interaction on cardiac function with β-agonists.

This study was supported by Almirall S.A., Barcelona, Spain.

P2117 Risk of pneumonia related to budesonide use in COPD: An updated pooled analysis

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Background: A meta-analysis of 7 clinical trials reported no increase in the risk of pneumonia as an adverse event (AE) in COPD patients taking the inhaled corticosteroid (ICS) budesonide; however, others have reported a numerical increase. Recently, an eighth trial (NCT00419744) fulfilling the meta-analysis inclusion criteria has been completed. This updated meta-analysis includes data from all 8 clinical trials of budesonide.

Methods: Patient data were pooled from 8 clinical trials of inhaled budesonide (320–1280 μg/day), with or without formoterol, vs control (placebo or formoterol alone) in patients with stable COPD and ≥6 months of follow-up. The primary analysis compared treatment groups for the risk of pneumonia as an AE or serious AE (SAE) during the trial or within 15 days of the trial end. Cox proportional hazards regression was used to analyse the data on an intention-to-treat basis.

Results: Data from 8260 patients were included; 4616 received budesonide and 3644 received control treatment, with 3395 and 2647 patient-years of exposure to treatment, respectively. No statistically significant difference was found in the incidence of budesonide compared with non-ICS treatment groups for the occurrence of pneumonia as an AE (3.9% [n=179 patients] vs 3.3% [n=120]; HR 1.13, 95% CI 0.89–1.43) or a SAE (1.8% [n=82] vs 1.6% [n=59]; HR 1.02, 95% CI 0.72–1.43). Similarly, there was no statistically significant difference between the budesonide and non-ICS treatment groups for time to pneumonia as an AE (log-rank test 0.30) or a SAE (log-rank test 0.56).

Conclusion: The updated pooled analysis shows that budesonide (320–1280 μg/day) does not increase the risk of pneumonia over 12 months in patients with COPD.

Funding: AstraZeneca.

P2118 Long-term safety of twice-daily aclidinium bromide in COPD patients: A one-year, double-blind study

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Introduction: Aclidinium bromide is a novel, long-acting muscarinic antagonist currently under investigation for the maintenance treatment of COPD. Safety data from a long-term efficacy and safety trial of twice-daily (BID) aclidinium are presented here.

Methods: In this 52-week study, moderate-to-severe COPD patients were randomised (1:1) to receive aclidinium 200 μg or 400 μg BID. Safety was assessed via adverse events (AEs), vital signs, and 12-lead ECG.

Results: A total of 605 patients were randomized, and 602 (99.5%) were included in the safety population. Postbronchodilator FEV1, and percent predicted at screening were (mean ±SD) 1.55±0.54 L and 52.3±13.2 L. The incidence of AEs was similar across the aclidinium 200 μg and 400 μg groups and most were mild or moderate. The most common AE and most frequently reported AE leading to discontinuation was COPD exacerbation, with a similar percentage of patients between groups who discontinued due to exacerbations (200 μg, 9 (2.9%); 400 μg, 8 (2.7%)).

The incidence of typically expected anticholinergic AEs was low and similar between groups (e.g. dry mouth: 200 μg, 1.3%; 400 μg, 2.7%; constipation: 200 μg, 2.9%; 400 μg, 1.7%). Cardiac and cerebrovascular AEs did not occur in a dose-related manner. The 200 μg and 400 μg groups had similar incidences of serious AEs, with values (n (%)) of 29 (9.3%) and 29 (10.0), respectively. One patient in each treatment group died during the study (200 μg, biliary sepsis; 400 μg, subarachnoid hemorrhage), but neither death was deemed to be related to treatment.

Conclusions: Twice-daily aclidinium 200 μg and 400 μg were safe and well tolerated over 52 weeks with a similar safety profile for both doses.

P2119 Effect of augmentation therapy on immune function of patients with severe Alpha-1-antitrypsin deficiency

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Alpha-1 antitrypsin (AAT) deficiency is a hereditary disorder caused by mutations in the SERPINA1 gene. Individuals homozygous for the most common mutation Z have markedly reduced AAT concentrations and are predisposed to developing early-onset emphysema. Approximately 3% of AATD individuals have other deficiency alleles including Null alleles which do not express AAT. Although AAT production in monocytes is relatively small in comparison with hepatocytes, local regulation of the antiprotease shield represents an important first line of defence in times of infection and inflammation.

Our aim was to investigate the anti-inflammatory properties of AAT by studying individuals homozygous for Null mutations who were receiving augmentation therapy with human plasma derived AAT, and comparing them to ZZ individuals and MM healthy controls.

We isolated peripheral blood monocytes from Null/Null and ZZ patients (with/without therapy), and comparing them to ZZ individuals and MM healthy controls.

Augmentation therapy was used to alternate IL-4 and IL-8 production from ZZ monocytes at both. Moreover, we noted a reduced chemotactic activity and superox-
ide production in AATD individuals receiving augmentation therapy in comparison to untreated AATD patients.

Augmentation therapy in AATD individuals (ZZ and Null/Null) appears to modulate immune function and may provide a rationale for reduced exacerbations in subjects receiving augmentation therapy.

P2120 NFAT subtypes in regulating Th2 lymphocytes

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Methods: Nuclear factor of activator T cells (NFAT), consists of five members and plays a pivotal role in regulating T lymphocyte activation. Among the five subtypes of NFAT, NFAT1, NFAT2, and NFAT4 were recognized as the key family members associated with allergic diseases. However, evidence regarding the functions of NFAT1 and NFAT2 in Th2 cells are still conflicting.

Aims and objectives: Therefore, we explored the functions of NFAT1 and NFAT2 on Th2 lymphocytes.

Methods: Knockdown of NFAT1 and NFAT2 using small interfering RNA (siRNA) was performed in the murine Th2 lymphocyte cell line (D10.G4.1). Real-time qPCR, Western Blotting and ELISA were performed to test the relative expression of Th2 cytokine mRNA and protein in cells and culture supernatant.

Results: D10 cells express IL-4, IL-5, IL-13 and GATA3 mRNA level. NFAT1 siRNA and NFAT2 siRNA selectively suppressed the expression of NFAT1 and NFAT2 respectively at both the mRNA and protein level. Higher levels of IL-4, IL-5 and IL-13 were seen in NFAT1 siRNA treated Th2 cells. This suggests that NFAT1 may play a negative role in Th2 cytokine expression. Interestingly, the opposite effect was seen with NFAT2 siRNA. NFAT2 siRNA down-regulated the expression of IL-4, IL-5 and IL-13 mRNA levels. This was associated with a reduction in the expression of GATA3 mRNA and protein.

Conclusions: NFAT1 may play a negative role in regulating Th2 cytokines whilst NFAT2 may have the opposite effect.

P2121 Umeclidinium (GSK573719) dose response and dosing interval in COPD

Akison Church1, Misha Beerahare2, Jean Brooks2, Rashmita Mehta2, Palvi Shah1. 1GlaxoSmithKline, Research Triangle Park, Durham, NC, United States; 2GlaxoSmithKline, GlaxoSmithKline R&D, Stevenage, United Kingdom

Introduction: Dose differentiation is important in selecting COPD treatments.

Objective: Characterize Umeclidinium (UMEC), a long-acting muscarinic antagonists, dose response in COPD patients.

Methods: Randomized, double-blind, placebo-controlled, crossover study. Subjects were randomized to a sequence of 3 treatments for 7 days separated by a 10-14 day washout. Four once-daily (OD) UMEC doses (15.6, 31.25, 62.5, 125mcg) or two twice-daily (BID) doses (15.6, 31.25mcg) were administered via dry powder inhaler: Tiotropium (18mcg) was an active control. Primary endpoint was morning trough FEV1; on Day 8; population model analysis was applied with ANCOVA. Population model analysis was applied with ANCOVA.

Results: 163 subjects (mean age 59.5yrs, 52% female) were randomized. Emax results were similar. 125mcg OD had more improvement in trough FEV1, was characterized with OD dose ordering of UMEC compared to placebo (n=115) for 24 weeks. Primary endpoint: trough FEV1 at 24 weeks. Powered secondary endpoint: change from baseline in % rescue-free 24h periods over 24 weeks. Safety assessments included adverse events (AEs), incidence of severe exacerbations and 24h urinary cortisol (UC) excretion.

Results: FF and FP significantly improved trough FEV1 compared with placebo (diff. 146mcL [p=0.009] and 145mcL [p=0.011], respectively). Significantly more % rescue-free 24h periods were reported for FF (44.8%) and FP (17.9%) than placebo (both p<0.001). Incidence of on-treatment AEs: FF 53%, FP 42%, placebo 40%. Incidence of on-treatment severe exacerbations: FF 3%, FP 2%, placebo 7%. Statistically significant UC suppression was seen with FF (t7=0.76, p=0.030) and FP (t7=0.77, p=0.036), relative to placebo.

Conclusions: FF 100mcg OD significantly improved trough FEV1 to a similar extent to FP 250mcg BD and reduced rescue use relative to placebo. FF was well tolerated with a similar AE profile and effect on 24h UC to FP. Funded by GSK (FAA1205P). NCT01159912.

P2122 Apolipoprotein A1 (ApoA1) abrogate cigarette smoke induced emphysema in mice

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Rationale: Apolipoprotein A-1 (ApoA1) have anti-inflammatory and antioxidant properties as well as cholesterol efflux.

Objectives: To determine if the expression of human ApoA1 within the lung protect against the development of emphysema.

Methods: Transgenic human ApoA1 mice (ApoA1 TG) were exposed to CS for 6 month and compared to control transgenic mice. Other ApoA1 TG mice were treated with intratracheal elastase in order to generate emphysema. Measurement; Lung inflammation, oxidative injury was measured in the lung. Emphysema was determined by measuring the mean intercept (Lm). Proinflammatory cytokines in the BALF were measured by ELISA and analysis of apoptosis using the TUNEL assay.

Results: Compared with control TG mice, ApoA1 TG mice had significantly less lung inflammation, oxidative damage and apoptosis as well as decreased levels of proinflammatory cytokines. ApoA1 attenuated the development of emphysema in both the smoke-induced and elastase-generated models.

Conclusions: Overexpression of ApoA1 prevents CS and elastase induced emphysema in mice. Augmentation of ApoA1 in the lung could be effective for the prevention or treatment of emphysema/COPD.

P2123 Efficacy and safety of once-daily (OD) fluticasone furoate (FF) in patients with persistent asthma: A 4-week randomised trial

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Introduction: The inhaled corticosteroid (ICS) CS is under development as a OD monotherapy for asthma and in combination with the OD long-acting beta antagonist montelukast for asthma and COPD.

Objectives: To evaluate the efficacy and safety of FF in patients ≥12 years with persistent asthma uncontrolled on a stable low-to-mid dose of ICS (≤500mcg fluticasone propionate [FP] equivalent total daily dose).

Methods: In this double-blind, double-dummy, placebo-controlled study, patients (N=343; ITT) received FF (100mcg OD in the evening via a new dry powder inhaler; n=114), FP (250mcg twice daily [BD] via DISKUS™; n=114) or placebo (n=115) for 24 weeks. Primary endpoint: trough FEV1 at 24 weeks. Powered secondary endpoint: change from baseline in % rescue-free 24h periods over 24 weeks. Safety assessments included adverse events (AEs), incidence of severe exacerbations and 24h urinary cortisol (UC) excretion.

Results: FF and FP significantly improved trough FEV1 compared with placebo (diff. 146mcL [p<0.009] and 145mcL [p<0.011], respectively). Significantly more % rescue-free 24h periods were reported for FF (44.8%) and FP (17.9%) than placebo (both p<0.001). Incidence of on-treatment AEs: FF 53%, FP 42%, placebo 40%. Incidence of on-treatment severe exacerbations: FF 3%, FP 2%, placebo 7%. Statistically significant UC suppression was seen with FF (t7=0.76, p=0.030) and FP (t7=0.77, p=0.036), relative to placebo.

Conclusions: FF 100mcg OD significantly improved trough FEV1 to a similar extent to FP 250mcg BD and reduced rescue use relative to placebo. FF was well tolerated with a similar AE profile and effect on 24h UC to FP. Funded by GSK (FAA1205P). NCT01159912.

P2124 RC kinase: A novel kinase expressed by alveolar macrophages that may play a role in COPD and IPF

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We have characterized a novel serine/threonine protein kinase, called RC kinase, that revealed expression in CD68+ alveolar macrophage and bronchial epithelial cells. Various cell lines upregulated RC kinase expression upon exposure to cigarette smoke extract, or conditions of oxidative or endoplasmic reticulum stress, and this
correlated with the production of IL-8. In acute (4 day) and sub-chronic (14 day) cigarette smoke-induced murine models of COPD, treatment with either intra-tracheally delivered KC kinase siRNA or orally administered novel and specific small molecule inhibitors caused a significant reduction in BAL neutrophilia, as well as decreased levels of KC and CCL-20. There was also a marked reduction in the amount of pulmonary inflammation. In a murine adoptive transfer model of idiopathic pulmonary fibrosis, both siRNA and small molecule antagonist treatment significantly inhibited hydroxyproline production, inflammation and cellular and biochemical markers of fibrosis. Taken together, these results strongly suggest that inhibition of TNF-α may provide a novel therapeutic approach for the treatment of COPD and IPF.

P2125
Statins worse pulmonary fibrosis through enhancing NLRP3 inflammasome activation

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1Department of Pulmonary Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; 2Pulmonary and Critical Care Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, United States

The role of statins is controversial. To evaluate the association between statin use and interstitial lung abnormalities (ILA) in a large cohort of smokers from COPDGene. Next, we evaluated the effect of statin pretreatment on bleomycin-induced fibrosis in mice and explored the mechanism behind these observations in vitro. In COPDGene, 38% of subjects with ILA were taking statins compared to 27% of subjects without ILA. Statin use was positively associated in ILA (odds ratio [OR] 1.60, 95% confidence interval [CI] 1.03-2.50, P=0.04) after adjustment for covariates including a history of high cholesterol or coronary artery disease. This association was modified by the hydrophilicity of statin and the age of the subject. Next, we demonstrate that statin administration aggravated lung injury and fibrosis in bleomycin-treated mice. Statin pretreatment enhances caspase-1-mediated immune responses in vivo and in vitro; the latter responses were abolished in bone marrow-derived macrophages (BMDM) isolated from Nlx-1-KO and Lpr-Gld mice. Finally, we provide further insights by demonstrating that statins enhance NLRP3-inflammasome activation by increasing mitochondrial reactive oxygen species generation in macrophages. Statin use is associated with ILA among smokers in the COPDGene study and enhances bleomycin-induced lung inflammation and fibrosis in the mouse through a mechanism involving enhanced NLRP3-inflammasome activation. Our findings suggest that clinicians should be aware that radiological evidence of ILD can develop in some COPD patients treated with statins.

P2126
Effects of combination of PI3Kδ and δ inhibitors on airway hyperresponsiveness in tobacco smoke-exposed mice

Yasuo Kurosawa1,2, Kenji Kikutani3,4, Keitaro Usuda5, Yuji Watanabe5, Shouichi Eto6,7, Tadashi Kusama1,2, Imperial College, London, United Kingdom

PI3Kδ and γ are known to be involved in inflammatory cell functions. We recently found upregulation of PI3Kδ in lung tissue of COPD patients and ability of a PI3Kδ inhibitor to restoration of steroid sensitivity in airway inflammation in tobacco-smoke (TS) exposed mice. Superior effects of combination of PI3Kγ and δ inhibitors to each inhibitor alone on airway inflammation in TS-exposed mice were also observed. The aim of this study is to evaluate role of PI3Kγ and δ in lung hyperresponsiveness (AHR) in TS-exposed mice. A/J mice were exposed to TS for 11 days and C57BL/10ScSn (C57) and/or fluticasone propionate (FP) were administered intranasally twice a day for 3 days after the last TS exposure. Airway responsiveness was determined as the increment of airway resistance (Δ(Raw)/Tdy) before and 1 min after histamine at 24 h after the last drug dosing. The effects of the PI3Kδ inhibitors on the contractile response to carbachol in guinea-pig tracheal smooth muscle preparation were also evaluated by the isometric tension recording. The concentration-response curve of carbachol was shifted to rightward and reduced the maximal response by AS (10-100 μg/ml) was limited in the tracheal smooth muscle. The AHR induced by TS was significantly reduced by AS (4 mg/ml; by 56% inhibition) and IC (4 mg/ml; 43%) alone. The inhibitory effects were enhanced by combination treatment of AS and IC (69%). Moreover, the combination of IC and FP showed stronger inhibition (96%) on the AHR. Considering with our previous findings, the combination of a PI3Kδ or PI3Kδ/δ inhibitor with corticosteroid may offer potential treatment of COPD.

P2127
A robust translational model of acute exacerbations in the tobacco-smoke and pol IC treated mouse

Vincent Russell1, Paul Woodman, Andrew Connolly, Diagne Spicer, Joanna Dlugozma, Alan Young. Pharmacology, Astranka, Stoke Court, Slough, United Kingdom

Exposure to tobacco smoke (TS) for 4 days induces steroid-insensitive lung inflammation in mice. The effect of adding the viral mimetic poly IC (PIC) to TS-exposed mice was examined.

Methods: Mice were exposed daily to either TS or air for 4d. Saline or PIC was administered intra-nasally. The time course of lung inflammation was examined 4-120hrs after the last exposure and cell numbers measured in the BAL fluid. The acute effects of oral Dexamethasone (DEX) 0.3mg/kg) or Rosflumilast (ROF 5mg/kg) on the peak inflammation were examined. The effects of DEX on the kinetics of the enhanced inflammation were also examined.

Results: TS caused a lung inflammation which was inhibited by ROF but not by DEX. PIC alone induced an inflammation that was not inhibited by DEX or ROF. Dosing PIC in addition to TS induced an exaggerated response that was significantly greater than the additive effect of the two stimuli. The enhanced response peaked 24hrs after the last exposure then slowly declined. Neutrophils were predominant over the first 48 hrs. Macrophage numbers increased at 24-72hrs and lymphocyte numbers peaked at 48-72hrs. The peak inflammation after TS/PIC exposure was significantly inhibited by ROF (56%, p<0.05) and DEX (56%, p<0.05), in contrast to the lack of efficacy of DEX against TS or PIC alone. A single dose of DEX after the last exposure reduced the exaggerated response over the entire 120hr study period, but did not fully resolve the inflammation.

Conclusions: TS exposure for 4 days induced a steroid-insensitive lung inflammation. Addition of PIC markedly enhanced the inflammatory response which was sensitive to both steroids and roflumilast, mimicking features of human COPD.

P2128
Inhaled cationic salts modulate macrophage function to reduce inflammation during LPS induced lung injury

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Pulmatrix is developing PUR118 as a host-targeted, dry powder therapy based on the inhalation of calcium salts for acute exacerbation (AE) control in chronic obstructive pulmonary disease and other inflammatory lung disease. Preclinical data suggest that this approach is effective against an array of pathogens and also reduces inflammation resulting from environmental stimuli such as tobacco smoke. We hypothesized that this treatment could have a beneficial effect in reducing lipopolysaccharide (LPS) induced lung inflammation by modulating the function of pulmonary macrophages. Mice were exposed to nebulized LPS (Pseudomonas aeruginosa) and PUR118, was delivered via a whole body exposure 1h post-LPS challenge. Four hours after LPS exposure inflammatory cell counts and chemokine and cytokine concentrations were determined in BAL. PUR118 treatment decreased total inflammatory cell counts and neutrophils in the BAL fluid of LPS challenged mice and correlated with reduced KC, IL-6 and TNF-α in BAL fluid. Separately, peritoneal macrophages were isolated from naïve mice and challenged with LPS in media supplemented with calcium to simulate conditions thought to be found in lung fluid lining after PUR118 treatment. Inflammatory mediator secretion and gene expression were determined 2h post LPS exposure. Macrophages stimulated with LPS in the presence of calcium exhibited a dose dependent decrease in KC, IL-6 and TNF-α secretion as compared to LPS-stimulated cells. Preclinical data from in vivo and in vitro studies strongly suggest that clinicians can be used to reduce lung inflammation and may reduce the risk of AE caused by infections during chronic lung disease.

P2129
Inhaled calcium salts reduce expression of inflammatory mediators associated with tobacco smoke exposure to reduce airway inflammation

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PUR118, an inhaled calcium based dry powder (DP) formulation exhibits preclinical anti-inflammatory and anti- infective activity. PUR118 may provide a novel approach for acute exacerbation control in patients with COPD and CF where the combination of underlying inflammation and pathogen infection results in reduced lung function and quality of life. The goal of this study was to evaluate the impact of PUR118 on gene expression in lung samples from a tobacco smoke (TS) exposure model. Mice were exposed to TS for 4d and treated with PUR118 or DP control 1h prior to TS. Mice were euthanized 4h after the last TS exposure and BAL and lung RNA were collected for cell counts, protein levels and QPCR analyses. Expression of 336 genes was evaluated using targeted QPCR arrays. TS exposure increased BAL cell counts that were reduced with PUR118 (79% reduction in neutrophils; p<0.005) and DEX (56%, p<0.05). Among genes found
downregulated with PUR118 treatment, many were associated with neutrophilic inflammation including: KC, MIP2, ENA78, IL-6, and MCP-1. BAL protein levels of several of these were similarly reduced by PUR118 compared to controls. Thus, PUR118 diminishes the inflammatory signals induced by TS exposure including many key drivers of neutrophilic inflammation at both the gene and protein level as a mechanism to reduce airway inflammation.

P2130

Protection against allergen-induced airway hyperresponsiveness (AHR) by olodaterol in guinea pigs is synergistically enhanced by tiotropium

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The ultra-long acting β2-agonist olodaterol has shown to be effective in asthma and COPD. Increased cholinergic tone, common to these diseases, may reduce β2-agonist responsiveness. In a guinea pig model of asthma, we investigated the protective effect of olodaterol combined with tiotropium. AHR was measured in the whole lung after a single injection of ovalbumin (OA), 1 h before OA, an intravenous injection of OA (4.9-fold decrease in PC100 compared to baseline), which was fully protected by olodaterol (2.3-fold increase in PC100), and tiotropium (1.3-fold increase). When combined, a synergistic 4.8-fold increase in PC100 was observed. After the LAR, AHR (2.8-fold decrease), was also protected by olodaterol, tiotropium and their combination (1.5-, 1.3- and 1.6-fold increase in PC100, respectively). OA-induced infiltration of inflammatory cells, measured by BAL, after the LAR, was not affected by any treatment. In conclusion, in a guinea pig model of asthma olodaterol and tiotropium protect against allergen-induced AHR after the EAR and LAR, without affecting inflammatory cell influx. Synergism between the drugs was found after the EAR, indicating that acetylcholine reduces the effectiveness of the β2-agonist and that the combination of olodaterol and tiotropium may be beneficial in the treatment of allergic asthma. (supported by Boehringer Ingelheim Pharma).

P2131

Effects of N-acetylcysteine on airway inflammation, airway hyperresponsiveness and abnormal lung function in chronic ozone-induced COPD model

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Background: Chronic exposure to ozone in mice induces chronic lung inflammation and emphysema, features of COPD. We determined to examine the preventive and therapeutic effects of N-acetylcysteine (NAC) on airway inflammation, airway hyperresponsiveness (AHR) and abnormal lung function.

Method: C57BL/6 mice were exposed to air or ozone (3ppm, 3h), twice a week over 6 wk, and then ozone exposure was discontinued for 6 wk. NAC treatment (100mg/kg, i.p. twice a week; for 6 wk) was carried out during exposure period or cessation period. Pulmonary function and airway responsiveness were measured and total cells and neutrophils cell in BALF were counted.

Results: Compared with air exposed mice, lung volume indices TFC, FRC, FVC were increased and respiratory indices FEV25/FVC, FEV50/FVC were decreased in ozone exposed mice and continued after ozone cessation. NAC inhibited AHR during cessation period. Total cells and neutrophils in BALF were increased in ozone exposed mice and returned to normal after ozone cessation. NAC given during exposure period reduced the total cell counts, but not the neutrophil counts.

Conclusions: AHR and abnormal lung function persisted in ozone induced COPD model despite cessation of ozone exposure. Though NAC had no effect on neutrophilic inflammation or abnormal lung function in ozone-exposed mice, it did inhibit AHR during cessation period. NAC interferes with airway smooth muscle dysfunction caused by chronic oxidative stress.

P2132

Interaction of the glutamatergic and nitricergic signaling system in the airway hyperactivity

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It is only little information regarding a possible interaction of glutamatergic and nitricergic system in the airways hyperactivity (AHR). We investigated the effect of agents modulating the activity of these systems on the experimental ovalbumin-induced AHR as well as on the changes of exhaled nitric oxide (eNO) levels. We used the agonists of NMDA receptors - N-methyl-D-aspartic acid (NMDA) and monosodium glutamate (MSG), selective competitive antagonist (D,L-2-amino-5-phosphonovaleric acid – AP-5) and selective non-competitive antagonist (dizocilpine - MK-801) of these receptors. We used also non-specific inhibitor of NO synthases N-omega-nitro-L-arginine metylester (L-NAME). The AHR to histamine or acetylcholine was evaluated in in vitro conditions. NMDA administration caused the increase of tracheal smooth muscle response in ovalbumin-induced HR to acetylcholine. The effect of MSG was less pronounced. MK-801 as well as AP-5 provoked the decrease of reactivity mainly to acetylcholine in tracheal smooth muscle, while the former, non-competitive antagonist was more effective. We recorded the changes in eNO levels. The activation of NMDA receptor with NMDA or MSG increased eNO levels. The inhibition of NO synthesis with L-NAME caused the fall of eNO levels. We suppose here the participation of constitutive isoforms of NO synthases mainly. MK-801 shows the more expressive effect on the eNO levels lowering sensitivity than other studied drugs. These results bring a whole new look regarding the relationship of the glutamatergic and nitricergic system in the airway inflammatory diseases.
Conclusion: Doxofylline significantly reduced cell transmigration in response to LPS, supporting an anti-inflammatory action.

P2135
Protective effect of fenpirofene on bronchi in rats with COPD
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Corticosteroid resistance in COPD is urgent problem so the search for drugs that have bronchodilator and anti-inflammatory effect at all stages of COPD is needed.

Aim: To study effect of non-corticosteroid drug fenpirofene (F) on contractile activity of bronchial smooth muscle (SM) in rats with COPD.

Methods: Model of COPD was induced in rats by nitrogen dioxide (NO2) exposure (15 ppm, 1,5 h/day, 60 days). F (0.15 or 1.5mg/kg) was administered per os daily before exposure to NO2. Control rats received 0.9% NaCl. Isometric contraction of bronchial segments caused by electrical stimulation (st) of preganglionic nerve or SM was recorded by displacement electromechanical transducer.

Results: Treatment with F at the acute stage of COPD (15 days) prevented the bronchial constrictor effect of NO2. Contractile reactions of bronchi were lower than in control with st both nerve (89.4%; 107.2%; for 0.15 and 15 mg/kg, control 118.5%; p < 0.05) and SM (89.5%; 88.4%; for 0.15% and 3.3% respectively, p < 0.05).

Dilatation effect of low dose F was mediated by interaction with capsaicin sensitive C-fibers that prevented the initiation of neurogenic inflammation as evidenced by lack of COPD structural changes in lungs. At stage of COPD (60 days) bronchodiator effect of low dose F did not appear; high dose F caused a greater SM relaxation with st muscle st (70.3%; 63.4%) than nerve st (91.2%; p < 0.05). Effect of high dose F was mediated not only the afferent component but due to its direct relaxing effect on SM.

Conclusion: Mechanism of F action on bronchial SM depends on its dose. Revealed bronchodilator and anti-inflammatory effect of extremely low dose F can be used for prevention of COPD development in persons exposed to aggressive environmental factors.

P2136
Effects of corticosteroid and montelukast treatment in inflammation in guinea pigs with chronic allergic inflammation
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The effects of montelukast or dexamethasone in asthma pathophysiology are barely understood. We evaluated the inflammation and the eosinophilic recruitment in distal lung parenchyma and airway walls in guinea pigs (GP) with chronic allergic inflammation. GP were inhaled with ovalbumin (OVA group-2xweek/4weeks). After 4th inhalation, GP were treated with montelukast (M group-10mg/kg/PD/day) or dexamethasone (D group-5mg/kg/IP/day). After 72 hrs of 7th inhalation, GP were anesthetized, lung strips were submitted to histopathological evaluation. On distal parenchyma both montelukast and dexamethasone were effective in reducing the number of eosinophils, RANTES and NF-κB positive cells compared to OVA group (p < 0.05). Montelukast was more effective in reducing the eosinax positive cells compared to dexamethasone treatment (p < 0.05). There was a more expressive reduction of IGF-1 and RANTES positive cells compared to OVA group (p < 0.05). Dexamethasone was more effective in reducing the number of eosinax and NF-κB positive cells than Montelukast (p < 0.05).

Conclusions: In this animal model, both corticosteroid and montelukast treatments contribute to the control of the inflammatory response in distal lung parenchyma and airway walls. Dexamethasone treatment induced a greater reduction of NF-κB expression in airway walls which supports one of the mechanisms that explains the higher efficacy of this therapeutic approach. Supported by: FAPESP, CNPq, LIM-20-HC-FMUSP.

P2137
Effect of low level light therapy (LLLT) on an experimental model of LPS-induced lung inflammation
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1Biophotonics, Nove de Julho - UNINOVE, São Paulo, SP, Brazil; 2Immunology, University of Sao Paulo - USP, Sao Paulo, SP, Brazil; 3Science and Technology, Federal University of Sao Paulo - UNIFESP, SP, Brazil

Acute lung injury (ALI) induced by lipopolysaccharide (LPS) exposure is characterized by cellular infiltrate, edema and altered airway responsiveness. Traditional treatments for ALI include strategies of mechanical ventilation and a variety of drugs such as, corticosteroids and other disease-modifying agents. However these conventional therapies may cause important side-effects that compromise long term therapies. In this sense, Low Level Light Therapy (LLLT) have already demonstrated promising data in reducing airway inflammation. Thus, in the present study we investigated the ability of LLLT to modulate neutrophil infiltration to the lungs. For that, Balb/c mice were submitted to daily doses of 10 mg of LPS for 3 consecutive days. LLLT group were submitted to irradiation daily at 2. 4 and 6 hours after LPS. CONTROL group received PBS and were not irradiated. On day 4, 24 hours after LPS exposure animals were sacrificed and LBA cellular, cytokine secretion and airway reactivity by FlexiVent were analyzed. Our results demonstrate a significant decrease in total cells and neutrophils recovered from the bronchoalveolar lavage (BAL) of LPS-treated animals after LLLT. We also detected reduced amounts of IL-6 but not IL-17 after LLLT. Airway reactivity to metacholine (MCh) also reduced. In conclusion, our data reveals a promising role for LLLT as an alternative therapeutic approach for acute lung inflammation.

P2138
Effect of CCR3 inhibitors on allergic airway responses in ascaris-sensitized cynomolgus monkeys
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Aim: CCR3 has historically been associated with the functional responses of eosinophils in various models of allergic disease. The goal of this study was to determine whether pre-treatment with CCR3 inhibitors via oral and inhaled routes attenuates asthma responses in ascaris sensitized Cynomolgus monkeys.

Methods: Animals received either oral (AP0 5 mg/kg, BID 10 days) or by inhalation (AR1) once or twice a day for 10 or up to 21 days prior to inhalated ascaris challenge. Changes in airway function (immediate and methacholine [MCh]) and inflammation (BAL & blood cells) were evaluated.

Results: Oral (AP0 5 mg/kg; BID 10 days) or inhaled (AR1 860 μg; BID 7 days) treatment showed a trend towards a reduced immediate ascaris and MCh response but did not reach statistical significance. A longer oral treatment (AP0 3 mg/kg; QD 20 days) resulted in a significant additive or synergistic effect on airway function but did lead to a greater reduction in BAL and blood eosinophils than AP0 or fluticasone alone.

Conclusion: Treatment with a CCR3 inhibitor in the non-human primates, Ascaris model of asthma, shows that a number of critical parameters can be affected which are significantly different to alterations in the recruitment of eosinophils. Overall, these observations suggest that CCR3 inhibition may have more global beneficial responses in an asthmatic setting than previously appreciated.

P2139
PK/PD profiles of the CXCL8 decoy protein PA401 after intravenous and intratracheal administration in saline and LPS exposed mice
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Neutrophils play a crucial role in acute and chronic lung diseases including ALI, COPD, and severe asthma, and their presence in the lung has been correlated to disease severity and progression. Among the mediators of neutrophil recruitment into the lung CXCL8 is considered the major player. CXCL8 exerts its chemotactic activity by binding to glycosaminoglycan (GAG) co-receptors on inhaled cells, thus creating a solid-phase haptotropic gradient and being properly presented to GPC receptors CXCR1/2 on neutrophils. We have engineered higher affinity for GAGs into human CXCL8 obtaining a protein-based competitor for the CXCL8/GAG interaction. By further knocking-out the GPCR domain, we have obtained a decoy protein (PA401) with potent anti-inflammatory characteristics.

PA401 has been tested in murine models of lung inflammation induced by lipopolysaccharide (LPS) showing strong dose-dependent neutrophil reduction in bronchoalveolar lavage fluid (BALF) after intravenous (IV) and subcutaneous (SC) administration. In the present study we have compared PA401 activity after IV and intratracheal (IT) administrations in the same model, using saline exposed mice as control. PA401 plasma levels were also measured to assess pharmacokinetic profiles. PA401 has strongly reduced BALF neutrophils number after IV and IT administration (up to ~76%). The blood cells increase due to LPS exposure was also partly normalized by IV, but not IT treatment, possibly due to the differences in plasma exposure. PA401 is a new biotherapeutic with a unique mode of action interfering with lung neutrophilic inflammation and with activity after systemic and local delivery to the lung.
247. The best of pharmacology treatments of airway diseases: new devices and drugs

P2141
Aerodynamic characteristics of dry powder inhaler (DPI) single-dose combination of budesonide with formoterol in vitro study validation
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Background: The aerodynamic properties of dry powder inhalers are essential for drug efficacy. Despite the availability of several devices, few studies have measured aerodynamic characteristics of the drug delivery using their proper device. Aim: To describe the aerodynamic characteristics of the combination dry powder inhaler (DPI) Alexina 1 single-dose AeroCops®(AA), which contains budesonide (BUD) and formoterol fumarate (FF) when compared with ForaSEF® Aerolizer®(FA) as the reference combination drug. Methods: They were assessed using quantitative sample analysis by high pressure liquid chromatography (HPLC), dose uniformity sampling apparatus (DUSA) and Andersen cascade impactor (ACI) to confirm the presence of active ingredients as well as the uniformity of released dose and the aerodynamic diameter of particles produced by their proper devices.

Results: Table 1 summarize the experiments.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Alexina®</th>
<th>ALB</th>
<th>ForaSEF®</th>
<th>BUD</th>
<th>ForaSEF®</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC %</td>
<td>111.41</td>
<td>103.80</td>
<td>110.59</td>
<td>104.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampling Uniformity mg</td>
<td>293.24 (12.91)</td>
<td>10.23 (0.47)</td>
<td>353.04 (11.48)</td>
<td>11.07 (0.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emitted dose delivered from the mouthpiece under specified in vitro</td>
<td>92.69 (109.25)</td>
<td>1.06-1.00</td>
<td>90.63-108.01%</td>
<td>91.31-107.14%</td>
<td>91.32-111.83%</td>
<td></td>
</tr>
<tr>
<td>Mass (% aerodynamic diameter &lt;5 μm (ACT))</td>
<td>140.67 (44.71)</td>
<td>6.18 (56.13)</td>
<td>181.53 (53.56)</td>
<td>5.46 (52.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Experiments recommended by European Pharmacopoeia.

Alexina showed microbial quality control within acceptable <100CFU/g and the water container were normal of 4.76% by Karl Fischer test.

Conclusions: Alexina® and ForaSEF® had active ingredients, dose uniformity and appropriate aerodynamic diameter to their respective dry powder inhalers. Funded by Acht Laboratórios.

P2142
Consider the turbulent energy not inhalation flow when patients use dry powder inhalers (DPIs)
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During an inhalation the formulation of a DPI is de-aggregated by a turbulent energy created by the interaction between the DPI’s internal resistance and the patient’s inhalation flow. We have measured the inhalation profiles of asthmatic children (CHILD; n=16, FEV1 79% predicted), asthmatic adults (ADULT; n=53, FEV1 72%) and COPD (n=29, FEV1 42%) when they inhale through an Aerolizer® (AERÖ), Accuhaler® (ACC), Turbulhaler® (THB) and Easyhaler® (EASY) using their real life DPI technique. These are low, medium, high and high resistance DPIs. A summary of the inhalation characteristics is presented below.

<table>
<thead>
<tr>
<th>Mean (SD) data</th>
<th>AERÖ</th>
<th>ACC</th>
<th>THB</th>
<th>EASY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIF (L/min)</td>
<td>71.4 (21.5)</td>
<td>53.3 (24.2)</td>
<td>44.8 (16.0)</td>
<td>45.5 (13.2)</td>
</tr>
<tr>
<td>P (kPa)</td>
<td>2.37 (1.33)</td>
<td>2.10 (1.70)</td>
<td>2.55 (1.79)</td>
<td>5.26 (2.89)</td>
</tr>
<tr>
<td>Accel (kPa)</td>
<td>7.2 (6.7)</td>
<td>5.4 (5.5)</td>
<td>6.7 (5.9)</td>
<td>11.7 (9.4)</td>
</tr>
<tr>
<td>IV (L)</td>
<td>1.22 (0.68)</td>
<td>1.95 (0.76)</td>
<td>1.90 (0.73)</td>
<td>1.00 (0.46)</td>
</tr>
<tr>
<td>Ti (sec)</td>
<td>1.69 (0.38)</td>
<td>1.50 (0.46)</td>
<td>1.52 (0.17)</td>
<td>1.62 (0.23)</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIF (L/min)</td>
<td>93.7 (25.9)</td>
<td>76.3 (23.8)</td>
<td>62.0 (17.2)</td>
<td>58.3 (14.4)</td>
</tr>
<tr>
<td>P (kPa)</td>
<td>4.05 (2.9)</td>
<td>3.96 (2.39)</td>
<td>4.44 (2.39)</td>
<td>8.48 (4.13)</td>
</tr>
<tr>
<td>Accel (kPa)</td>
<td>12.6 (9.8)</td>
<td>11.9 (8.8)</td>
<td>13.2 (15.0)</td>
<td>20.9 (15.9)</td>
</tr>
<tr>
<td>IV (L)</td>
<td>1.96 (0.77)</td>
<td>1.91 (0.73)</td>
<td>1.63 (0.74)</td>
<td>1.68 (0.74)</td>
</tr>
<tr>
<td>Ti (sec)</td>
<td>1.54 (0.34)</td>
<td>1.61 (0.56)</td>
<td>1.63 (0.45)</td>
<td>1.55 (0.47)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIF (L/min)</td>
<td>81.8 (25.4)</td>
<td>62.0 (22.4)</td>
<td>50.9 (15.3)</td>
<td>49.6 (15.3)</td>
</tr>
<tr>
<td>P (kPa)</td>
<td>3.13 (1.88)</td>
<td>2.68 (1.80)</td>
<td>2.94 (1.9)</td>
<td>6.29 (3.55)</td>
</tr>
<tr>
<td>Accel (kPa)</td>
<td>8.68 (6.78)</td>
<td>6.74 (7.28)</td>
<td>8.51 (6.66)</td>
<td>14.0 (9.9)</td>
</tr>
<tr>
<td>IV (L)</td>
<td>1.71 (0.83)</td>
<td>1.79 (0.87)</td>
<td>1.50 (0.80)</td>
<td>1.52 (0.80)</td>
</tr>
<tr>
<td>Ti (sec)</td>
<td>1.71 (0.64)</td>
<td>1.53 (0.24)</td>
<td>1.57 (0.20)</td>
<td>1.68 (0.68)</td>
</tr>
</tbody>
</table>

PIF, peak inhalation flow; P, peak turbulent energy; Accel, acceleration rate; IV, inhalation volume; Ti, duration of inhalation.

Inhalation flow should not be considered in isolation. The turbulent energy and acceleration rate of the inhalation were the greatest for the DPI with the highest resistance.

P2143
The effect of airway alkalization by nebulized sodium bicarbonate on airflow blood flow
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Background: The airway acidities in a variety of inflammatory lung diseases as measured by exhaled breath condensate (EBC). We have demonstrated in vitro that alkalization improves absorption of cationic bronchodilators, such as albuterol and tiotropium, both in airway epithelia and smooth muscle cells; however, the rationale of airway alkalization therapy is not fully understood.

Objective: The purpose of the study was to determine the effect of nebulized sodium bicarbonate (NaHCO3) solution on airway vascular smooth muscle function.

Methods: Ten healthy non-smoker volunteers participated in the study. To assess airway pH, EBC was collected pre- and post-administration of 4.2% NaHCO3 (pH4.8). NaHCO3 induced CO2 production was evaluated with a real-time mass spectrometer gas analyzer by measuring Phase 1 and end-tidal CO2 levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec. Airway vascular smooth muscle responses were assessed by measuring airway blood flow (Qaw.).

Results: After NaHCO3 administration for 15 min using a heated ultrasonic nebulizer, EBC pH increased from 7.54±0.2 to 8.07±0.09 units (p<0.05). Pre- and post-treatment exhaled CO2 levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec. Airway vascular smooth muscle responses were assessed by measuring airway blood flow (Qaw.).

Conclusion: Nebulized NaHCO3 can increase airway pH without significant effects on exhaled CO2 levels in healthy subjects. NaHCO3 induced increase in Qaw, together with elevated airway pH, could improve absorption of inhaled cationic bronchodilators.
P2144

The investigation of inhalation continuous duration for dry powder inhalers in asthmatic patients

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Background: Dry powder inhalers (DPIs) have been important for management of asthmatic patients. And instruction for use of inhaler devise was effectively for control of asthma. Although inhalation technique of DPIs that inhalating fast with maximum force from start to stopping was reportedly important, effective inhalation continuous duration was unknown. In this study, we evaluate effect of instruction considering inhalation continuous duration in asthmatic patients.

Methods: One hundred and thirty nine asthmatic patients who use fluticasone propionate discus or budesonide turbuhaler were studied. Insufficient peak inspiratory flow rate (PIF) and length of inspire continuous time were evaluated by discuss-trainer or turbuhaler-tester or In-Check. Of 139 patients, 22 without sufficient PIF were omitted from the study. InstructIon considering inhalation continuous time was done for 117 patients and effects for forced expired volume in one second (FEV1.0) and peak expiratory flow rate (PEF) was evaluated.

Results: In all patients groups distinguished by inhalation continuous duration before instruction, significant increase of inhalation continuous duration was found after instruction (p value of all groups were p<0.01). And Significant improvement of FEV1.0 and PEF was found after instruction in patients group with inhalation continuous time less than one second (both of FEV 1.0 and PEF, p<0.01).

Conclusion: In control of asthmatic patients, instruction considering inhalation continuous duration was useful and instructing not only inhale fast and forcefully, adding “continue inhalation with deeply breath more than one second” is considered to be recommend from our results.

P2145

Pharmacokinetics (PK) of single doses of mometasone furoate (MF) delivered via the Breezhaler® (BH) and Twisthaler® (TH) devices in healthy subjects

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Background: QMF149 is being developed as a fixed dose combination of the long-acting β2 agonist indacaterol and the inhaled corticosteroid MF for treatment of asthma and COPD. Indacaterol is approved in the single dose dry power inhaler (DPI), BH for treatment of COPD (Onbrez® Breezhaler®). MF is approved in the multiple-dose DPI, TH for treatment of asthma (Asmanex® Twisthaler®). Due to its low oral bioavailability, systemic exposure after inhalation of MF reflects the amount of drug delivered to and absorbed from the lung.

Objective: To evaluate the PK of single doses of MF administered by oral inhalation via BH and to compare the systemic exposure to MF delivered via BH and TH devices.

Methods: This open-label, single-dose, crossover study recruited 24 healthy subjects to sequentially receive MF TH (400 μg) and escalating doses of MF BH (50, 100, 200, 400 μg). PK data were obtained up to 72h post-dose.

Results: Twenty subjects completed all treatments. Dose-normalized AUC last for all treatments (mean T 1/2: 12-13h). For the Visit 2 procedure, the mean number of inhalations to sequentially receive MF TH (400 μg) and escalating doses of MF BH (50, 100, 200, 400 μg). PK data were obtained up to 72h post-dose.

Conclusion: Systemic exposure of MF increased in a dose proportional manner over the dose range 50-400 μg for the MF BH. The estimated average dose of MF BH expected to provide systemic exposure comparable to the approved MF TH dose of 400 μg was 195 μg (90% CI: 175, 215).

P2146

An open-label trial to investigate the dose delivery and tolerability of inhalable dry powder mannitol (IDPM) using low output and high output Orbital® inhalers across defined flow rates in healthy volunteers

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Introduction: Current dry powder inhalers (DPIs) typically deliver up to 30mg as the emitted powder mass. The Orbital® DPI is a disposable, single-use, pre-filled product being developed to deliver 400mg of mannitol to the lung via a number of inhalations. The assessment of emitted powder mass and tolerability is the focus of this trial.

Methods: Open-label trial in healthy subjects >18 years with baseline FEV1 >70% of predicted to determine the tolerability and dose delivery of IDPM across two defined flow rates using low and high output Orbital DPIS. Subjects who completed a full inhalation at any flow rate at Visit 1 progressed to Visit 2 at which time up to a maximum dosage of 400mg of IDPM was administered by sequential dosing.

Results: The single inhalation shot weights from the sequential assessments are shown in Table 1. For the Visit 2 procedure, the mean number of inhalations required to empty the DPI was 7.5 (SD 1.76; Range 5-12). The mean shot weight per inhalation was 43.9μg, mean cumulative shot weight after 5 inhalations was 300μg (SD 36). Visit 1 shot weights (μg)

Conclusion: Compared to conventional DPIS, the Orbital DPI is capable of delivering many-fold greater masses of dry powder over repeated inhalations. Further development is warranted to investigate the upper limits of dose delivery and to examine the utility of the device with other engineered particles.

P2147

Lung bioavailability of beclomethasone dipropionate and formoterol fumarate fixed dose combination administered using a pMDI or a novel DPI: NEXThaler®

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Introduction: NEXThaler® is a novel, easy to use, dry power inhaler (DPI) containing the fixed combination of beclometasone dipropionate (BDP) 100 μg and formoterol fumarate (FF) 6 μg, formulated for extrarne delivery. This will provide physicians and patients with an alternative inhaler device for treatment of asthma able to ensure delivery of the drugs to the lungs especially in patients with poor hand-breath coordination.

Objective: To compare the lung bioavailability of beclometasone monopropionate B17MP (active metabolite of BDP) and FF after administration of the fixed combinations using NEXThaler® or the pMDI Foster®

Methods: An open-label, two-way crossover, single-dose design was used. Activated charcoal was administered to block gastrointestinal absorption and pMDI use was optimized via space device. Adult asthmatic patients (n=24) were randomised to undergo two single dose treatment clinic visits, separated by a 7-day wash-out period. At each treatment visit, blood samples were collected over 24h for pharmacokinetic evaluation.

Results: The ratios (and 90% CI) for AUClast of B17MP and FF when comparing NEXThaler® to pMDI fell entirely within the bioequivalence region of 80-125%, showing that the lung bioavailability of both components was equivalent. No clinically significant trend to change in blood pressure or heart rate after dosing with either NEXThaler® or pMDI was observed.

Conclusion: BDP and FF lung bioavailability using the fixed dose combination NEXThaler® and pMDI was equivalent in the target population. Furthermore, treatment with NEXThaler® was well tolerated with no safety concerns.

P2148

Comparative in vitro performance of a new re-usable breath-actuated nebulizer (BAN) with other high performance systems intended for domiciliary use – 2: Portable battery-compressor

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Rationale: Treatments with home based compressor/nebulizer systems can of-
fer very different delivery characteristics. We evaluated a new, reusable BAN
(AeroEclipse-XL®, Trudell Medical International) in breath-actuated mode with
its portable (Ombra®) battery-compressor.
Methods: The nebulizer-on-test (n=5/group) was filled with 2.5–mL, 1.0 mg/mL
albuterol (Ventolin®, GSK Canada Inc.), and connected to a breathing simula-
tor (ASL5000, InMar Medical, Pittsburgh, PA) mimicking adult tidal breathing
(VT= 600 mL; duty cycle = 33%; rate = 10 cycles/min). Emitted aerosol was
captured on a filter at the mouthpiece, replaced at minute intervals until onset
of sputtering, defining run time. Recovery/assay of salbutamol was undertaken
by HPLC-UV spectrophotometry. Fine droplet fraction (FDF<4.7 μm) and mass
median droplet diameter (MMD) were determined by laser diffractometry. Total
fine droplet mass (FDM<4.7 μm) was the product of total mass and FDF<4.7 μm.
Comparative measurements were made with the Sprint® (PARI, Germany) and
MicroPlus® (Philips-Respironics, Germany) nebulizers using PARI BOY® Mobile
S® and Inspiration Micro Elite® portable compressors respectively.
Results: See Table

<table>
<thead>
<tr>
<th></th>
<th>BAN</th>
<th>Sprint</th>
<th>Sidestream</th>
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<tbody>
<tr>
<td>FDF&lt;4.7 μm (%)</td>
<td>68 ± 4.9</td>
<td>52 ± 0.7</td>
<td>52 ± 2.8</td>
</tr>
<tr>
<td>MMD (μm)</td>
<td>3.55 ± 0.04</td>
<td>4.55 ± 0.05</td>
<td>4.46 ± 0.23</td>
</tr>
<tr>
<td>FDM&lt;4.7 μm (μg)</td>
<td>47 ± 32</td>
<td>34 ± 20</td>
<td>297 ± 20</td>
</tr>
<tr>
<td>Run-time (min)</td>
<td>12</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Conclusions: The BAN/Ombra® system provided highly respirable aerosol with
FDM<4.7 μm substantially greater than the benchmark systems. Its run time reflects
the fact that aerosol is only delivered during inhalation and not wasted to the
environment.

P2149
The absorption, distribution, metabolism and excretion (ADME) of single
oral doses of AZD5069, a novel CXCR2 antagonist, in healthy male
volunteers
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Background: AZD5069 is a CXC chemokine receptor-2 (CXCR2) antagonist with
potential as a novel COPD treatment. Initial studies have indicated an acceptable
safety profile for AZD5069. This study characterised the ADME of a single oral
dose of AZD5069.

Methods: In this phase I, open-label, non-comparative, single centre study, healthy
male volunteers received a single oral dose of 120 mg [14C]AZD5069. Blood and
urine samples (for radioactivity analysis, metabolite profiling, identification and
bioanalysis of AZD5069) and faeces samples (for radioactivity analysis and
metabolite profiling) were collected. Safety and tolerability were also assessed.

Results: Subjects (n=6) were white males (aged 50–65 years, mean BMI 25.6
kg/m²). The mean recovery of radioactivity in urine and faeces was 100% (range
98–103% [65% in urine, 35% in faeces]). 6.7% of the AZD5069 dose was re-
covered unmetabolised in urine. AZD5069 was rapidly absorbed and the apparent
terminal elimination half-life was 10 hours. There were no deaths, serious adverse
events (SAEs) or withdrawals due to AEs. Four subjects reported 6 AEs, with
terminology that is most commonly observed event. There were no clinically significant
safety and tolerability findings, other than the expected reversible reduction
in circulating neutrophil numbers.

Conclusion: Absorption of AZD5069 was rapid. Complete recovery of radioac-
tivity was attained, with the majority being excreted in the urine. Only a small
fraction was renally excreted as parent drug, suggesting that metabolism is the
primary route of elimination. No safety concerns were identified.

P2150

P2151
The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone
furoate (FF) and vilanterol (VI) combination in subjects with severe renal
impairment
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Background: A combination of the novel corticosteroid FF and long-acting beta,
agonist VI (FF/VI) is being developed as a once-daily inhaled treatment for asthma
and COPD.

Objectives: To investigate the effect of severe renal impairment on FF and VI PK
and PD.

Methods: Open-label, parallel group study of repeat dose once-daily FF/VI
200/25mcg (7 days) in 9 subjects with severe renal impairment (CrCl<30mL/min)
and 9 matched control healthy subjects (by gender, ethnicity, age (±5 years) and
BMI (±15%)). FF and VI PK parameters were assessed on Day 7. PK parameter
point estimates (90% confidence interval [CI]) were constructed for the ratio of
geometric means (renally impaired:healthy subjects). Non-inferiority was to be
concluded if the upper 90% CI for the ratio was >2 for the Day 7 comparison.

Systemic PD effects of FF (0–24h serum cortisol) and VI (0–4h heart rate and
serum potassium) were assessed on Day 7.

Results: For FF AUC(0–24) and Cmax the geometric mean ratio [90% CI] for renal:
healthy was 0.91 [0.60, 1.38] and 0.96 [0.57, 1.61], respectively. For VI
AUC(0–24) and Cmax the geometric mean ratio [90% CI] for renal: healthy was
1.56 [1.27, 1.92] and 0.70 [0.49, 1.00], respectively. Administration of FF/VI
200/25mcg to subjects with severe renal impairment did not result in significantly
greater effects on serum cortisol, heart rate or serum potassium compared with
healthy subjects.

Conclusions: There was no evidence of clinically relevant increases in FF or VI
systemic exposure or systemic pharmacodynamic effects in subjects with severe
renal impairment compared with healthy subjects.

Funded by GSK (HZ1113970; NCT01266980).

P2152

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383s
P2153

Absorption, distribution, metabolism, and elimination (ADME) of umecilidinium (UCEM) in healthy adults

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Introduction: Umecilidinium (UCEM, GSK573719) is a new, long-acting muscarinic antagonist in development for treatment of chronic obstructive pulmonary disease (COPD).

Objectives: Evaluate the absorption, distribution, metabolism and elimination (ADME) of UCEM following single IV and oral doses of [14C]-UCEM.

Methods: This was an open, non-randomised ADME study of 6 healthy male subjects. There were two dosing periods: (1) a 65mcg IV dose of [14C]-UCEM (7.1mcCi) infused over 30min, and (2) a 1000mcg dose of [14C]-UCEM (50mcCi) administered orally. The dosing periods were separated by a washout of ≥28 days. Total radioactivity was measured in plasma, urine and faeces for 7–10 days following each dosing period.

Results: Following IV administration, the derived area-under-the-curve (0–∞) demonstrated that only ~20% of total radioactivity in plasma was parent UCEM, suggesting the predominance of UMEC metabolites. The geometric mean volume of distribution of IV UMEC was 86l, suggestive of tissue compartmentation. By day 8, approximately 58% and 22% of IV UMEC-associated radioactivity was excreted in the faeces and urine, respectively. Oral UMEC is poorly absorbed with <1% of administered parent drug detected in plasma (all concentrations non-quantifiable). Following oral administration, total radioactivity in the faeces and urine was 92% and 3% of the administered oral UMEC dose respectively, confirming negligible gut absorption.

Conclusions: Oral UMEC bioavailability is negligible. Intravenous UMEC is mainly removed from plasma by metabolism and subsequent biliary secretion, and to a lesser extent by urinary excretion.

Funded by GSK (AC4112014; NCT01362257).

P2154

Not all antistatic valved holding chambers have equivalent performance: An example of a packed holding chamber (VHC)-inhaller combination should be considered unique

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Rationale: Electrostatic charge mitigation by the use of charge dissipative materials with VHCs is common, since initial pre-washing can be avoided. We provide a rationale for testing antistatic VHCs.

Methods: Charge was measured on samples of the VHCs with and without an actuator, with and without delay. Charge measurements were performed on 30 samples for 2 devices (ACFlow-Vu® , ACFlow-Vu® with Airdelay®) using an apparatus simulating in-use conditions. The following studies were performed to evaluate the stability of the drug product (DP: Aclidinium bromide 400μg formulation & inhaler).

Results: A highly-flexible 4-part protocol was designed, submitted to and approved by the MHRA and EC in 27 days. Parts 1 and 2 in HS is complete, Parts 3 and 4 are ongoing. Preliminary results show PUR118 is well tolerated in HS and subject 2% with COPD.

Conclusions: This multi-part dose-ranging protocol, developed and implemented in the UK, demonstrates its regulatory framework embraces innovative, highly flexible, multi-part trials in early clinical development strategies.

MONDAY, SEPTEMBER 3RD 2012

P2156

Drug product stability of aclidinium bromide in Genuair®,

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Introduction: Aclidinium bromide is a novel, long-acting inhaled anticholinergic bronchodilator developed for the treatment of COPD. It is administered using a novel multidose dry powder inhaler called Genuair®, designed with an intuitive feedback system. The following studies were performed to evaluate the stability of the drug product (DP: Aclidinium bromide 400μg formulation & inhaler).

Methods: The stability of commercial scale batches were tested (Appearance, impurity, particle size, content of active, delivered dose (DD), fine particle dose (FPD) and microbial purity) as follows:

1. Packed DP: ≤24 months storage in 2 orientations at different climatic conditions.
2. Opened DP:
   - In use: 12 months packed storage at different climatic conditions, then open storage, without the protective cap during the in use period.
   - Effect of moisture: 4 weeks open storage at 20°C/34%R.H. versus 25°C/75%R.H.
3. Stability under extreme stress conditions was tested:
   - Temperature cycling study: 2 weeks storage at -10°C to 40°C (alternating every 24 h)
   - Vibrational stability: stressed at 50 Hz, amp. 1 mm using 3 durations.
4. Photo-stability evaluated according to ICH conditions.

Results: All tested samples and parameters confirmed the excellent stability of the packed and unpacked DP. Especially, the data for the pharmaceutical parameters DD (mean values: 362.4μg - 385.7μg) and FPD (mean values: 138.7μg - 164.3μg) were consistent and remained unchanged independent of storage time and conditions.

Conclusion: The advanced design and technological features of the Genuair® combined with the Aclidinium bromide inhalation powder guarantee a stable and robust product under various climatic, mechanical, and light radiation stress conditions.

P2157

The pharmacokinetics (PK) and pharmacodynamics (PD) of the fliucetasone furoate (FF) and vilanterol (VI) combination in subjects with hepatic impairment

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Introduction: A combination of the novel corticosteroid FF and long-acting beta2-agonist VI (FF/VI) is being developed as a once-daily inhaled treatment for asthma and COPD patients.

Objectives: To investigate the effect of hepatic impairment (HI) on FF and VI PK and PD.

384s
Methods: Open-label, repeat dose (7 day) study in subjects with mild, moderate or severe HI (Child-Pugh classification) and healthy subjects (HS) (matched with moderate HI). Subjects received FF/VI 200/25mcg or 100/12.5mcg (severe HI) once daily. FF and VI PK (Day 7) parameter point estimates and 90% confidence intervals (CIs) were constructed for the ratio of geometric means (HI/HS). Systemic PD effects of FF (0–24h weighted mean serum cortisol) and VI (0–4h heart rate and serum potassium) were assessed on Day 7.

Results: There was no effect of HI on dose-normalised VI Cmax or AUC(0–24) and no clinically relevant effects of FF/VI on heart rate or serum potassium compared with HS. Dose-normalised FF systemic exposure (AUC(0–24); Day 7) was higher in subjects with mild, moderate and severe HI (ratio vs. HS [90% CI]): 1.34 [0.82, 2.20], 1.83 [1.11, 2.99] and 1.75 [1.05, 2.91], respectively. Serum cortisol was only reduced in subjects with moderate HI (average 34% reduction [90% CI] 11%, 51%) compared with HS. A similar effect would be predicted in severe HI with FF/VI 200/25mcg.

Conclusions: In subjects with HI there was no increase in VI systemic exposure or systemic effects. FF exposure was increased by 3-fold in subjects with HI and was associated with a reduction in serum cortisol of approximately 30%.

Funded by GSK (HZA111789; NCT01266941).

P2158
No relevant drug-drug interaction between inhaled NVA237 and oral cimetidine
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1Translational Sciences, Novartis Institutes for BioMedical Research, Basel, Switzerland; 2Translational Sciences, Novartis Institutes for BioMedical Research, Basel, Switzerland; 2Translational Sciences, Novartis Institutes for BioMedical Research, Hyderabad, India; 3Biostatistics, Novartis Institutes for BioMedical Research, Hyderabad, India

Introduction: NVA237 (glycopyrronium bromide) is a once-daily long-acting muscarinic antagonist for the treatment of COPD. Renal clearance is a major elimination pathway of NVA237 and active tubular secretion in the kidneys contributes to this process. This study investigated the effect of inhibition of the organic cation transport in the kidneys on NVA237 disposition. Cimetidine was used as a probe inhibitor.

Methods: 20 healthy volunteers participated in this two-sequence crossover study. They inhaled a single 100 μg dose of NVA237 via the Breetherager® device on two occasions, i.e. alone (Treatment A) and on the 4th day of a 6-day treatment regimen with cimetidine 800 mg twice-daily (Treatment B). Treatments were separated by a washout period of 7 to 10 days. Plasma concentrations and urinary excretion of NVA237 were determined after each NVA237 dose. The primary PK parameters were plasma peak concentration (Cmax), AUC up to the last measured concentration (AUClast) and renal clearance (CLR) of NVA237. Trough plasma concentrations of cimetidine were determined throughout cimetidine dosing.

Results: Cimetidine trough concentrations indicated that the inhibitor drug had reached PK steady state prior to NVA237 inhalation in Treatment B. The concomitant administration of cimetidine resulted in an increase of total systemic exposure (AUClast) of NVA237 by 22%. This exposure increase correlated with a slight decrease of 23% in CLR. Cmax was not affected. Both treatments were safe and well tolerated.

Conclusions: Based on the magnitude of the PK changes, no relevant drug interaction is expected when NVA237 is co-administered with cimetidine or other inhibitors of the organic cation transport in the kidneys.

P2159
Drug-drug interactions in hospitalized patients with chronic obstructive pulmonary disease
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Aim: Chronic obstructive pulmonary disease (COPD) patients are treated with several drugs for their primary disease and comorbidity, which carries the risk of clinically relevant drug-drug interactions (DDIs). We aimed to evaluate DDI in hospitalized COPD patients.

Methods: This retrospective study included COPD patients hospitalized from January 2011 to July 2011 in a tertiary care clinic. Pharmacological therapy at admission and discharge was evaluated for DDI with electronic Lexi-Comp database:

- C: monitor therapy; D: consider therapy modification; X: avoid combination.

Results: We included 196 patients (68% male, age 71±9 years). The average number of prescribed drugs was significantly lower at hospital admission than at discharge (6±3 vs. 7.2±, p<0.01). Overall, more than 90% of patients had at least one interaction and Table 1 summarizes type C, D, and X interactions at hospital admission and discharge. The most prevalent type C interaction was between two β2-agonists (10% of cases) and the most prevalent type D interaction between β-blocker and α-blocker (9%). There were 15 type X interactions recorded at discharge, among which the most common was between non-selective β-blocker and β2-adrenoceptor agonist (8 cases).

Conclusions: DDI are common in hospitalized patients with COPD but few carry clinically relevant risk. Most type X interactions were between non-selective β-blocker and β2-adrenoceptor agonist which likely was indicated and should be safe in COPD patients.

P2160
Aerosol deposition in asthmatic subjects breathing helium-oxygen vs. air
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Introduction: Helium-oxygen (He/O2) mixtures are known to facilitate breathing due to their low density compared to air, and therefore, may be valuable to treat obstructive lung diseases such as asthma.

Objectives: The objective is to study the effect of air vs. He/O2 on the aerosol deposition of a nebulized radiolabel in stable, moderate asthmatic subjects.

Methods: 16 evaluable male subjects (6 asthmatics, 10 healthy volunteers) were studied. Each subject performed two inhalations which differed by a single controlled parameter (particle size, ventilation, or carrier gas). 2 of the asthmatics inhaled aerosols with either air or He/O2 (78%He/22%O2), and aerosol deposition was imaged with 3D-SPECT.

To characterize the sites of aerosol deposition, the 3D Central to Peripheral ratios, C/P, were calculated for right and left lungs.

Results: The effect of He/O2 on aerosol deposition was very visible for one of the asthmatic subjects (A06) with a large decrease in central deposition (Right C/P=9.1 and Left C/P=5.58 for air, vs. 1.32 and 1.37 for He/O2) when He/O2 was used to drive the nebuliser, but the other asthmatic did not respond to the change in carrier gas (Right C/P=3.87 and Left C/P=6.66 for air, vs. 3.87 and 7.53 for He/O2).

Figure 1. 3D-SPECT images of aerosol deposition superimposed with HRCT for subject A06 inhaling either air (top) or helium/oxygen mixture (bottom).

Conclusion: These results suggest that He/O2 can reduce aerosol deposition in central airways and increase deposition in peripheral airways in some asthmatic patients, but this response is not consistent among all patients.

Table 1. Number of patients with at least one interaction (percentage)

<table>
<thead>
<tr>
<th>Type of interaction</th>
<th>Hospital admission</th>
<th>Hospital discharge</th>
<th>p-value (McNemar test)</th>
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<tr>
<td>C</td>
<td>177 (90)</td>
<td>180 (92)</td>
<td>0.648</td>
</tr>
<tr>
<td>D</td>
<td>39 (20)</td>
<td>47 (24)</td>
<td>0.243</td>
</tr>
<tr>
<td>X</td>
<td>4 (2)</td>
<td>12 (6)</td>
<td>p=0.05</td>
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</table>
248. Treatment of asthma, bronchiectasis and cough: inhaler use

P2161
Efficacy of fluticasone furoate (FF) and vilanterol (VI), separately and in combination (FF/VI), in an allergen challenge model
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Introduction: FF and VI are respectively, a novel inhaled corticosteroid and long-acting beta agonist. FF is efficacious in asthma over 24 h as monotherapy and combined with VI.

Objectives: Evaluate the effect of FF/VI on the allergen-induced early and late asthmatic response (EAR/LAR) and airway hyper-responsiveness (AHR) relative to placebo (PBO) and individual components.

Methods: Randomised, double-blind, 4-way crossover study of 27 mild asthma patients who received FF (100 mcg), VI (25 mcg), FF/VI (100/25 mcg) and PBO once daily for 21 days (4 periods). Allergen challenge was performed on Day 21 of each period 1 h post dose. AHR was assessed 24 h later by PC20 methacholine challenge.

Results: FEV1 maximum decline during EAR (0–2 h post-challenge) was significantly less with FF/VI and FF vs PBO. Treatment differences in minimum FEV1 (mL [95% CI]) vs PBO at 6 h post-challenge were 484 [332, 636], 484 [330, 638] and 168 [9, 638] for FF/VI, FF and VI, respectively. For LAR (4–10 h post-challenge) weighted mean (mL [95% CI]) vs PBO were 477 [282, 672], 265 [66, 463] and 135 [–72, 343] with FF/VI, FF and VI, respectively. For LAR (4–10 h post-challenge) weighted mean (mL [95% CI]) vs PBO were 477 [282, 672], 265 [66, 463] and 135 [–72, 343] with FF/VI, FF and VI, respectively. For LAR (4–10 h post-challenge) weighted mean (mL [95% CI]) vs PBO were 477 [282, 672], 265 [66, 463] and 135 [–72, 343] with FF/VI, FF and VI, respectively.

Conclusions: FF/VI and FF protected from all components of the asthmatic response. Overall FF/VI provided superior protection from the response to inhaled aeroallergens than monotherapy, with bronchoprotective effects lasting for over 24 h.

Funded by GSK (HZA113126; NCT01128595).

P2162
How frequent is bronchodilator reversibility in patients with stable asthma bronchiale and chronic obstructive lung disease (COPD) receiving maintenance therapy?
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Lung function measurement is the most important tool in the diagnosis and differentiation of obstructive lung diseases. While asthma is characterized by variable bronchial obstruction, increase of airway resistance is mostly irreversible in COPD. As response to short acting bronchodilators seems highly variable, we tested bronchodilator reversibility in stable asthma and COPD patients receiving standard care.

In patients treated with stable COPD (N=77; male: female=43:57%; age: 62±3.5 years) or asthma (N=57; male: female=33:67%; age: 46±6.7 years) pre- and postbronchodilator values of bodyplethysmography measurements were analyzed using 400 μg salbutamol via easyhaler® (Buventol, Orion Pharma, Finland) during their regular out-patient visit.

Smoking was significantly more common in COPD patients than asthma patients (90 vs. 37%; p<0.05). Airway obstruction was more severe in COPD patients as compared to asthmatics (FFC: 2.38±0.26 vs. 3.14±0.43 L; FVC%: 72.6±5.1 vs. 87.4±6.4 L; FEV1/FVC: 1.45±0.21 vs. 2.13±0.31 L; FEV1%: 53.5±5.2 vs. 70.3±5.5, p<0.05). Reversible airway obstruction was present in 26% of COPD and 36% of asthma patients. Average response to salbutamol was similar in COPD patients compared to asthmatics (FFC: 195±22 vs. 189±25 mL; FVC%: 6.34±0.71 vs. 5.89±0.77), while smaller in FEV1 (FEV1: 126±17 vs. 254±30 mL; FEV1%: 4.97±4.08 vs. 8.67±0.88; p<0.01).

High proportion of COPD patients, whereas low proportion of asthmatics on regular treatment is showing ATS/ERS guideline defined reversibility using salbutamol easyhaler. Re-evaluation of diagnosis and/or therapy might follow these results.

P2163
Impact of age, age at diagnosis and duration of asthma on the risk of exacerbations in the EuroSMART study
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Background: Information about the influence of age and duration of asthma are limited.

Methods: EuroSMART, an open, randomised 6-month study (NCT00438368), compared two maintenance doses of budesonide/formoterol (BUD/FORM) (Symbi- smart® Turbuhaler®), 160/4 μg vs 1x2 and 2x2, plus as-needed BUD/FORM, in asthmatics ≥18 y with symptoms when treated with INH/LABA. Mean age of patients was 48 y, (range: 18–96 y) and 62% were females. The effects of biological age, age when asthma was first diagnosed, and duration of asthma were assessed. Among 8053 randomised patients, 4402 (54.6%) were ≥30 y of age when first diagnosed and 3411 (42.3%) had had asthma for ≥15 y. Data on allergic status (rhinitis, conjunctivitis) were collected. Severe asthma exacerbations were defined as: need for oral steroids for ≥3 days, emergency room treatment or hospitalisation.

Results: Presence of the allergic component decreased with increasing age at first asthma diagnosis. Patients >65 y had more exacerbations, and the risk of a first severe exacerbation was increased by 55.3% (p=0.0001; HR=1.533; 95% CI 1.249, 1.931). Severe asthma exacerbations were more frequent in patients diagnosed >30 y of age (p=0.0167; HR=1.248; 95% CI 1.040, 1.477) and more frequent in patients who had had the diagnosis for >15 y (p=0.0021; HR=1.289; 95% CI 1.107, 1.582). However, there were no differences in time to first exacerbation between the two randomised treatments 1x2 and 2x2 inclusions in any of the above three age measures.

Conclusion: Older patients, those with higher age at diagnosis and patients with long-term asthma have more exacerbations but did not show any difference between the 1x2 and 2x2 groups.

P2164
Patient and physician perspectives on asthma control and management strategies are discordant; a primary care study in Canada
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Background: Patients and physicians’ evaluations of asthma are often discordant.

We undertook this study to compare prescribed management strategies to patients’ actual strategies.

Methods: In 136 primary care practices, patients with asthma described their control using the asthma control test (ACT), current medication use, number of caregivers and health care utilization. Their physicians provided their understanding of each patient’s care while blinded to the patients’ responses.

Results: Of 904 patients (65% women, 21% current smokers), 54% had ACT scores < 20 although only 9% would describe their asthma as poorly controlled or uncontrolled. By contrast, 73% of physicians felt that the majority of patients had achieved control. In the 12 months prior, urgent care for uncontrolled asthma was obtained by patients in the following offices: 32% in their physicians’ offices; 19% at a walk-in clinic; 13% in the emergency room; and 3% in hospital. 21% of respondents had received at least one short course of prednisone. Of 247 patients described by their physicians as taking single maintenance and reliever therapy (SMART) only 60 (25%) used medications consistent with this regimen; 39% had separate relievers as well as their maintenance drug and 35% were not using a budesonide/formoterol inhaler.

Conclusion: Physicians overestimate the asthma control achieved by their patients; in Canada, patients are commonly uncontrolled and have frequent need for urgent asthma care. Physicians have not successfully implemented SMART therapy, either because prescribing is confounded by other caregivers or because physicians misunderstand the strategy.

P2165
Halotherapy – A possible method to enhance airway treatment on patients with obstructive pathology
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Introduction: The clinical benefits of halotherapy is advocated, but the mechanisms are scarcely studied and there is not enough available clinical data. Halotherapy may influence mucociliary, antibacterial and anti-inflammatory actions, also the immunomodulator - hyposensibilizing agents. We conducted a perspective study where we use a dry-salt inhaler on patients with asthma and COPD.
P2166 Safety and efficacy of ectoin inhalation solution in patients with inflammation and airflow obstruction: The EFFECT study

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Introduction: Ectoin is a compatible solute used for symptomatic treatment of chronic obstructive pulmonary disease (COPD), airway hyper-reactivity, and inflammatory epithelitis. Results from different studies demonstrated the efficacy of ectoin in reducing inflammation in the airways. Based on the positive results of a trial with asthmatic patients a study was set up to evaluate Ectoin Inhalation Solution (EIL) in subjects with mild airflow obstruction and inflammation.

Methods: The study was designed as double blind, placebo-controlled cross-over trial. Subjects were randomly assigned to EIL or placebo (0.9% saline). Primary endpoint was defined as reduction of inflammatory markers IL8 and neutrophilic granulocytes.

Results: Of the 52 patients enrolled, in the EIL treatment group and a patient in control group developed exacerbation and no patients in either group reported side effects. The microbiology results showed colonization of P. aeruginosa and K. pneumonia without any reported emerging antimicrobial resistance.

Conclusion: 12-week roxithromycin 300 mg once daily in symptomatic stable bronchiectatic patients did not show significant improvement of QoL, by SGRQ scores, reduced sputum volume nor improved lung function. Further long term study of anti-inflammatory macrolide should be done in symptomatic bronchiectatic patient.

P2169 Can roxithromycin improve quality of life in bronchiectatic patients?

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Introduction: Azithromycin is an effective prophylactic antibiotic in non-CF bronchiectasis. However, it is known to cause side effects including hearing loss and liver dysfunction, necessitating appropriate patient monitoring. In addition, some experts advocate periods of temporary cessation of treatment, “azithromycin holidays”, to minimise potential toxicity. We have examined our use of azithromycin and how we screen for complications in our specialist non-CF bronchiectasis clinic.

Methods: Data was collected on all patients with non-CF bronchiectasis who attended our specialist clinic over a 3-month period commencing 07/11/2011. In those patients receiving long-term azithromycin, we collected data on patient adherence and any complications, including liver function tests (LFTs), audiometry testing and advice given regarding “azithromycin holidays” over the previous 12-month period.

Results: Seventy patients were studied, of whom 28 (40%) were prescribed long-term azithromycin. Of these, 7 (25%) had been on azithromycin for less than 12 months. Twenty three (82%) patients on long-term azithromycin had had LFTs and 1 (3.5%) had had audiometry testing in the preceding 12 months. Four (17%) of the patients treated for more than 12 months had had an “azithromycin holiday” in the preceding 12-month period.

Conclusion: Monitoring of LFTs was satisfactory in our treatment group but more attention could be paid to audiology testing and the possibility of “azithromycin holidays”. Work to raise awareness of optimal practice in long-term azithromycin prescribing in non-CF bronchiectasis is needed.

P2170 The p38 MAP kinase inhibitor dilmapimod ameliorates airway inflammation induced by ozone challenge in healthy volunteers

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Introduction: p38 MAP kinase is involved in inflammatory airway diseases. We studied the effects of the selective oral p38 MAP kinase inhibitor SB-681323 (Dilmapimod) on airway inflammation induced by ozone challenge.

Methods: This was a double-blind, randomized, four-period, cross-over study with two doses of Dilmapimod (5 mg, 25 mg), Prednisolone (50 mg), and Placebo...
in healthy ozone responders (increase of neutrophils by >10% in sputum after inhalation of 250 pgbp ozone for 3 hours with intermittent exercise). Study drug was administered 30 minutes prior to each ozone challenge. Induced sputum was collected 3 hours after the ozone challenge for measurement of neutrophils, interleukin-8 (IL-8), and myeloperoxidase (MPO). Treatment periods were separated by 14 days wash-out.

Results: 16 subjects were randomized and 11 subjects completed all treatment periods. There was no evidence of a statistically significant difference for the number of neutrophils in sputum between Placebo and any active treatment. Relative to Placebo, statistically significant reductions of MPO and IL-8 levels in sputum supernatant were observed after treatment with Dilmapimod 25 mg and Prednisolone. Differences based on an exploratory population of 14 subjects with sufficient sputum quality indicated a statistically non-significant reduction of neutrophils by 38%, 31% and 26% in subjects treated with Prednisolone, Dilmapimod 25 mg and Dilmapimod 5 mg, respectively.

Conclusion: Dilmapimod ameliorates ozone-induced airway inflammation. Further studies in appropriate patient populations are needed.

The Study was funded by GSK (GSK number SB-681323/10).

P2171

Effect of lidocaine and its delivery in chronic cough

Rayid Abdulqawi

Effect of lidocaine and its delivery in chronic cough rated by a 14 days wash-out.

Introduction: There are no consistently effective treatments for chronic cough. Patients frequently report an urge to cough sensation in the throat. Nebulised Lidocaine has previously been reported to subjectively improve cough but there are no objective data.

Aims: To compare the effect of lidocaine throat spray, nebulised lidocaine and placebo on subsequent 10-hour ambulatory cough rate (Vitalojak®) and urge to cough visual analogue scores.

Methods: 26 patients with chronic cough completed a randomised double blind, placebo controlled, three-way crossover study. The different treatments were:

- Placebo: nebulised placebo followed by placebo throat spray
- Nebulised lidocaine (600 mg): nebulised lidocaine followed by placebo throat spray
- Throat spray Lidocaine (100 mg): nebulised placebo followed by lidocaine throat spray

Data were analysed using generalised estimating equation models.

Results: 26 patients completed (22 female, mean age 53.5 yrs, median cough duration 10 yrs)

- Median 10 hour cough rate (n=25) (coughs/hr; IQR) was nebulised lidocaine 34.4 (13.5–57) vs placebo 32.7 (19–56). For the natural log transformed cough rate, there was significant difference between placebo and lidocaine throat spray (p=0.02), but not nebulised lidocaine (p=0.8), with most of the effect in the first 3hrs. Compared with placebo, both nebulised (p=0.01) and throat spray lidocaine (p=0.02) substantially reduced the urge to cough, but with no difference between them (p=0.6).

Conclusion: Lidocaine throat spray significantly reduced the 10-hour cough rate compared with placebo. This suggests that local treatment targeting the pharynx may be an effective anti-tussive in chronic cough patients.

P2172

Bidirectional modulation of urge to cough by nasal TRPA1 and TRPM8 agonists in healthy human subjects

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Cough, the most important airways defensive mechanism is modulated by manyafferent inputs either from respiratory tussigenic areas, but also by afferent drive from other organs. Modulation of cough by nasal afferent inputs could either facilitate cough response or inhibit it in animal models, depending on the type of tussigenic afferents which are stimulated. In recent study we addressed the question of possible bidirectional modulation of cough response in human healthy volunteers by nasal challenges with TRPA1 and TRPM8 agonists respectively. After the challenges with AITC, cinnaamilide, (+) menthol and (+) menthol (all 10-3 M, nasal symptom score, cough threshold (C2), urge to cough (Cu) and cumulative cough response did not reach significance level. Both TRPM8 agonists administered to the nose significantly modulated all parameters including C2 (p<0.05), Cu (p<0.01) and cumulative cough response (p=0.001) documenting strong anti irritating potential of menthol isomers. Except the role of trigeminal afferents expressing TRP channels, also olfactory nerve endings, trigemino – olfactivis relationships, smell perception process and other supramedullar influences have to be taken into consideration as relevant enough to modulate cough in human subjects.

Supported by VEGA 1/0031/11.

P2173

A new rapid-onset dextromethorphan formulation for cough

Caroline Wright1, Rebecca Gordon2, Rachel Thompson2, David Hall2, Jaymin B. Morjaria1, Alyn Morice1.

supported by VEGAEuroMed 1/0031/11.

Introduction: Dextromethorphan (DEX) is known to be an efficacious anti-tussive agent. A novel DEX gel formulation (Arnold D®; Proctor & Gamble), with supra-oesophageal absorption, has been developed for fast relief from cough.

Aim: To evaluate the time to onset of action of 22mg DEX gel (equivalent to 30mg DEX) compared to standard 50mg oral DEX in a normal volunteer citric acid aerosol (CAA) induced cough model.

Method: Healthy subjects aged 18-65 years with a cough count between 7-20 coughs following five inhalations over 5 min. of 10% citric acid at screening were recruited. Subjects were administered oral DEX 50mg and at a subsequent visit at least 5 days later, DEX 22mg gel. Cough frequency was measured at baseline and at t = 15 min, 1, 2, 4 and 6 hours post dose.

Results: 42 (20 male) subjects were enrolled onto the study. At 15 minutes post dose there was a significant (p=0.001) difference in the mean ± (S.D.E.V) % reduction in cough from baseline of 32.1 (±(4.99) with DEX gel vs 12.8 (±(2.8) with oral DEX. Over the 6 hour time period (AUCt6h) there was a significantly (p=0.02) greater % change in cough/ Lilly following DEX gel AUCt6h= -118.7 compared to oral DEX 50mg. AUCt6h= -114.2. There were no major safety issues.

Conclusion: In the evoked cough model, DEX gel has faster onset of action compared to oral DEX and was more effective over the 6 hour time period despite there being a lower concentration of DEX in the gel preparation. A lack of blinding due to different routes of administration may contribute to this effect. A buccal route of delivery with this formulation holds promise for this and other indications where rapidity of onset is required. This study was supported by unrestricted grant aid from P+G.

P2174

Progressive case of recurrent respiratory papillomatosis successfully treated with gefitinib

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Recurrent respiratory papillomatosis (RRP) or juvenile laryngeal papillomatosis is a rare disease, caused by human papilloma virus (HPV). It is characterized by epitelial neoplastic polyps in larynx, trachea (2 - 5%) and lungs (1%). Typical symptoms are hoarseness, chronic cough and dyspnea. Diagnosis is based on laryngo/bronchoscopy, chest x-ray, biopsy and HPV testing. We describe a case of a woman with progressive laryngeal papillomatosis from the age of 1 year. Disease slowly progressed to trachea, although patient underwent about 80 endoscopic laser procedures. In the age of 37 y, chest X ray showed multiple nodules and cysts filled with fluid. VATS biopsy proved paranchymal papillomatosis. Patient was treated unsuccesfully with interferon, antiviral vaccine and Cidofovir. In the age of 41 y, therapy with gefitinib 250 mg bid was started. Bronchoscopy revealed regression of papillomas after 2 months and normal laryngeal and tracheal mucosa after 6 months. Chest X-ray was normal and CT showed tiny cysts without fluid. Patient felt well without dyspnea and tolerated treatment without problems.

Gefitinib - tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) was chosen according to knowledge of EGFR overexpression in papillomas and sporadic information about treatment of children with laryngeal papillomatosis. To our knowledge, this is the first report of successful gefitinib treatment of RRP in adult patient. The role of HPV in tumor forming tissue reaction is not known. Frequent HPV detection in gefitinib-responsive lung adenocarcinomas gives another support for gefitinib indication in RPP and a new hope for patients, too.

P2175

Erdosteine – A new drug in the treatment of chronic rhinosinusitis

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Introduction: Antiinflammatory macrolide antibiotics proved efficient in chronic rhinosinusitis (CRS). Since this medication is associated with potential side effects such as the danger of development of resistant bacteria, alternative drugs are being sought.

Objectives: Another drug exerting similar, cytokine-mediated antiinflammatory effects is Erdosteine. However, it has not been tested in this diagnosis yet.

In a prospective post-authorisation study we therefore assessed the efficacy of Erdosteine in patients with CRS.
**Conclusions:** The results of our pilot study suggest Erdosteine treatment efficacy in CRS. Additional in vitro and clinical studies are required to determine its precise action.

**P2176**

A cross-sectional study examining inpatients’ metered dose inhaler technique and the impact of assessment and education on its effective use

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**Introduction:** Metered dose inhalers (MDI) are often prescribed during hospital admission. MDI technique influences clinical effectiveness, yet inpatient assessment and education regarding this skill may not happen routinely.

**Objectives:** We hypothesised that a) inpatients on an acute medical ward often have poor MDI technique and b) simple assessment and education could improve MDI technique.

**Methods:** A cross-sectional study was conducted on inpatients prescribed an MDI on an acute medical ward during the month of October 2011. Technique was assessed using an Aerosol Inhalation Monitor, by a Health Care Assistant (HCA) trained in its use. Patients with poor technique had simple training and assessment was repeated.

**Results:** A total of 38 patients were studied (M:F=1:1.1, Age range=40-91). Initial assessment showed only seven patients (18.4%) were able to use the device effectively. The 31 patients (81.5%) that failed initial assessment had simple education and technique; showed common errors; omitting exhaling before inhalation (10-15%), mouth rinsing or incorrect inhalation (20%) and omission of mouth rinsing. Evaluation of asthma control was performed at baseline and following visits, 22% of asthma patients were under control at baseline, increasing to 43%. Fixed combination inhalers BDP/FP solution spray, F/S discus, B/F Turbuhaler significantly reduced the rate of uncontrolled patients by p=0.004, p=0.001, p=0.003 respectively where no significant decrease was seen with B+F Aerolizer for related asthmatic group (p=0.10).

Table 1. Asthma treatment with inhalers, % of uncontrolled asthma (n=572 patients)

<table>
<thead>
<tr>
<th>Inhaler Device</th>
<th>V1, n(%)</th>
<th>not controlled</th>
<th>V4, n(%)</th>
<th>not controlled</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerolizer B+F</td>
<td>36 (42.8%)</td>
<td>12 (23.5%)</td>
<td>p=0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discus F/S</td>
<td>58 (82.8%)</td>
<td>9 (11.4%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solution Spray BDPF</td>
<td>55 (32.7%)</td>
<td>6 (10.1%)</td>
<td>p=0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turbuhaler B/F</td>
<td>65 (61.7%)</td>
<td>13 (14.9%)</td>
<td>p=0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** This study collected information on specific use of inhaler devices in persistent asthma patients and a correlation in a balanced perception of use for every device by physicians and patients were shown.

**P2178**

The asthmatic patient and inhaler treatment devices profile in Turkey:

Asthma inhaler treatment study

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**Aim:** Factors such as severity, duration of asthma, concomitant diseases, smoking habits, influence asthma control, besides compliance to inhaler devices. In this study, we aimed to profile contributing factors and conditions and inhaler devices in Turkey.

**Methods:** In this non-interventional study asthma patients were surveyed at baseline for asthma history, demographics, concomitant medical conditions and smoking habits, with possible impact on asthma and its prognosis, including exacerbation rates. The profile of treatment agents and devices were also evaluated.

**Results:** A total of 572 patients were enrolled at 31 centers. The majority of asthma patients registered to the study was female (76%) and mean age was 42.7±12.1, the mean asthma age was 7.98±6.28 years. BMI was 28.0 kg/m². During enrolment, asthma symptoms were under control in 22% of patients enrolled, in 38% was not under control and 40% was partially controlled. During enrolment 56% of patients had co-morbid conditions, and 65.5% had rhinosinusitis, 12.8% had GERD, with high percentage of uncontrolled asthma. One in every five patient (18.2%) were current smokers and 49% had uncontrolled asthma during baseline.

Table 1. Asthma treatment at baseline (n=572)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed combinations</td>
<td>455</td>
<td>79.5</td>
</tr>
<tr>
<td>Bronchodilators, as required</td>
<td>166</td>
<td>32.5</td>
</tr>
<tr>
<td>ICS</td>
<td>116</td>
<td>20.3</td>
</tr>
<tr>
<td>LABA</td>
<td>78</td>
<td>13.6</td>
</tr>
<tr>
<td>ICS-LABA</td>
<td>126</td>
<td>22.6</td>
</tr>
<tr>
<td>Others (i.e., montelukast)</td>
<td>130</td>
<td>22.7</td>
</tr>
</tbody>
</table>

**Conclusion:** Patient profile of asthmatics receiving inhaler treatment showed that one out of every five patients enrolled were effectively controlled, despite smokers and presence of complicating concomitant medical conditions. Fixed combinations are the mainstay of therapy in Turkey, with all types of inhaler devices.
P2180
Oxygen use and nasal symptoms
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It is recognised that oxygen should be prescribed as a drug, but little has been studied about the comfort or side effects of oxygen.

Aim: We wished to see if oxygen had significant nasal side effects for our in-patients.

Method: A snapshot questionnaire was asked to all patients on oxygen on the medical wards of our large teaching hospital during a one week period. We used the Lund score, using predominantly questions in the nasal domain (rating 1-4; normal to severe), to compare their symptoms pre and during admission.

Results:

24 patients were able to answer the questionnaire; the majority were on nasal oxygen and using it for more than 2 days. 42% reported that oxygen wasn’t comfortable, but there was only a significant difference in the symptom of a dry throat (mean difference 0.71, p= 0.009). 4 patients had worsening epistaxis whilst comfortable, and this further supports the need for care regarding the prescription use of steroids in some. However, nearly half found some aspect of oxygen use uncomfortable, but there was only a significant difference in nasal symptoms; it is possible this was ameliorated by the domiciliary use – 1: Table-top compressors

Discussion: In our patient group using predominantly nasal non-humidified oxygen there was no change in nasal symptoms; it is possible this was ameliorated by the use of steroids in some. However, nearly half found some aspect of oxygen use uncomfortable, and this further supports the need for care regarding the prescription of this drug.

P2181
Comparative in vitro performance of a new re-useable breath-actuated nebulizer (BAN) with other high performance systems intended for domiciliary use – 1; Table-top compressors

Rationale: Treatments by portable compressor/nebulizer systems can offer very different delivery characteristics. We evaluated a new, reusable BAN (AeroEclipse-XL®, Trudell Medical International) optimized with its table-top (Ombra®) compressor.

Methods: Each nebulizer (n=5/group) was filled with 2.5 mL, 1.0 mg/mL albuterol (Ventolin®, GSK Canada Inc.) and, connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA) mimicking adult tidal breathing (Vₜ= 600 mL; duty cycle = 33%; rate = 10 cycles/min). Emitted aerosol was captured on a filter at the mouthpiece, replaced every minute until onset of sputterling, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction (FDF, <4μm) and mass median droplet diameter (MMD) were determined by laser diffraction method. Total fine droplet mass (TDM, <4μm) was the product of total mass and FDF, <4μm. Comparative measurements were made with the Sprint® (PARL, Germany) and reusable SideStream® (Philips-Respiracms, Germany) air entrainment nebulizers using PARI BOY® SX® and Inspiration Elite® table-top compressors respectively.

Results: See Table.

P2183
Pharmaceutical development of a liquid formulation for pulmonary application of a peptide
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ALIARDS are acute and severe conditions with mortality up to 50%. Currently, no specific drug-related treatment exists. ALIARDS are characterized by pulmonary oedema due to increased permeability of the endothelial/epithelial barrier. Oedema clearance is linked to Na uptake at the apical side of Type I/II alveolar cells through the amiloride-sensitive epithelial sodium channel "ENaC". AP301, a synthetic peptide derived from the lectin-like domain of TNFα, enhances Na transport through ENaC and thus oedema clearance. As ENaC is located at the inner surface of alveolus, the water soluble AP301 is administered by inhalation of a nebulised aqueous solution. Hence, pharmaceutical development of AP301 as potent new drug for oedema resolution differs from standard orally or parenterally applied medicine and has to follow specific pharmaceutical and medicinal regulations of the Pharmacopoeia and inhalation medicine guidelines. AP301 is nebulised by a mesh-type not a jet or supersonic type nebulizer due to simplicity and effectiveness, but gentle aerosol generation. In order to reach the alveoli the particle size of the aerosol was optimized to <5μm by testing a range of different concentrations of AP301 in combination with various nebulizers. Analyses of biological activity of AP301 in the generated aerosol showed that it was retained during nebulisation. To
Muscarnic and β2-adrenergic receptors of resident lung cells are modulators of airway inflammation and remodeling. Here, we used human primary lung fibro- 

Asmus and A. M. M. Hacker.

Methods and results: The effect of Dex on 39 IL-1β-induced genes was examined in human pulmonary A549 cells by real-time PCR. Dex showed a range of activity in terms of the extent (E_{max}) and potency (EC_{50}) of repression on these genes. These parameters correlated such that the most highly repressed genes were also the most potently repressed. While all 39 genes were NF-κB-dependent, this did not correlate with repression by Dex. Finally, inhibition of protein translation by cycloheximide (CHX) reduced IL-1β-induced expression of 19 genes (secondarily response genes). Of the remaining 21 genes, CHX significantly prevented the Dex-dependent repression of 11 (~50%), suggesting a role for transactivation. These 11 genes were significantly more sensitive (E_{max} and EC_{50}) to repression by dexamethasone when compared to genes showing repression that was insensitive to CHX (and which may represent a classical transrepression mechanism).

Conclusions: Repression of inflammatory gene expression by dexamethasone involves multiple mechanisms. Transactivation appears to play a significant role showing both high potency and high level of repression on target genes.

P2187 Tiotropium provides sustained bronchodilatation in asthmatics with persistent airflow obstruction uncontrolled despite treatment in accordance with guidelines

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Introduction: In some asthmatics airflow obstruction persists despite high-dose (HD) inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) use. In a recent study, adding a long-acting anticholinergic (tiotropium) showed favourable effects over 8 weeks (wk) (Kerstjens HA, et al. ACI. 2011). Methods: In 2 replicate 48-wk, doubleblind, parallel-group trials a total of 912 asthmatics with postbronchodilator (BD) FEV1 <80% predicted and asthma control questionnaire score ≥1.5 while on at least HD ICS+LABA were randomised to additional tiotropium Respimat® 5 mg or placebo. Prespecified co-primary endpoints included peak and trough FEV1; at 24 wks. Secondary endpoints were FEV1 at other time-points, FVC, and daily PEFs.

Results: Baseline characteristics were similar between trials and treatment groups (mean post-BD FEV1: 62% ±11%). Mean change from baseline tiotropium vs placebo after 24 wks in peak pre-BD FEV1 was 86 ±34 mL (P=0.01) or 154 ±32 mL greater (P<0.001), and in trough FEV1, 88 ±34 mL (P=0.01) or 111 ±30 mL greater (P<0.001) in trials 1 and 2, respectively. Improvements in FVC and daily PEFs were also significantly greater with tiotropium. There were no signs of tachyphylaxis. No deaths occurred; adverse events were balanced across both treatments in trials. Conclusion: In asthmatics uncontrolled despite at least HD ICS+LABA, adding tiotropium provided significant lung function improvement at which were sustained over 48 wks. Tiotropium is likely to improve severe uncontrolled asthma on top of treatment in accordance with guidelines.

Study supported by Boehringer Ingelheim and Pﬁzer.

P2186 Transactivation and transrepression in the repression of inflammatory gene expression by dexamethasone

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Background: The anti-inflammatory activities of glucocorticoids are attributed to the repression of inflammatory gene expression. Dogma states that this occurs via direct repression (transrepression) by the glucocorticoid receptor (GR) of transcription factors, such as NF-κB. However, evidence also suggests that gene induction (transactivation) by GR is important for repression.

Aims: To assess the roles of transrepression and transactivation in the repression of inflammatory gene expression by dexamethasone (Dex).

Methods and results: To determine the extent of inflammation polymorphonuclear neutrophils (PMN) from asthmatics with persistent airflow obstruction uncontrolled despite treatment in accordance with guidelines.

Results: A total of 33 patients were studied, 61% male. Baseline spirometry: FEV1(1) 1.13 (SD 0.41), FEV1% 45% (14.7), FVC(1) 2.75 (0.76), FVC(1) 86.3% (17.2), slow VC (l) 2.77 (0.85), slow VC% 84.9 (18.3). Slow VC significantly increased by 303 ml [95% CI 29-297] p=0.01 and 149 ml [95% CI 19-280] p=0.01 at 0.5 and 1 hours respectively. FEV1 significantly increased by 51 ml [95% CI 16-86] p<0.001 and 78 ml [95% CI 40-116] p<0.001 at 0.5 and 1

P2184 Tiotropium enhances the inhibitory effect of the long acting β2 agonist olodaterol on the release of IL-6 and IL-8 by primary human lung fibroblasts of asthma patients

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Introduction: Inhaled LPS challenge – Reproducibility of the inflammatory

P2185 Low dose inhaled LPS challenge – Reproducibility of the inflammatory response

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Results: Peak dose LPS caused a reproducible inflammatory response. How-

ever, we found evidence for a more pronounced increase in monocytes in the second challenge. This needs to be considered in proof of concept studies for novel inflammatory compounds.

CCRE was kindly provided by Dr. A. S. Suredini, NIH, Bethesda.

P2187 Tiotropium provides sustained bronchodilatation in asthmatics with persistent airflow obstruction uncontrolled despite treatment in accordance with guidelines

P2188 The effects of sildenafil on lung function in COPD

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Background: Sildenafil is a pulmonary vasodilator drug used to treat pulmonary hypertension (PH) via PDE5 inhibition. The precursor to Sildenafil, nitric oxide, has moderate bronchodilator effects in exercise induced asthma. A recent study investigating the haemodynamic effects of sildenafil in COPD associated PH (COPD-PH) noted small but significant improvements in FEV1 and FVC.

Aims: To study the effects of sildenafil on bronchodilation and gas trapping in those with COPD-PH. Methods: COPD patients were invited for echo. RVSP >30mmHg and/or a pul-

monary acceleration time of 120ms defined PH. Subjects with COPD-PH were given 50mg of sildenafil(PO). Spirometry was recorded at 0.5, 1 and 3 hours (t_{1/2}).

Results: A total of 33 patients were studied, 61% male. Baseline spirometry:

FEV1(1) 1.13 (SD 0.41), FEV1% 45% (14.7), FVC(1) 2.75 (0.76), FVC(1) 86.3% (17.2), slow VC (l) 2.77 (0.85), slow VC% 84.9 (18.3). Slow VC significantly increased by 303 ml [95% CI 29-297] p=0.01 and 149 ml [95% CI 19-280] p=0.01 at 0.5 and 1 hours respectively. FEV1 significantly increased by 51 ml [95% CI 16-86] p<0.001 and 78 ml [95% CI 40-116] p<0.001 at 0.5 and 1

Aims: To assess the roles of transrepression and transactivation in the repression of inflammatory gene expression by dexamethasone (Dex).
Conclusion: Acute selenadil use resulted in transient airways dilatation and reduced gas trapping. In the absence of placebo control, spirometric changes due to natural variability cannot be ruled out, although the return to normal at 3 hours suggests a real effect.

P2189 Tolerability and efficacy of budesonide/formoterol via Turbuhaler® vs standard treatment in Japanese patients with moderate to severe COPD: 52-week phase III study results
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Background: This study evaluated the tolerability and efficacy of budesonide/formoterol (BUD/FORM) vs standard COPD treatment (SCT) in Japanese patients with moderate to severe COPD.

Methods: In this randomised, open-label, parallel-group, phase III study (NCT01070784), patients ≥40 years of age with moderate to severe COPD for ≥2 years received either BUD/FORM 160/4.5 μg 2 inhalations twice daily via Turbuhaler® or SCT (as judged by the investigator) for 52 weeks. Reliever medication: salbutamol via pMDI. Primary outcome: nature, incidence and severity of adverse events (AEs). Secondary outcome variables included: COPD symptoms, lung function and exacerbations.

Results: 260 patients were randomised. BUD/FORM was well tolerated; 404 AEs were reported by 123 patients (94.6%) receiving BUD/FORM vs 367 AEs by 112 patients (86.2%) on SCT. The majority of AEs were of mild or moderate intensity and the AE profile was similar in the two groups. The most commonly reported AEs (BUD/FORM vs SCT) were nasopharyngitis (42.3% vs 39.2%), COPD (10.8% vs 19.2%) and bronchitis (11.5% vs 11.5%). The frequency of pneumonia-related AEs was similar in both groups (13.1% vs 12.3%) while dyspnoea was more frequent with BUD/FORM (5.4% vs 0.8%). Serious AEs were more frequent with SCT (7.6%) vs BUD/FORM (1.5%). No deaths were reported. Efficacy of BUD/FORM was maintained over 52 weeks.

Conclusions: BUD/FORM 160/4.5 μg inhalations twice daily was well tolerated and efficacy was maintained during 52-week treatment in Japanese patients with moderate to severe COPD.

Funding: AstraZeneca.

P2190 Effectiveness of tiotropium in low-risk patients according to new GOLD severity grading
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Background: GOLD recently updated their COPD severity classification to include risk of exacerbations. Increased risk is typically defined by a FEV1 of <50% pred and/or ≥2 exacerbations in the previous year (C/D) and low risk by a FEV1 ≥50% pred or ≤1 exacerbation in the previous year (A/B).

Aims and objectives: To examine the effect of tiotropium 18 μg qd via Handihaler® in GOLD low risk patients (pts) using data from a 4–year, randomised, double-blind, placebo-controlled trial in COPD (UPFLIT®).

Methods: Retrospective analysis of exacerbations, lung function and QoL, (SGRQ) in low-risk pts (pts with a baseline postbronchodilator (BD) FEV1 ≥5%pred ≥50% and ≤1 oral steroid/antibiotic course in the previous year). Pts with high risk (FEV1 <5%pred <50% or more than 1 course of oral steroids/antibiotics) were also analysed.

Results: 2012 pts were analyzed (mean age 64.5±8.6 y, male 74%, mean (±SD) baseline postBD FEV1 1.65 (0.37) L and FEV1 ≥5%pred (±SD) 58.9 (5.8). The HR (tiotropium vs control) for time to first exacerbation was 0.76 (95% CI: 0.68; 0.86; P<0.0001); mean annual exacerbation rates were 0.43 (95% CI: 0.40; 0.48) vs 0.61 (0.56; 0.66), rate ratio 0.72 (0.63; 0.81; P<0.0001). The SGRQ total score after 4 y was significantly improved by tiotropium vs placebo: −3.63 (95% CI: −5.14; −2.12; P<0.0001) and the respective increase for trough FEV1 was 110 mL (95% CI: 84; 136; P<0.0001). SGRQ and trough FEV1, were significantly improved at all time points. The above-mentioned endpoints were also significantly improved in the high-risk population.

Conclusion: Tiotropium qd was effective throughout 4 y in reducing exacerbations and improving lung function and QoL, in low-risk pts with COPD (GOLD A+B).

P2191 Efficacy and safety of fluticasone/formoterol compared to fluticasone alone in patients with asthma
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Background: To demonstrate efficacy and safety of fluticasone propionate/formoterol fumarate MDI (FLUT/FORM) compared with fluticasone (FLUT) alone based on the change in FEV1 from morning pre-dose at baseline over 2 hours post-dose and SCORing in Asthma (SIAQ). From a 2 month, all-cause exacerbation study in asthma.

Methods: Patients included in the study were ≥12 years with symptomatic asthma for ≥1 year; steroid-requiring, had FEV1 ≥50% to 80% [inclusive] of predicted normal values, and documented reversibility within 12 months of the study. Following a 2 week open-label run-in phase with FLUT (100 or 200 μg b.i.d.), 438 patients were randomised to treatment with FLUT/FORM (250/10 μg b.i.d.) or one of two pMDI formulations of FLUT alone (250 μg b.i.d.). The formulations were SkyPharma HEA, pMDI (SKP) and GSK fluticasone pMDI (FLO), with n=146 in all groups. Albuterol/salbutamol was given as rescue medication.

Results: There was a clinically important and statistically significant difference in mean change from pre-dose FEV1, at baseline to 2 h post-dose at week 12 between the FLUT/FORM and both formulations of FLUT (SKP:LS mean difference=0.161 L,P<0.001; FLO:LS mean difference=0.185 L,P<0.001). Results from multiple secondary and tertiary efficacy endpoints assessing lung function, asthma symp- toms, exacerbations and rescue medication use supported a superior efficacy of the FLUT/FORM combination over FLUT. Treatment-emergent adverse events were lowest in the FLUT/FORM group (32.9%) compared to SKP (39.7%) and FLO (40.4%). FLUT/FORM was generally well tolerated.

Conclusion: FLUT/FORM was superior to FLUT alone in the management of moderate to severe asthma in adolescents and adults. The overall safety profile of FLUT/FORM was consistent with that of FLUT.

P2192 Does eosinophil cationic protein (ECP) predict asthma outcome and response to treatment in asthmatic patients? Elena Bacci1, Silvana Cianchetti, Manuela Latore, Lorenza Melosini, Antonella De Franco, Federico D’Amico, Pietro D’Agostino. Cardiothoracic and Vascular Department, University of Pisa, Italy

In order to test whether sputum Eosinophil Cationic Protein (ECP) predicts asthma outcome and response to treatment, we studied 119 mild/moderate, steroid-naive asthmatic patients. All patients underwent spirometry, methacholine test, induced sputum analysis before and after treatment, and recorded symptom score and rescue beta(2)-agonist use on a diary card throughout the study. In patients with high (≥75 mg/mL) sputum ECP baseline FEV1 was lower (high-ECP: 85±17%; low-ECP: 96±14%; p=0.01). Sputum eosinophil percentages were higher in patients with high ECP (high-ECP: 16.3±17.1%; low-ECP: 6.1±8.3%; p=0.01), although the concordance between sputum eosinophils and ECP was poor (κ=0.52, p=0.01). Patients were then treated with either inhaled corticosteroids (ICS, n=76) or long-acting beta2-agonist (LABA, n=43) for 3 to 6 months. In LABA-treated patients, symptom score and beta(2)-agonist rescue use improved regardless of baseline sputum ECP levels; after treatment, however, patients with high baseline ECP levels had greater rescue beta(2)-agonist use (high-ECP: 0.2±0.2; low-ECP: 0.02±0.03, p=0.05). In ICS-treated patients, PEFR symptom score, beta(2)-agonist rescue use and PD20FEV1 methacholine improved regardless of ECP levels; however, FEVI1 significantly improved in ICS-treated patients with high ECP levels only, possibly because they had lower baseline FEV1 values. Thus, high sputum ECP levels may predict less asthma control, as shown by greater rescue beta(2)-agonist use, when treatment does not affect airway inflammation; on the other hand, high sputum ECP levels may predict the response to ICS treatment, possibly because they are associated with poorer baseline lung function.
Methacholine challenge test as an evaluator of response to statins in bronchial hyperresponsiveness

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Results: 

Changes in airway responsiveness categories (moderate to severe, mild, border-
line, normal) after the intervention were not significant in atorvastatin group as in placebo group (p=0.04 for atorvastatin in group and p=0.04 for placebo group). Also, changes in methacholine solution number (different concentrations of methacholine) which caused at least 20% decrease in FEV1 were not significant between groups (p=0.03 for atorvastatin group). Although we could not find a significant difference, the patients’ fall in FEV1 in atorvastatin group was observed in higher concentrations of methacholine. Median before treatment versus after treatment in atorvastatin group was 1 versus 4 mg/ml, while those were 2 versus 1 mg/ml in placebo group.

This study showed a better but no significant hyperresponsiveness control in the treatment group. The result may be presented more pronounced, if we could increase the sample size.

P2194 The GOLDEN-1 study: Safety and bronchodilatory effects of nebulized glycopyrrolate (EP-101) using high efficiency nebulizer in patients with COPD

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Introduction: EP-101 is a long-acting muscarinic antagonist bronchodilator for nebulization using a high efficiency nebulizer for the treatment of COPD. The safety and efficacy of once daily nebulized EP-101 was assessed in this Phase 2b study after 7 days of dosing in patients with COPD.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, 4-period cross-over, incomplete block design study. A total of 140 patients with moderate-to-severe COPD were randomized to receive 4 of 7 treatments: EP-101 (placebo, 25, 50, 100, and 200 μg) once daily via high efficiency nebulizer, open-label ipratropium 18 μg once daily, and open-label ipratropium 500 μg 3 times daily via jet nebulizer. There was a 7-day washout period before treatment.

Results: All doses of EP-101 were well tolerated with similar AE rates between placebo and EP-101 (31.2%, 29.7%, 26.9%, 35.5% and 30.7% for placebo, 25, 50, 100, and 200 μg, respectively). There was no apparent dose-response relationship for incidence and severity of AEs. Mean changes in vital signs and ECG parameters from baseline on Day 7 were comparable between the treatment groups. All doses of EP-101 demonstrated dose-related and significant improvements in FEV1, AUC (0-24hr) on Day 7 compared with placebo, with estimated differences between EP-101 doses and placebo ranging between 110-169 mL.

Conclusion: Once daily dosing with nebulized EP-101 was well tolerated over a 7-day treatment period and provided rapid onset of bronchodilation with clinically meaningful and sustained improvement in lung function over 24 hours in patients with COPD.

Funded by Elevation Pharmaceuticals Inc.

P2195 Spacer cleaning: Nurse and patient survey examines current UK practice

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Introduction: Washing spacers improves drug delivery by reduction of electrostatic charges, and is hygienic. Contamination of spacers and masks has been shown (JAMA 2003;290: 2, 195-196). The ERS/ISAM guideline (ERI 2011;37:1308-1331) identified a lack of standard instructions for good spacer cleaning practice.

Methods: Online structured interview questionnaires by a market research agency, 100 asthma patients (Pts) using pMDI with spacer and 50 respiratory nurses (RN) to establish current practice. Pts: 49 adults, parents of child aged 2-9 yrs (n=30) or 10-15 yrs (n=21).

Results: 74% of RN told Pts to wash spacers weekly, 4% instruct daily and 22% instruct < than weekly. RN reported that Pts describe correct washing: 4% always, 42% mostly, 36% sometimes, 14% rarely and 4% never. RN confidence in patients keeping spacers hygienically was low, with 48% not very not or not at all confident, this figure increased to 56% in respect of masks. 71% of Pts said their RN or doctor explained how to wash the spacer, and 63% received drying instructions. 5% were told how to wash and dry, but 24% were not told either. 13% could not recall being told. 21% of adult Pts don’t wash + dry their spacer (not been told); 6% of children’s spacers were not washed. Of 83 who wash their spacer: 35% do so after each use, 20% every day, 27% once a week and 18% < weekly: 72% report air drying and 27% use a cloth.

Conclusions: RN spacer washing instructions frequently conform tomanufacturer’s instructions. Many Pts wash spacers more frequently than instructed but some do not wash at all; neither may be helpful. Many may disuade the electrostatic benefits of air-drying and encourage contamination.

P2196 Patterns of bronchodilator reversibility of FEV1 in asthma and COPD patients

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SAMA (Short Acting Muscarinic Antagonist) has been said to be superior to SABA (Short Acting Beta Agonist) in COPD whereas SABA is preferred bronchodilator in asthma patients. In practice however we observe that the response is variable for individual patient. Therefore we evaluated improvement in FEV1 in 27 asthmatics and 27 COPD patients in response to inhaled SABA (Salbutamol) and SAMA (Ipratropium) on separate days. These patients were in respiratory care with no exacerbation or change of regular treatment in last 4 weeks.

The washout period of their regular treatments was adhered to, before performing their spirometres. SABA produced mean increase of 16.66% and 401 ml in FEV1 of asthmatics vs -1.54% and -150 ml in COPD. SAMA produced 4.07% and 161 ml increase in FEV1 in asthmatics vs. 8.59% and 166 ml in COPD patients. The similar increase in FEV1 in ml in response to SAMA was more significant in FEV1% due to lower baseline FEV1 in COPD patients. An interesting fact observed was that with the increasing duration of Asthma and COPD, the reversibility with SAMA sequentially increased. With a cut off of more than 8 years of duration of disease, the average improvement in FEV1 in response to SAMA was 45 ml (vs. 77 ml in less than 8 year duration) in asthma and 222 ml in COPD, whereas there was no significant change in response to SABA in both groups. There was no correlation with patient’s age or baseline FEV1 value. We conclude that inhaled muscarinic antagonists can be a beneficial adjunct to beta agonists in persistent asthmatics with longer duration of asthma.

P2197 Bronchodilator response and airway cytology as parameters for asthma control: A randomized clinical trial Protocol ID: APITA, NCT00597064, on August 1st, 2008

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Background: Clinical control is hard to define in asthma and there is little experimental data on the optimal timing, sequence and magnitude of treatment. Aim: Measuring the effects of short course of oral corticoid in airway inflammatory and spirometrical values of asthmatic patients to define control.

Methods: A double blind randomized clinical trial to observe the change in spirometry, nasal and sputum cytology in patient under combination therapy, receiving either short course of oral corticoid (OC) or placebo(P). Controlled asthma was defined by ACQ<1.5. They were submitted to clinical evaluation, nasal and sputum cytology, spirometry before and after 15±5 days of randomization. Intervention efficacy was defined by improvement of 200 ml in FEV1.

Results: n=70, 73% female, age 46 ±13.1, 35 received OC and 35 P. Who received OC showed significant improvement in all spirometrical parameters and abolished their positive bronchodilator response related to P. The eosinophils count in the nasal and induced sputum also reduced in OC arm. The logistic regression model identifies for each one year increasing in age there was a 6% decrease in odds of intervention efficacy, associated to 19 times increase in odds related the usage of oral corticoid (related to placebo), and for each increase of 1% in bronchodilator response was associated to 9% increase in odds of efficacy (p=0.02).

Conclusion: The RCT allowed define uncontrolled asthma at baseline and the degree of bronchodilator response, younger age and usage of OC were significant predictors for functional improvement at the end of the trial. Partially funded by FAPESP.
P2198
The effect of smoking on severity of asthma and quality of life in patients treated with inhaled corticosteroids and long-acting β2-agonist (ICS/LABA)
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Background: The aim of this study was to assess the effect of smoking on severity of asthma and quality of life in asthmatic patients treated with ICS/LABA in real clinical practice.
Methods: 122 out-patients (aged 20 – 82 yrs, mean age 55 yrs, 28% males) with moderate-to-severe asthma were treated with medium/high doses of ICS/LABA (GINA2010) and LABA in one inhaler for ≥2 years. Quality of life was measured by using Russian version of St. George’s Respiratory Questionnaire (SGRQ).
Results: Never smoked 36% of patients, former smokers were 31% and current smokers were 33%. Among never smoked asthmatics 80% were treated by medium doses of ICS/LABA and 20% received high doses. Patients with history of smoking (current or previous) have administered medium doses of ICS/LABA in 68% and high doses in 32%. FEV1 differed in nonsmokers and current smokers: 70% vs 56%, p < 0.05. History of smoking was associated with FEV1 level (r=0.25, p<0.05) and severity of disease (r=0.3, p<0.05). The difference of Symptom score between smokers (current or former) and nonsmokers was significant (57.6 versus 66.7, p<0.05). We revealed the impact of smoking on all scores of SGRQ in females: Symptom (57 vs 65, p<0.05), Activity (53 vs 51, p<0.05). Impact (39 vs 40, p<0.01), and Total score (46 vs 48, p<0.01) but not in males.
Conclusion: Smoking is common and may decrease effectiveness of ICS and LABA in asthmatic patients in real clinical practice. There were significant correlations between smoking, severity of asthma and SGRQ scores, especially in females.

P2199
The correction of monocyte-derived neohepatocytes from alpha1 antitrypsin deficient patients
Gillian McNab1, Robert Stockley2.1 Centre for Translational Inflammation, University of Birmingham, United Kingdom; 2 Lung Investigation Unit, Queen Elizabeth Hospital Birmingham, United Kingdom
This study explores the culture of monocyte-derived neohepatocytes from PiZ alpha antitrypsin deficient (α1ATD) patients and homologous replacement using small DNA fragments (SDFs) to correct the Z defect.
Monocytes from 6 patients were de-differentiated with MCSF and IL3 and then differentiated into neohepatocytes with FGF-4. Albumin, urea and α1AT secretion. Development of neohepatocytes and cDNA checked for the M or Z message.
SDFs were produced 163±2 g/ml/24h, 298±4 g/mL/24h of protein. Neohepatocytes produced PCR products from Z primers. M SDF treated neohepatocytes and cDNA checked for the M or Z message.
Conclusion: Smoking was associated with FEV1 level (r=0.25, p<0.05) and severity of disease (r=0.3, p<0.05). The difference of Symptom score between smokers (current or former) and nonsmokers was significant (57.6 versus 66.7, p<0.05). We revealed the impact of smoking on all scores of SGRQ in females: Symptom (57 vs 65, p<0.05), Activity (53 vs 51, p<0.05). Impact (39 vs 40, p<0.01), and Total score (46 vs 48, p<0.01) but not in males.

Results: Vno50-200 was strongly correlated with Vno in normal subjects (p=0.94, p<0.001), asthma (r=0.98, p<0.001), COPD (r=0.93, p<0.001), and CF patients (r=0.74, p<0.05). This agreement was confirmed by the Bland and Altman test.

Conclusions: The flow dependent component of exhaled NO is determined by its bronchial production which can be estimated by measuring Vno50-200. This method is simple, does not require sophisticated equipment or mathematical models and is in agreement with Jno calculated mathematically with the conventional linear regression method.

P2201
Endogenous and exogenous metabolites in exhaled breath condensate in asthma
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Profile of metabolites in different biological fluids reflects the physiological and pathophysiological processes in the human organism initiated by internal and external factors. Exhaled breath condensate (EBC) analysis can provide information about the state of metabolic processes in the respiratory tract.

Method: Evaluation of exhaled breath condensate(SVMs) in EBC in asthma patients and healthy subjects. SVMs belong to different classes of chemical compounds: saturated fatty acids (SFAs), hydrocarbons, alcohols, aldehydes, ketones, esters, phenols and aldehydes. The limit of compounds detection was 0.1-10 ppb. 18 SVMs are presented in the Human Metabolome Database (HMDB): 13 endogenous metabolites and 5 exogenous metabolites. SVMs were determined earlier in the blood, urine, but there is still no information in HMDB about these metabolites in EBC. The most representative group consisted of 12 SFAs, 11 of them are endogenous metabolites. The content of steatic and palmitic acids in EBC of patients with asthma was significantly decreased in compared with healthy. We found negative correlations between SFAs in EBC and spirometry parameters (FVC, FEV1 and FEV1/FVC) (p<0.05) in asthma patients.

Conclusion: The pathological process in the respiratory tract changes the expression of SFAs in EBC, indicating the involvement of these metabolites in the pathogenesis of asthma.

P2202
Exercise increases the hydrogen peroxide release in exhaled breath condensate
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Background: Exhaled breath condensate (EBC) contains numerous mediators of oxidative stress (NO, H2O2). Exercise is characterised by an increase of reactive oxygen species (ROS), which can also be found in EBC. Building of hydrogen peroxide (H2O2) can be induced by ROS. In order to get inside into the correlation of H2O2 release in EBC and exercise, we investigated H2O2 release at rest and at different levels of exercise.

Methods: 20 healthy subjects, (23.3±1.5 years), were investigated, during resting conditions as well as at 60%, 75% and 90% of maximal work capacity(pmax) (each lasting 5 minutes) on a cycle ergometer. 100 L exhaled air along with capillary blood samples were collected under stationary load conditions. EBC was obtained by cooling the exhaled air volume to -20°C. H2O2 was analyzed using the EcoCheck device (EcoCheck, FILT). H2O2 was analyzed using the EcoCheck device (EcoCheck, FILT). In further analysis the release per minute and the release for the total amount of water from 100 L exhaled breath were calculated.

Results: At rest H2O2 concentration in EBC was 216±52 mmol/L. H2O2 release in the collected EBC was 115±45 mmol/min. At 60%, 75% and 90% of pmax, H2O2 concentration in EBC increased to 338±80, 322±71, 334±95 mmol/L (p<0.01). Taking the theoretical water volumes of 4.4 ml EBC derived from 100 L exhaled air into account, H2O2 release increased to 167±75, 250±88 and 357±162 mmol/min (p<0.001). The correlation of H2O2 release and ventilation can be described by a linear relationship.

Conclusions: In healthy subjects, a nearly 3-fold increased of H2O2 release in EBC was observed during moderate and high intensity exercise as well as during high intensity exercise.
EBC was found during exhausting exercise. The elevated levels of H$_2$O$_2$ may be interpreted as an increase of ROS during exhausting exercise.

**P2003**

**Protein markers in the exhaled breath condensate of lung carcinoma patients**

Gabriel Garcia 1, Miguel Burgos 2, Orlando Lopez-Jose 2 1Pneumology, CENASMA, La Plata, Argentina; 2Pneumology, Hospital Antonio Cerradigo, Vicente Lopez, Argentina

Introduction: Chronic obstructive pulmonary disease (COPD) is a common airway inflammatory disorder with structural degradation of the airway tissue. Previous reports showed that patients with COPD had EBT lower than normal subjects. Recently, a new combined COPD assessment was based on the symptoms, spirometric classification and risk of exacerbation (GOLD 2011).

**Objectives:** Evaluate the EBT in COPD patients according to the new combined COPD assessment and compare to healthy subjects.

**Methods:** EBT was measured (using the Xhalo, Delmedica, Singapore) in 80 COPD patients (FEV1: 54±14, age 60±8 years, 46 males) and 80 healthy controls. Lung function, COPD Assessment Test (CAT), exacerbations and previous treatment was performed.

**Results:** There was no differences EBT between COPD patients 34.2±9 vs. healthy subjects 33.9±9. There was no correlation between EBT and FEV1% (r=0.23). EBT and CAT (p=0.01) but patients with previous exacerbations had EBT higher than patients without exacerbations (34.7±8 vs 33.9±9, p=0.001). According to the new combined COPD assessment (20 subjects for each group), the EBT was: Group A 34.1±9, Group B 33.9±9, Group C 34.7±9 and Group D 34.8±9 (p<0.001 between Group B vs Group C and D).

**Conclusion:** Our results showed that COPD patients with frequent exacerbations, 2 or more per year, had increased of Exhaled Breath Temperature, therefore may reflect inflammation in the COPD lung.

**P2004**

**Particle content in exhaled air depending on breathing maneuver**

Per V. Larsson 1, Bergen Baken 1 1, 2, Ekaterina Mirgorodskaya 2

The airway opening generates particles in the distal airways. At high exhalation flows, particles can be formed due to dynamic compression in more central airways. The aim with the present study was to compare particle number and size distributions as well as concentrations of SpA in PEs formed during tidal breathing, airway opening and dynamic compression using forced exhalations.

Ten healthy volunteers performed three different types of breathing maneuvers in randomized order; Reference maneuver (R): no airway closure and no dynamic compression (slow expiration), Dynamic compression (DC): maximal exhalation for surfactant protein A (SpA) content using ELISA. Compared to the R maneuver, the DC maneuver doubled the particle concentration and the AO maneuver gave a ten times increase in the amount of particles per liter exhaled. Flow volume curves indicated that dynamic compression was limited by the back pressure in the instrumentation.

The mass ratio of Sp-A in the PEs were highest in PEs using the R maneuver; 13% ±5%/DC (p<0.001) and 3%/AC (p<0.001), DC to AC difference was not significant (p=0.1). The size distributions were similar in all maneuvers.

**Conclusion:** In conclusion, fast exhalation flows generates more particles than slow exhalation flows, but probably not by the dynamic compression mechanism.

**P2005**

**Exhaled breath temperature in COPD patients**

Gabriel Garcia 1, Miguel Burgos 2, Orlando Lopez-Jose 2 1Pneumology, CENASMA, La Plata, Argentina; 2Pneumology, Hospital Antonio Cerradigo, Vicente Lopez, Argentina

Introduction: Chronic obstructive pulmonary disease (COPD) is a common airway inflammatory disorder with structural degradation of the airway tissue. Previous reports showed that patients with COPD had EBT lower than normal subjects. Recently, a new combined COPD assessment was based on the symptoms, spirometric classification and risk of exacerbation (GOLD 2011).

**Objectives:** Evaluate the EBT in COPD patients according to the new combined COPD assessment and compare to healthy subjects.

**Methods:** EBT was measured (using the Xhalo, Delmedica, Singapore) in 80 COPD patients (FEV1: 54±14, age 60±8 years, 46 males) and 80 healthy controls. Lung function, COPD Assessment Test (CAT), exacerbations and previous treatment was performed.

**Results:** There was no differences EBT between COPD patients 34.2±9 vs. healthy subjects 33.9±9. There was no correlation between EBT and FEV1% (r=0.23). EBT and CAT (p=0.01) but patients with previous exacerbations had EBT higher than patients without exacerbations (34.7±8 vs 33.9±9, p=0.001). According to the new combined COPD assessment (20 subjects for each group), the EBT was: Group A 34.1±9, Group B 33.9±9, Group C 34.7±9 and Group D 34.8±9 (p<0.001 between Group B vs Group C and D).

**Conclusion:** Our results showed that COPD patients with frequent exacerbations, 2 or more per year, had increased of Exhaled Breath Temperature, therefore may reflect inflammation in the COPD lung.

**P2006**

**Concentrations of nitric oxide metabolites in the exhaled breath condensate in children with different bronchiasthma control**

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Although bronchial asthma (BA) is an inflammatory disease, the clinical tools that evaluate asthma control today do not include the qualitative measures of inflammations.

**Objective:** Determination of correlations between total concentration of nitrates and nitrites (TNN) in the exhaled breath condensate (EBC) and children asthma control level determined by the Asthma Control Questionnaire (ACQ).

**Material and methods:** 81 patients with atopie BA (from 6 to 17 years old) were clinically evaluated. Patients completed ACQ, underwent spirometry, and measure-ments of their TNN in EBC. In 55 children, the high BA control (ACQ=0.29±0.26) was diagnosis. 13 children had partially controlled BA (ACQ=0.96±0.20), and 13 children had only bad BA control (ACQ=1.95±0.33). Among the children with high BA control, 27 had no steroid (IGKS) treatment, 28 had only basic IGKS therapy, 19 had with partial or bad control had IGKS therapy. In 27 steroid-naive patients with high-controlled asthma, the TNN in EBC was 6.24±2.93 mMk. In 28 patients with controlled BA taking IGKS, TNN was 4.66±2.34 mMk (p=0.03). In patients with partially controlled BA, TNN level was 2.62±2.62 mMk in patients with bad control - 6.52±2.62 mMk. The correlation between TNN and ACQ scores was found in the whole group (p=0.047), however, the significance was varying in groups with different therapy. In the group of steroid-naive patients, p=0.027; in patients treated with IGKS, p=0.024. The interpretation of TNN in patients with BA, if it is performing for the additional characterization of the control level, should include the consideration of therapy taking by patients.

**P2007**

**Saturated fatty acids in exhaled breath condensate in COPD patients**

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In recent years suggest that individual saturated fatty acid (SFA) has specific prop-erties which are associated with important biological functions. The composition of SFAs in exhaled breath condensate (EBC) has not previously been studied.

**Aim:** To identify SFAs in EBC and to assess their relationship with clinical and functional parameters in patients with COPD.

**Methods:** We have studied 20 patients with COPD and 30 healthy non-smok-ers. EBC was collected using E-CScreen. SFAs in EBC have been identified by gas-chromatography - mass-spectrometry method (GC-MS) and NIST-2005 library.

**Results:** 12 SFAs (palmitic acid, stearic acid, myristic acid, etc.) have been identified in EBC in COPD patients. There were no differences in the contents of SFAs in EBC in COPD patients and healthy subjects. We have found the relationship between EBC content of caproic acid (R=0.46), enanthic acid (R=0.61), caprylic acid (R=0.50) and PFC in COPD patients (p<0.05). In addition, the content of myristic acid in EBC significant correlated with oxygen saturation (R=0.798).
on subjective or objective measures. It has been advocated that fractional exhaled nitric oxide (FeNO) can be used to monitor airway inflammation as it correlates with some markers of asthma.

The aim of our study was to assess the clinical usefulness of the assessment of FeNO for monitoring asthma during pregnancy.

Methods: We used the medical data of 72 pregnant asthmatic women: FeNO results, atopic status, spirometry and ACT (asthma control test) (monthly, 257 visits in all; first visit between 8.22-28). We assessed asthma severity on the basis of anamnesis considering mean doses of inhaled glucocorticosteroids taken by the patients and a management approach based on control according to the newest guidelines of Global Initiative for Asthma (GINA) throughout the last three months before pregnancy.

Results: We did not find correlation between FeNO levels at visit one (pregnancy) and asthma severity before pregnancy (p=0.97). In 22 women with worsening asthma during pregnancy, the mean FeNO during visits without asthma symptoms and with asthma worsening did not differ. A comparison of FeNO levels in the groups of women with well controlled asthma during pregnancy and FeNO with visits without asthma symptoms in the group of women with at least one asthma exacerbation did not differ. There was a statistically significant but low correlation between FeNO levels and ACT total scores results, and FeNO levels and FEV1 (r=0.21 and r=0.25 respectively).

Conclusions: FeNO does not seem to be clinically applicable to predict asthma prognosis during pregnancy, especially because of its high coefficient variation.

P2211
Inflammation on the effectiveness of the Mostgraph and fractional exhaled nitric oxide measurement in chronic cough

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Objectives: Mostgraph, Fractional exhaled nitric oxide (FeNO) measurement, and pulmonary function tests were conducted in patients with chronic cough. The effectiveness of Mostgraph, FeNO measurement, and pulmonary function tests were examined in elucidation of pathology, differential diagnosis, and therapy evaluation of chronic cough.

Method: 1. The subjects were 120 patients who presented with chronic cough. The respiratory resistance measuring device Mostgraph (Chest MI, Inc) was used. For FeNO, NIOX-MINO (Aerocrine) was used. Pulmonary function tests used spirometry. Imaging and blood tests were performed as diagnostic aids. Patients treated with combination of stimulants and inhaled corticosteroid.

Results: Airway resistance at 5 Hz (Rr5) and 20 Hz (Rr20) as well as FeNO tended to increase in patients with chronic cough. Airway resistance and FeNO showed a significant reduction as symptoms improved. Pulmonary function tests showed no significant changes.

Conclusion: 1. In patients with chronic cough, Rr5 and Rr20 increased, and FeNO tended to increase, but decreased with treatment. A combination of Mostgraph and FeNO measurement can be conducted quickly and noninvasively, and this study suggests that this combination may be useful in diagnosis of chronic cough, and in assessing the effectiveness of treatment.

P2212
FeNO (fractional exhaled nitric oxide) measurements in pregnant asthmatic women. The long-term, intra-subject variability of FeNO in controlled asthma

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Background: Fractional exhaled nitric oxide (FeNO) is considered a good non-invasive marker to assess airway inflammation in asthma and allergic rhinitis. It has been also been proposed that adjusting anti-inflammatory drugs guided by the monitoring of exhaled NO could improve overall asthma control. However standards, the assessment of long-term repeatability of this parameter as well as the ratio of change which can be considered significant have not been established yet.

The aim of our study was to assess the long-term, intra-subject variability of FeNO in pregnant asthmatic women with controlled asthma.

Methods: Pregnant, non-smoking women with asthma were recruited between 8 and 24 weeks of gestation. Exhaled nitric oxide (FeNO), lung function, and the asthma control test (ACT) were performed at monthly visits up to delivery. The data of 50 subjects with well controlled asthma (20-25 ACT, normal spirometric parameters, no change in treatment) during pregnancy were analyzed. The variability of the FeNO parameter was assessed in asthmatics using the variation coefficient (standard deviation x 100/average).

Results: FeNO showed high coefficient of variation (CV): 35.8% (Me 32;Min 2.45, Max 121.9) in all women with well controlled asthma during pregnancy. There was no significant difference in CV between astatic 36.2% (35.5; 2.45-121.9) and nonatopic 33.9% (25.5; 11-71.9) asthmatic women (p= 0.98).

Conclusions: Long-term variation of FeNO was found to be not satisfactory be
cause the variation coefficient was 35.8%. It means that changes of FeNO should be interpreted with caution.

P2213

No effect of breathing dry gas on exhaled nitric oxide concentration at rest

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Background: The prevalence of asthma in elite endurance athletes is high, in particular among skiers. Prolonged high ventilatory demands in a cold and dry environment may contribute to the development of, or worsening of the asthma. Training periods often take place at altitudes of 2-3000 meter where ventilatory demand and respiratory heat and water loss are higher. Measurement of exhaled nitric oxide concentration (FeNO) is useful for monitoring eosinophilic asthma, but not neutrophilic asthma.

Aim: To assess the effect of breathing dry air on FeNO.

Methods: Nine healthy subjects aged 21 – 27 yrs (4 men) breathed dry air and humidified air for 90 min at rest in random order on separate days. FeNO was measured with a chemiluminescence analyser (Eco Medics AG, Duernten, Switzerland) at an expiratory flow rate of 50 ml/sec to ~15 min before and ~15 min after the exposures.

Results: There was no difference in the baseline FeNO between the two days. After exposure to dry air, FeNO decreased from 23.3 (SD=17.5) to 20.9 (SD=15.2) ppb, and after humid air it increased from 24.9 (SD=14.6) to 22.9 (SD=13.6) ppb.

Discussion: Breathing dry air at rest did not influence FeNO. Higher ventilatory demands result in larger respiratory water loss, which may be a trigger of a bronchomotor response. The transient reduction in FeNO after exercise must be controlled for when studying the combined effects of exercise and dry air on FeNO.

P2214

Fractional exhaled nitric oxide in bronchiectasis

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Fractional exhaled nitric oxide (FeNO) can be measured easily, rapidly, and non-invasively for assessment of airway inflammation, especially mediated by eosinophil, such as asthma. In bronchiectasis, the pathogenesis has been known as chronic airway inflammation and infection with abnormal airway dilatation; however, there is little information to evaluate the clinical application of exhaled nitric oxide in bronchiectasis.

From March 2010 to September 2011, 30 patients with bronchiectasis diagnosed by chest high resolution CT performed FeNO, compared with various pulmonary diseases, including asthma (n=24), COPD (n=21) and other infectious diseases (n=25). All patients carried out eosinophil count with chemistry, simple radiograph, sputum examination and spirometry, if indicated. FeNO (mean, ppb) in patients with bronchiectasis was 19.1, compared to 68.4, 31.7 and 18.9 in asthma, COPD and other infectious diseases, respectively. FeNO in bronchiectasis was significantly lower than asthma (P<0.001), however, no statistical differences were seen between bronchiectasis and other pulmonary diseases except asthma. No correlation of FeNO with eosinophil count in bronchiectasis was seen, despite the correlation was true in all of patients enrolled in study. FeNO in bronchiectasis with co-infection of nonmycobacterium tuberculosis was slightly lower than without co-infection (14.8 vs. 20.8). FeNO also tended to decrease along with multi-lobe involvements on CT.

FeNO in bronchiectasis was lower than other respiratory diseases, especially asthma. In bronchiectasis, the pathogenesis has been known as chronic airway inflammation and infection with abnormal airway dilatation; however, there is little information to evaluate the clinical application of exhaled nitric oxide in bronchiectasis.

P2215

The usefulness of the simultaneous measurement of IOS and FeNO in the management of asthma

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Background: The evaluation of airway lesions by impulse oscillometry (IOS) and the evaluation of fractional exhaled nitric oxide (FeNO) as the indicator of asthmatic airway inflammation attract attention. [Aim] To evaluate asthmatic airway lesions by simultaneous measurement of IOS and FeNO.

Methods: The subjects were the good controlled 65 patients with asthma (good controlled group), and 42 symptomatic treatment-free initial-visit patients with asthma (initial-visited group). Those subjects were nonsmoker. For the patients in both groups, we measured IOS and FeNO at the same time. IOS measured by MasterScreen and FeNO measured by NIOX MINO.

Results: The mean value of FeNO was 73.1±7.5 ppb in initial-visited group, and was 25.0±2.3 ppb in good controlled group, and the initial-visited group significantly showed high level. In the good controlled group, the positive correlation was accepted between the following IOS parameters, such as the total airway resistance, the small airway component, the peripheral capacitive reactance and the reactance area, the resonant frequency and FeNO (p<0.0001), but the correlation was not found between the large airway component and FeNO. Whereas, in the initial-visited group, the association was not found between these IOS indicators and FeNO.

Conclusions: FeNO mainly shows the inflammation of the small airway in the good controlled patients with asthma. Whereas, in the treatment-free initial-visited patients with asthma, FeNO was reflecting the inflammation of various airway regions.

Discussion: By the simultaneous measurement of IOS and FeNO, the information about asthmatic airway lesions as the target of treatment is obtained in greater detail.

P2216

Asthma control test (ACT), fractionated exhaled nitric oxide (FeNO) and forced expiratory volume in 1 second (FEV1) correlation in asthma control

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Background: The current goal of asthma treatment is to achieve and maintain control. Numerous markers or measurements of control are available. Among them, functional parameters (spirometry), clinical assessment (symptoms and quality of life) and biomarkers of inflammation are the most widely used.

Objective: This study aimed to clarify the relationship between the Asthma Control Test (ACT), lung function especially forced expiratory volume in 1 second (FEV1) and fractionated exhaled nitric oxide level (FeNO).

Patients and methods: There is a prospective study, for two months, including 37 asthmatic patients followed up outside of an exacerbation. A clinical protocol was followed with an assessment of asthma control by an ACT, spirometry and measurement of exhaled NO.

Results: There were 18 males and 19 females with a mean age of 43 years (12-7 years). The ACT score ranged from 12 to 25 (median=19). Total control of asthma (ACT≥20) was obtained in 18 patients. The average value of FeNO in the total control group (29.1 ppb) was significantly better than those in the less controlled groups with an ACT<20 (48.2 ppb).

There was no correlation between FEV1 and ACT (r=0.05), and between FEV1 and FeNO (r=-0.02). On the contrary, a negative correlation was found between ACT score and FeNO (r = -0.2).

Conclusion: We can postulate that the degree of bronchial inflammation is more sensitively detected by FeNO than by FEV1. The ACT is a good subjective tool for assessing the degree of asthma control which is more correlated with FeNO than FEV1.

P2217

Standardization procedures for in-vitro measurements using differential ion mobility spectrometry (DMS)

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Introduction: Air contains a couple of non-gaseous volatile organic substances (VOCs). Differential Ion Mobility Spectrometry (DMS) is an analytical method for detection of VOCs with sensitivity in the ppt-range and the possibility of processing native steam coming samples. A common problem is the pollution of samples by environmental agents, even with similar VOCs as in the samples. The method already was used for detection of bacterial growth.

Methods: For evaluation of ambient air influences on standardized in-vitro samples, bacteria-breeding grounds in closed vials were measured with room air as well as with filtered room air. This method should keep the water-content of the samples unchanged. The spectra were analyzed by a statistical program based on cluster analysis.

Results: The evaluation included up to 120 clusters of peaks. The number of peaks in filtered pure room air was significantly reduced and the total intensity was about halved. The reactive ion peak (RIP) of room air was 1.5-fold increased. Peaks and total intensity of the measured breeding grounds remained virtually unchanged.

Discussion: The filtering of air was capable to reduce environmental pollutants of in-vitro DMS measurements, even if the sample contains ambient air itself. The RIP of the sample tracings remains unchanged or was slightly increased, which can improve the sensitivity of DMS-measurements.

The investigation shows that it is possible to dispense with expensive carrier gases, which allows inexpensive diagnostic measurements in a contaminated environment.

P2218

Volatile organic compounds may provide a new and promising tool for diagnosing interstitial lung diseases

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Diagnosing interstitial lung diseases (ILD) requires invasive techniques. A new, non-invasive diagnostic tool includes analyzing volatile organic compounds

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These preliminary findings suggest that ventilatory patterns during speech tasks compared to the healthy group found in other parameters, the asthma group had a higher mean RR during all speech in adults with a self-reported history of asthma are characterised by a shorter TI and faster RR compared to ‘healthy’ participants. Research with larger VOCs currently investigated as a new tool for diagnosing ILD in vitro.

**P2219**

**Speech breathing pattern analysis in adults with a self reported history of asthma.**

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**Background:** While speech and breathing patterns are known to alter in acute episodes of respiratory disorders like asthma, it is not known if they alter in respiratory pathology, during stable periods of the disease.

**Aims and objectives:** To compare speech breathing patterns in healthy adults and those with a self-reported history of asthma.

**Methods:** Eleven adults with a self reported history of asthma (mean age = 29) and 29 ‘healthy’ adults (mean age = 34) with no history of respiratory disease were recruited from the University of Southampton. Breathing patterns were recorded non-invasively using Respiratory Inductive Plethysmography during 4 minutes each of quiet breathing, and 3 speech tasks: reading, describing and conversation.

**Offline analysis** was performed where 6 breathing parameters were extracted; inspiration and expiration time (TI, TE), breath cycle time (Ttot), inspiration and expiration time (TI, TE), breath cycle time (Ttot), inspiration and expiration (Tins, Texp) of the TI, TE, Ttot.

**Results:** Inspiration time was significantly shorter at the 95% level in the asthma group compared to the healthy group.

**Conclusion:** These preliminary findings suggest that ventilatory patterns during speech in adults with a self-reported history of asthma are characterised by a shorter T1 and faster RR compared to ‘healthy’ participants. Research with larger samples is needed to confirm these initial findings, as breathing patterns during structured tasks like speech could be useful for monitoring lung health.

**251. Cell biology, blood and sputum biomarkers in airway diseases**

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**P2220**

A novel, simple and rapid method to measure soluble mediators in dithiothreitol-treated sputum

Roberta Milone 1, Peter Chalk 2, Ken Grace 1, David Singh 2, Raminder Aul 4, Richard Knowles 1, 2.

1Respiratory TAU, GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom; 2Aurora Pharma, Steventon, Hertfordshire, United Kingdom; 3Medicines Evaluation Unit, University of Manchester, United Kingdom.

**Sputum** is most often processed by the addition of dithiothreitol (DTT) to liquefy the sputum plug and release cells and soluble mediators for subsequent analysis, but DTT treatment can perturb substantially with these analyses. The aim of this study was to develop a method to reverse this, to allow for the sensitive determination of analytes in DTT treated sputum by the addition of the thiol oxidising agent dithiothreitol. This was applied to the immunoassay of a panel of 21 analytes.

**Methods:** Assays of these analytes were shown to be suppressed to a highly variable degree (0-900-fold, median 25-fold) by the presence of DTT, as a result of a worsening of both background and maximal signal. Treatment of DTT-containing matrix with diastase resulted in a substantial improvement in the signal to background ratio, representing a 1-150 fold improvement (median 5-fold) in the assay. This diastase method was applied to the assay of analytes in the presence of DTT and permitted the sensitive (limit of detection (LOD) <10ng/ml) assay for all analytes except MDC (LOD 136ng/ml), with a high signal to background ratio (median 3700 at 1ng/ml) and acceptable recoveries of spiked sputum supernatants (median 72%).

This protocol was applied to DTT sputum obtained in a study of the dose- and time-dependence of responses to LPS inhalation in healthy smokers as a model of COPD bacterial exacerbations (Aul et al 2012, Brit J Clin Pharmacol in press). We were able to demonstrate significant increases in IL-1β, TNFα, MCP-1 and MIP-1β in sputum, with a maximal effect at 6h.

A simple and rapid dithiothreitol protocol provides a novel way to treat DTT sputum to allow for the sensitive immunoassay of a wide range of analytes.

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**P2221**

**C-reactive protein levels in COPD according to clinical parameters, smoking behavior and pulmonary hypertension.**

Funda Akün 1, Nermine Capan 2, Kurtulus Akun 1, Ruhsar Olhoğlu 1, Serma Canbakan 1, Kadır Ökkan Akın 1, Bünyanım Yavuz 1, Chest Diseases, Eskisehir Yunus Emre Hospital, Eskisehir, Turkey; 2Chest Diseases, Atatürk Chest Diseases and Surgery Training and Education Hospital, Ankara, Turkey, 3Division of Immunology and Allergy, Department of Chest Diseases, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Turkey; 4Biochemistry, Kecioren Training and Education Hospital, Ankara, Turkey.

**Aim:** To assess relationship between serum CRP levels and clinical parameters known to predict outcome, smoking history and biomarker exposure in COPD.

**Methods:** Spirometry, echocardiography, SpO2 measurements and serum CRP levels were assessed in 89 stable COPD patients and 60 age- and sex-matched healthy subjects. BODE index scores were assessed in COPD patients. Associations between CRP levels and clinical parameters were evaluated.

**Results:** Of the COPD group (11 stage 1, 48 stage 2, 29 stage 3, 11 stage 4) mean age is 60.6±8.5 years. CRP levels are significantly different between COPD patients treated with inhaled corticosteroids and those not treated (7.90±10.65 mg/L, 6.17±8.46 mg/L, p<0.05). Significant relationship is found between CRP levels and FEV1, FEV1%, FVC, FVC%, SpO2, MRC dyspnea scale, 6 minute walk distance and BODE scores. Using multivariate analysis BODE scores and coexistence of systemic hypertension manifested the strongest association. CRP levels in COPD patients with and without pulmonary hypertension were significantly different (11.86±13.38 mg/L, 5.78±8.05 mg/L, p<0.012). CRP levels did not differ significantly according to smoking status and biomarker exposure in COPD patients though COPD cases due to biomass exposure were never smoked and also had higher CRP levels compared to healthy controls (9.16±10.03 mg/L, 3.14±2.27 mg/L, p=0.028).

**Conclusion:** Systemic inflammation is related to disease severity and to constant systemic hypertension and pulmonary hypertension in COPD patients independent of smoking status or biomass exposure.

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**P2223**

**Serological detection of elastin fragments in COPD and IPF patients.**

F. Genovesio, H.B. Skjot-Arkil, E.R. Clausen, F.J. Martinez, C.M. Hogaboam, M. Han, M.A. Karlstad, D.J. Leentjens, Fibrosis Group, Nordic Bioscience, Herlev, Denmark.

**Introduction:** Elastin plays a critical role in the development of respiratory system disorders including COPD and IPF, whose pathogenesis involves an inflammatory response and tissue turnover mediated by proteases, especially matrix metalloproteinase (MMP-12) secreted by activated macrophages.

**Aims and objectives:** Our aim was to evaluate whether a novel biochemical marker of elastin degradation mediated by MMP-12 may provide information in relation to lung tissue destruction during pulmonary disease and aid in the diagnosis of respiratory disease.

**Methods:** Human elastin was in vitro cleaved by different proteases and the resulting peptides were analyzed by LC-MS/MS. Among more than 400 fragments, the MMP-12 generated elastin neopeptipe cleaved at the amino acid position 444 (ELN-441/ELM) was chosen as candidate for antibody generation for its uniqueness for human elastin following assay development. This novel marker was assessed in serum collected in a small cohort of COPD (n=10), IPF (n=29) patients and controls (n=11) using a competitive enzyme linked immunosorbent assay (ELISA).

**Results:** Serum levels of ELM were significantly higher in patients diagnosed with COPD (p<0.0003) and with IPF (p<0.0001) compared to controls. The diagnostic value, measured by means of the area under the curve of receiver operating characteristic (AUROC) was best in COPD patients (AUROC 97%, p=0.00025) and lower but still significant in IPF patients (AUROC 90%, p=0.0001).

**Discussion:** Even though these findings need to be validated in larger clinical settings, the ELM marker described showed potential for the separation of controls from COPD or IPF patients.
P2224 Laryngopharyngeal reflex in chest clinic patients with upper airways symptoms Alexander Spyridoulakis1, Siobhan Lillie3, Jemma Haines1, Aashish Vyas1, Stephen Fowler1,2, Respiratory Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 2Respiratory Research Group, University of Manchester, United Kingdom

Introduction: Laryngopharyngeal reflex (LPR) may underlie both chronic cough and laryngitis, and one explanation for a lack of response to standard anti-reflux therapy may be the presence of non-acid reflux. Salivary pepsin is a potential biomarker for LPR. The aim of this study was to evaluate if the detection of pepsin in saliva was associated with signs of laryngopharyngeal reflex in patients having nasendoscopy for investigation of upper airway symptoms.

Methods: We recruited patients from the Airways Clinic requiring nasendoscopy. All patients had the reflex Finding Score (RFS) recorded at nasendoscopy. Salivary pepsin was quantified with a lateral flow device using monoclonal antibody labelling (Peptest, RD Biomed, UK).

Results: Of 20 patients recruited, 12 were confirmed to have VCD and 13 a clinical suspicion of LPR (based on an RFS ≥ 7). Pepsin was detected in the saliva of 11/20 subjects (55%), including 67% of the VCD patients and 61% of those with a high RFS, although 43% of those with a low RFS also had a positive pepsin. Salivary pepsin had a sensitivity of 62% and specificity of 57% for predicting a high RFS. There was no significant correlation between RFS scores and salivary pepsin. Seven of the 10 patients already on treatment for a clinical diagnosis of reflux had a positive pepsin assay.

Conclusions: Salivary pepsin was frequently present in patients with upper airway symptoms, and not strongly related to clinical findings of reflux, suggesting a high prevalence of sub-clinical LPR. Further investigation should determine the clinical relevance of this, and whether LPR treatment results in an improvement in pepsin levels and the associated upper airway symptoms.

P2225 Comparison of serum osteopontin levels in patients with exacerbations and stable chronic obstructive pulmonary disease Yu Che, Kim, Yi Jong, Long Lee, Yome Huang, Internal Medicine, Gyeongsang National University Hospital, Jinju, Gyeongnam, Korea

Background: Osteopontin is recognized as an important adhesive bone matrix and a key cytokine involved in immune cell recruitment, tissue repair and remodeling. Then serum levels of osteopontin have not been evaluated in patients with chronic obstructive pulmonary disease (COPD). The aim of this study is to evaluate and compare the serum levels of osteopontin in patients with exacerbations and stable COPD.

Methods: Serum samples were obtained from 22 healthy control subjects, 18 stable COPD subjects and 13 exacerbation patients. Serum concentrations of osteopontin were measured by the ELISA method.

Results: Serum levels of osteopontin were higher in patients with exacerbation than with stable COPD and in healthy controls (24.5±4.6, 1477±19 mg/ml, 6.3±5.1, p=0.0003). Osteopontin levels were significantly decreased after clinical improvement than during exacerbation (45.2±6.2, 20.0±1.9, 980.1±160.0 p=0.160). Also osteopontin levels showed a significantly negative correlation with forced expiration volume in one second (r=-0.491, p=0.01). No significant correlation was found between absolute macrophage count and osteopontin level. However, osteopontin level was significantly increased after clinical improvement than during exacerbation (45.2±6.2, 20.0±1.9, 980.1±160.0 p=0.0003).

Conclusions: Serum osteopontin level was associated with co-morbidity, and females had higher SAA level than males. Systemic markers were not associated with airway inflammation. The overlap of asthma and COPD is common in older people with obstructive airway disease (OAD). Systemic inflammation is associated with adverse clinical outcomes and co-morbidities in OAD, but its role on asthma-COPD overlap syndrome is unknown. This study aimed to examine systemic inflammation in asthma-COPD overlap, and the potential clinical relevance with OAD.

Method: Serum high sensitivity C-reactive protein (hsCRP), Interleukin 6 (IL-6) and serum amyloid A (SAA) were measured in 108 adults older than 55 years comprising healthy controls (n=27), asthma (n=7), COPD (n=29) and asthma-COPD overlap (n=45). Spirometry, induced sputum, quality of life, co-morbidities and medications were assessed. Levels of systemic inflammatory mediators were compared, and the associations with clinical characteristics were tested in multivariate regression model.

Results: Patients with asthma-COPD overlap had significantly elevated IL-6 levels. SAA level was raised in both the COPD and asthma-COPD overlap groups. CRP was positively associated with BMI, whereas IL-6 was predicted by age, FEV1/predicted, and cardiovascular disease. SAA level was associated with co-morbidity, and females had higher SAA level than males. Systemic markers were not associated with airway inflammation.

Conclusion: Systemic inflammation is an common and important component of the asthma-COPD overlap. The pattern of systemic inflammation in asthma-COPD overlap is differing from COPD characterized as an elevated IL-6 and SAA levels. It is not related to airway inflammation, and may be an independent treatment target.
P2229 Repeatability and inter-relationships of small airway biomarkers in asthma
Sherif Goneim1, SushilaNdevi Natarajan1, Steven Corkill2, Anusha Singapuri1, Dhanamary Dasili,1, Per Gustafsson3, Christopher Brughling1, Saleh Sadaliu1
1Respiratory Medicine, Glenfield Hospital, Leicester, United Kingdom; 2Department of Paediatrics, Central Hospital, Skövde, Sweden

Background: There is evidence that small airway dysfunction may have an important role in asthma. We aimed to determine the within-visit and between-visit repeatability of small airway biomarkers in asthma, and explore the inter-relationships between them and with standard pulmonary function tests.

Methods: We recruited ninety-eight patients with asthma. All participants attended a baseline visit at which they underwent spirometry, body plethysmography, measurement of carbon monoxide diffusion capacity, impulse oscillometry (IXS), multiple breath washout (MBW) and induced sputum cell count. Eighteen patients undertook two-week and three-month follow-up visits, and twenty-six patients undertook six-month follow-up visits, at which all physiological tests were repeated.

Results: Small airway biomarkers displayed excellent within-visit repeatability (intraclass correlation coefficient [ICC] > 0.9), with the exception of S const, which was only moderately repeatable (ICC = 0.629). The biomarkers were all very stable over a three-month time frame, but S cond and Sacin were only moderately stable over six months. Principal components analysis of the variables derived five components, corresponding to the concepts of:
1) Expiratory flow limitation/air trapping
2) Heterogeneous airway constriction/closure
3) Ventilation heterogeneity
4) Airway inflammation
5) Impaired diffusion capacity

Conclusions: Small airway biomarkers are repeatable and stable over three months. Moreover, they appear to provide additional and independent physiological information over and above standard pulmonary function tests.

P2230 Metabolic syndrome and chronic diseases in COPD
Emel Bulcug, Aydanur Ekici, Mehmet Ekici. Department of Pulmonary Medicine, University of Kirkıkkale, Faculty of Medicine, Kirkıkkale, Turkey

Introduction: In this study, we examined accompanying comorbidities and metabolic syndrome (MS) in patients with COPD.

Method: Sixty-six patients with COPD and 40 subjects as control group were included. The index severity of chronic diseases was evaluated by using the MCIRS. MS was defined according to National Cholesterol Education Program.

Results: MS was detected in 18 patients (27.3%) in patients with COPD and in 8 patients (20%) in control group. The rate of MS in patients with stage II COPD was higher than in patients with stage IV COPD (p: 0.04).

Table 1. The predictors of presence of MAB in all subjects

<table>
<thead>
<tr>
<th>Presence of MAB</th>
<th>Presence of MAB</th>
<th>Presence of MAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.003</td>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
<td>0.4</td>
<td>Sex</td>
</tr>
<tr>
<td>Smoke p</td>
<td>0.7</td>
<td>Smoke p</td>
</tr>
<tr>
<td>Severity of COPD</td>
<td>0.04</td>
<td>BODE index</td>
</tr>
</tbody>
</table>

Statistical significance p<0.05. BMI: Body Mass Index, MCIRS: Modified Cumulative Illness Rating Scale.

Conclusion: Microalbuminuria may be seen in patients with COPD depending on severity of disease and hypoxemia.

P2232 Chronic mucus hypersecretion in asthma: Relation to smoking status and disease severity
Rekha Chaudhuri, Charles McSharry, Mark Spears, Neil C. Thomson. Respiratory Medicine, University of Glasgow, United Kingdom

Background: Chronic mucus hypersecretion occurs in chronic asthma, but the effects of smoking status and disease severity on this symptom are not clearly established. We assessed the prevalence of chronic mucus hypersecretion in patients with asthma recruited to the Glasgow COPD and Asthma Biomarker study.

Methods: One hundred and twenty subjects with asthma, smokers and never smokers of different GINA severity and fifty-four COPD subjects of different GOLD severity were recruited. Assessments included demographics, history of chronic cough and sputum production and spirometry.

Results: Baseline demographic and lung function data in the smokers with asthma and never smokers with asthma were similar. The COPD group were older and had a higher pack year history than the asthmatic group. Chronic mucus hypersecretion was strongly associated with smoking in the whole asthma group (Chi-sq=22.8, p<0.001). The proportion of patients with asthma and COPD of different disease severity and smoking status giving a history of chronic mucus hypersecretion is shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers with asthma (n=61)</td>
<td>10/20 (50.0%)</td>
<td>6/18 (33.3%)</td>
<td>18/25 (72.0%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Never smokers with asthma (n=59)</td>
<td>1/19 (5.3%)</td>
<td>3/18 (16.7%)</td>
<td>8/22 (36.4%)</td>
<td>0.045</td>
</tr>
<tr>
<td>COPD (n=54)</td>
<td>8/14 (57.1%)</td>
<td>15/23 (65.2%)</td>
<td>8/16 (50.0%)</td>
<td>0.644</td>
</tr>
</tbody>
</table>

*p<0.05. Fisher’s Exact test.

Conclusion: Chronic mucus hypersecretion increased with asthma severity overall (p=0.003) and in the smokers and never smokers with asthma, but not in COPD.

P2233 Microalbuminuria in chronic obstructive pulmonary disease
Emel Bulcug1, Mehmet Ekici1, Aydanur Ekici1. 1Department of Chest Disease, Kirkıkkale University, Faculty of Medicine, Kirkıkkale, Turkey; 2Department of Chest Disease, Kirkıkkale University, Faculty of Medicine, Kirkıkkale, Turkey; 3Department of Chest Disease, Kirkıkkale University, Faculty of Medicine, Kirkıkkale, Turkey

Introduction: We investigated levels of microalbuminuria and the factors determining in patient with COPD.

Method: 66 patients with COPD and 40 subjects as control group were included.

Abstract P2230 – Table 2. The predictors of MCIRS in all subjects

<table>
<thead>
<tr>
<th>MCIRS</th>
<th>B values</th>
<th>p values</th>
<th>MCIRS</th>
<th>B values</th>
<th>p values</th>
<th>MCIRS</th>
<th>B values</th>
<th>p values</th>
<th>MCIRS</th>
<th>B values</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.46</td>
<td>0.0001</td>
<td>Age</td>
<td>0.31</td>
<td>0.0001</td>
<td>Age</td>
<td>0.40</td>
<td>0.0001</td>
<td>Age</td>
<td>0.38</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.16</td>
<td>0.08</td>
<td>Sex</td>
<td>-0.19</td>
<td>0.02</td>
<td>Sex</td>
<td>-0.19</td>
<td>0.02</td>
<td>Sex</td>
<td>-0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02</td>
<td>0.7</td>
<td>BMI</td>
<td>-0.10</td>
<td>0.4</td>
<td>BMI</td>
<td>-0.13</td>
<td>0.1</td>
<td>BMI</td>
<td>-0.07</td>
<td>0.4</td>
</tr>
<tr>
<td>PO2</td>
<td>-0.11</td>
<td>0.3</td>
<td>BODE index</td>
<td>0.34</td>
<td>0.0001</td>
<td>FEV1%</td>
<td>-0.31</td>
<td>0.0001</td>
<td>FEV1%</td>
<td>-0.25</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Statistical significance p<0.05. BMI: Body mass index, MCIRS: Modified Cumulative Illness Rating Scale.
The role of regional distribution (RD) of body fat mass (BFM) in fat-bone interactions in men with chronic obstructive pulmonary disease (COPD) Sviatlana Lemiashukska1, Alexander Makarevich1, Alla Shelepkovich1, Natalia Vasileva2.

1Department of Internal Medicine No. 1, Belarussian State Medical University, Minsk, Belarus; 2EXA, Republic Centre of Medical Rehabilitation and Balneotreatment, Minsk, Belarus

The aim: Evaluation of the relationships between RD of BFM and TNF-α, some hormones and markers of bone metabolism.

Methods: We used DEXA to analyze RD of BFM. We determined: serum leptin (L), testosterone free (TF), TNF-α, parathyroid hormone (PTH), beta-croscals (beta-CTX) and osteocalcin.

We examined 83 COPD pts (40-70 yrs old) and control group – 15 healthy comparable men. The COPD pts were subdivided into 3 groups (GOLD).

Results: Fat mass (FM) in Android region (A) positively correlated with TNF-α (r=0.33; p<0.01) in all pts groups. Trunk and Arms FM were positively related to L (r=0.36 and r=0.35; respectively) in all pts groups. L level exerted negative influence on bone mineral density (BMD) in lumbar spine (r=-0.43; p<0.01), but not at TNF-α and BMD of the whole body. We found the positive correlations between beta-CTX and total FM (r=0.33) and FM in A (r=0.52) in all pts groups. The total, arms, legs and trunk FM, FM in Android and Gynoid (G) regions were increased in pts with a lower level of TF (p<0.05). Loss of BMD positively correlated (p<0.05) to loss of BMI, AGR ratio, FM in all body regions, PTH, calcium ionized and was inversely related with L in all pts group. Although these pts had decrease of BMD, BMI was increased (29.4 in pts with osteopenia and 24.7 kg/m² – with osteoporosis). Lowering of BMD might result from other factors, such as TNF-α and some hormones which are produced by the adipose tissue.

Conclusion: The study of RD of adipose tissue in the patient’s body is more informative than BMI for assessing the likelihood of developing osteoporosis in men with COPD.

P2234

The indices of body composition (IBC) consideration the changes of serum TNF-α, hormones and oxygen saturation (SO2%) in men with chronic obstructive pulmonary disease (COPD) Sviatlana Lemiashukska1, Alexander Makarevich1, Natalia Vasileva2.

1Internal Medicine No. 1, Belarussian State Medical University, Minsk, Belarus; 2Rep. Center of Medical Rehabilitation and Balneotherapy, Minsk, Belarus

Aim and objectives: to analyze dynamics of changes of IBC and the relationships between IBC and TNF-α, leptin (L), parathyroid hormone (PTH), testosterone free (TF), markers of bone metabolism, SO2%.

Methods: 63 patients (27 male, 36.9±18y) with COPD were recruited and 16 controls (7male, 56.8±18y), perfectly matched. Each patient was evaluated by spirometry, Leicester Cough Questionnaire (LCQ) and Sputum Colour Chart (SCC). Sputum was induced with hypertonic saline inhalation and succeeded in 49 COPD patients and 12 controls. Total/differential cell count in sputum was assessed and total gelatinolytic activity (TGA), neutrophil elastase (N) and MMP-9 were measured.

Results: TGA and NSE were higher in patients vs controls (p=0.05 and p=0.003) and both correlated with neutrophil count (NSE: p=0.009; r=0.38 and TGA: p<0.0001; r=0.60). Subanalysis of high value TGA showed that NSE accounted for 82% of the activity vs 18% MMP-9 (p<0.0001). There was an inverse correlation between neutrophils and FVC% (r=0.02; r=0.35) and NSE and FVC% (r=0.04; r=0.29) in NCFB. No relationship was seen between total LCQ score, LCQ subcores and enzymatic gelatinolytic activity. There was however a significant relationship between the SCC and TGA (p<0.0003) and NSE (p=0.01). SCC also correlated with neutrophils (p=0.001).

Conclusion: TGA is significantly higher in NCFB and correlates with indices of inflammation and infection (neutrophils and SCC). The majority of TGA was exercised by NSE (82%) in NCFB. No correlation was seen with radiologic score or LCQ.

P2233

The role of regional distribution (RD) of body fat mass (BFM) in fat-bone interactions in men with chronic obstructive pulmonary disease (COPD) Sviatlana Lemiashukska1, Alexander Makarevich1, Alla Shelepkovich1, Natalia Vasileva2.

1Department of Internal Medicine No. 1, Belarussian State Medical University, Minsk, Belarus; 2EXA, Republic Centre of Medical Rehabilitation and Balneotreatment, Minsk, Belarus

The aim: Evaluation of the relationships between RD of BFM and TNF-α, some hormones and markers of bone metabolism.

Methods: We used DEXA to analyze RD of BFM. We determined: serum leptin (L), testosterone free (TF), TNF-α, parathyroid hormone (PTH), beta-croscals (beta-CTX) and osteocalcin.

We examined 83 COPD pts (40-70 yrs old) and control group – 15 healthy comparable men. The COPD pts were subdivided into 3 groups (GOLD).

Results: Fat mass (FM) in Android region (A) positively correlated with TNF-α (r=0.33; p<0.01) in all pts groups. Trunk and Arms FM were positively related to L (r=0.36 and r=0.35; respectively) in all pts groups. L level exerted negative influence on bone mineral density (BMD) in lumbar spine (r=-0.43; p<0.01), but not at TNF-α and BMD of the whole body. We found the positive correlations between beta-CTX and total FM (r=0.33) and FM in A (r=0.52) in all pts groups. The total, arms, legs and trunk FM, FM in Android and Gynoid (G) regions were increased in pts with a lower level of TF (p<0.05). Loss of BMD positively correlated (p<0.05) to loss of BMI, AGR ratio, FM in all body regions, PTH, calcium ionized and was inversely related with L in all pts group. Although these pts had decrease of BMD, BMI was increased (29.4 in pts with osteopenia and 24.7 kg/m² – with osteoporosis). Lowering of BMD might result from other factors, such as TNF-α and some hormones which are produced by the adipose tissue.

Conclusion: The study of RD of adipose tissue in the patient’s body is more informative than BMI for assessing the likelihood of developing osteoporosis in men with COPD.

P2234

The indices of body composition (IBC) consideration the changes of serum TNF-α, hormones and oxygen saturation (SO2%) in men with chronic obstructive pulmonary disease (COPD) Sviatlana Lemiashukska1, Alexander Makarevich1, Natalia Vasileva2.

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Results: TGA and NSE were higher in patients vs controls (p=0.05 and p=0.003) and both correlated with neutrophil count (NSE: p=0.009; r=0.38 and TGA: p<0.0001; r=0.60). Subanalysis of high value TGA showed that NSE accounted for 82% of the activity vs 18% MMP-9 (p<0.0001). There was an inverse correlation between neutrophils and FVC% (p=0.02; r=0.35) and NSE and FVC% (p=0.04; r=0.29) in NCFB. No relationship was seen between total LCQ score, LCQ subcores and enzymatic gelatinolytic activity. There was however a significant relationship between the SCC and TGA (p<0.0003) and NSE (p=0.01). SCC also correlated with neutrophils (p=0.001).

Conclusion: TGA is significantly higher in NCFB and correlates with indices of inflammation and infection (neutrophils and SCC). The majority of TGA was exercised by NSE (82%) in NCFB. No correlation was seen with radiologic score or LCQ.

P2237

Asthma phenotyping: Correlation between inflammatory phenotype, clinical parameters and associated comorbidities Annemie Van Den Bergh1, Sven Seys1,2, Pieter Goeminne1, Liesven Dupont1, Dominique Ballemans3, Respiratory Disease, University Hospital, Leuven, Belgium; 2Microbiology and immunology, Catholic University of Leuven, Leuven, Belgium

Introduction: Cluster analysis revealed 5 clinically different clusters of asthma: mild atopic (1), mild to moderate atopic (2), late-onset non-atopic (3), severe atopic (4) and severe with fixed airflow obstruction (5) (Moore et al, 2009).

Aim: To link differential cell count and associated comorbidities (BMI, smoking, atopy, reflux, sinussitis and broniectasis) to 5 clusters of asthma based on clinical features (baseline FEV1, maximal FEV1 and age of onset).

Methods: We retrospectively evaluated clinical records from 140 asthma patients (44% male; 43y ± 14) with induced spusa, recruited from outpatient clinic of the University Hospital Leuven between January 1st 2008 and November 1st 2009 and were free of exacerbation for three months prior to sputum induction.

Results: Cluster 1 accounted for 37%, cluster 2 for 26%, cluster 3 for 14% and cluster 4 for 12%. Cluster 5 was too small for further analysis. Cluster 4 as defined by Moore and coworkers is significantly associated with more neuorphils (median: 72%, interquartile: 60-82%); p<0.02) in induced sputum as compared to the other clusters. Relative number of patients with reflux was highest in cluster 3 (55%) compared to cluster 1, 2 and 4 (29%, 34% and 38%). Presence of sinussitis was equally distributed between all clusters (p<0.95).

Conclusion: Severe atopic asthma have a predominant neuorphilic airway inflammation. Patients with late-onset non-atopic asthma have the highest rate of reflux. Previously unrecognized broniectasis were detected in 9% of patients.
As a result of air trapping and hyperinflation. IC decreases further with activity and may correlate more strongly to exercise capacity than measures of airflow (FEV1). 6 minute walk test (6MWT) is an objective measure of functional exercise capacity.

**Objectives**: The objective was to examine the correlation between IC and exercise capacity using 6MWT and FEV1 and exercise capacity in COPD patients and to compare the correlation between IC and exercise capacity with FEV1 and exercise capacity in COPD patients.

**Methods**: This was a retrospective study. All COPD patients undergoing both 6MWT and spirometry and lung volumes in CGH from 1/1/2008 till 9/11/2011 were included.

**Results**: 144 subjects were included. Mean age (years) was 69.12±8.93. 138/144(96.5%) were male. Mean FEV1 (L) was 1.33±0.57. There was statistically significant correlation between FEV1 and 6MWT distance (simple linear regression coefficient, r=29.89, p<0.01, 95% confidence interval 4.42 to 53.57). After adjusting for cardiovascular disease, the correlation was still statistically significant(r=29.00, p<0.01, 95% CI 4.36 to 53.63). There was statistically significant correlation between IC and 6MWT distance(r=38.81, p<0.003, 95% CI 13.08 to 64.53). After adjusting for cardiovascular disease, correlation was still statistically significant(r=39.09, p<0.003, 95% CI 13.22 to 64.96).

**Conclusion**: IC is better correlated with 6MWT distance (functional capacity) (p<0.003) than FEV1(0.021) in COPD patients. Thus, we concluded from this study that IC is a better predictor of exercise capacity than FEV1 in COPD patients.

**P2241**

**Comparison of validity of methacholine and mannitol bronchial challenges in asthma diagnosis**

**Konstantinos Porpodis, Kaliopi Domvri, Theodoros Kontakiotis, Dimitrios Liatsos, Dimitrios Ioannidis, Paschalina Gouleka, Konstantinos Zarogoulidis, Despoina Papakosta, Department of Pneumonology, Aristotle University of Thessaloniki, Hospital “G. Papanicolaou”, Ereschi, Thessaloniki, Greece**

**Background**: Detection of BHR with methacholine or mannitol have been highly sensitive tests to identify asthma diagnosis.

**Purpose**: The purpose of this study was to demonstrate the diagnostic validity of the two bronchial challenges and their correlation with symptoms, atopy and inflammatory markers.

**Methods**: Eighty-eight patients, 47 women and 41 men, aged 14-75 years who presented with asthma related symptoms and were not on any anti-asthma medication, were challenged with mannitol and methacholine. Medical history, physical examination, skin prick tests, Asthma Control Test (ACT) and FeNO levels were also assessed. The clinical diagnosis of asthma was lost on bronchodilator reversibility test.

**Results**: Sixty seven patients were diagnosed with asthma and 21 without asthma. Both methacholine (p<0.014) and mannitol (p<0.000) challenges were significant in diagnosing asthma. The sensitivity/specificity was 62.68%/85.71% for methacholine, 64.17%/95.23% for mannitol and 64.76%/93.75% for both methods together, whereas the positive/negative predictive value was 93.33%/41.86%, 97.72%/45.45% and 97.05%/45.45%, respectively. There was a negative correlation between PD15 of methacholine and the FeNO level p<0.001, and positive with the PD15 of mannitol p<0.001 and the pre-test FEV1 pred p<0.05, whereas PD15 of mannitol was negatively correlated with the FeNO level p<0.001. Furthermore, dyspnoea was the only asthmatic symptom associated with FeNO level p<0.035 and the positivity of mannitol p<0.014 and methacholine p<0.04.

**Conclusions**: Both provocation methods were equivalent in diagnosing asthma, although sensitivity/specificity values appeared to be slightly higher in mannitol challenge.

**P2242**

**Repeatability of peak nasal inspiratory flow rate (PNIF) measurements and its change after administration of 0.05% oxymetazoline**

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**Background**: Measurement of PNIF is a cheap and easily performed method to assess nasal patency. However, the assessment of repeatability of this parameter as well as the threshold value of change which can be considered significant have not been established yet.

The aim of this study was to assess the repeatability of PNIF measurements and its change after the administration of 0.05% oxymetazoline.

**Methods**: Repeated measurements of PNIF (In-Check’s Clement-Clark) were performed in 333 (174 women) healthy volunteers. Subjects were divided into three age groups (6-7, 13-14 and 20-45 years). Each subject carried out 5 measurements. PNIF was retaken 30 minutes after inhaling 0.05% oxymetazoline in 294 subjects. The variability of the PNIF measurements appeared to be significantly higher in mannitol challenge.

**Results**: The first four PNIF measurements significantly differed from each other. There was no statistically significant difference only between the fifth and fourth
Evangelia Daniil, Georgios Kaltsakas

P2243 Detection of air leaks and their effects on forced oscillometry measurements
Andreas Bikos,1,2, Omar Usman1, Neil Pride1, James Bull1, Ilidiko Horvath1,
Peter Barns2, Paolo Pareli1,1. Airway Disease, National Heart and Lung Institute, Imperial College, London, United Kingdom. 2Department of Pulmonology, Semmelweis University, Budapest, Hungary

Introduction: Forced oscillation technique (FOT) is a method to estimate respiratory resistance (Rrs) and reactance (Xrs). However, some common artefacts may affect the accuracy of FOT readings. In particular, air leaks from lips not sealed around the mouthpiece, or those from the equipment. We studied the significance of this artefact and identified possible markers to detect it.

Methods: 11 healthy subjects (33±6 years) underwent FOT measurements (Jaeger, Wurzburg, Germany) which generated 0.4-kPa peak-to-peak input signals. The Rs and Xrs values at 5 and 20 Hz (R5, R20, X5) were registered in parallel with breathing volumes. To simulate air leaks, we applied artificial holes of increasing sizes (3.5 mm, 6 mm, and 8.5 mm diameters) on the breathing filter at 1 cm from the circumference. FOT data were compared to normal values obtained with no air leaks.

Results: With increasingly bigger filter holes and resulting air leaks, we identified corresponding larger indentations in the descending limb of the breathing volume (ΔV 2.2±0.6 mL, 5 ±2.3 mL, and 7.6±3.1 mL and 14±4.2±9 mL; respectively, p<0.001), indicating that ΔV may be a marker for air leak. This was confirmed by a significant correlation between ΔV and R5 (p<0.001, r=0.74), R20 (p<0.001, r=0.71), X5 (p<0.001, r=0.50). In line with this, a 1 mL increase in ΔV was associated with a 10% decrease in R5 values.

Conclusion: Indentations on the descending limb of the breathing volume may be used to detect the presence and magnitude of air leaks. Visual inspection of the data is required to exclude records where indentations are caused by artefacts.

The first author is receiving an ERS Long Term Fellowship.

P2244 Early diagnosis of small airway disease
Evangelia Danili, Georgios Kaltsakas, Sofia-Antiopi Gennimata, Anastasios Palamidas, John Jordanoglou, Nikolaos G. Koulouris. 1st Respiratory Medicine Dept, Athens University, Sotiria Hospital, Athens, Attica, Greece

Inflammatory changes in the peripheral airways of smokers are detected when “normal” spirometry is still present, indicating that early structural damage in the small airways develop before the diagnosis of overt COPD is established. Therefore, the early diagnosis of COPD is a feasible hypothesis (Thorax 1980; 35: 375-378) and its variations, advocated to early detect small airways disease and discriminate between smokers and non-smokers. However, it is not clear whether of the aforementioned tests is the “best” for early detection of small airways disease.

We studied 30 (15 men) Caucasian subjects (10 never smokers, 10 smokers with normal spirometry, and 10 COPDxers in GOLD I), aged (mean±SD) 52±14 y with FVC%pred=11±12, FEV1%pred=81±14, FEV1/FVC%73±10. All smokers had smoking history more than 10 pack-years. Simple spirometry, the slope of phase III (ANf/AN), and the effective time at the 60-70% part of the forced vital capacity of the lung (TEFFf;3-70) were measured. The ANf±TEFFf;3-70 (64±29) was abnormal in 16/30 subjects. The ANf/ANf;30 (182±150) was abnormal in 14/30 subjects. TEFFf;3-70 was 155±88 and was abnormal in 17/30. Multiple linear regression analysis showed that TEFFf;3-70 was more appropriate, among the tests performed, for discriminating smokers from never smokers (p=0.008). In conclusion, TEFFf;3-70 appears to be a sensitive test for the early detection of small airway disease.

P2245 Prognostic factors in COPD patients controlled in two outpatient clinics
Verónica Hernández, Patricia Sobradillo, Laura Tomás, Lucia Canelo, Francisco Ribas, Mikel Azpiarzu, Vanesa Zorrilla, Begoña Lahladaga, José Luis Lobo. Respiratory, HUA - Taussigutta, Vitoria - Getaria, Araba, Spain

FEV1 and a number of composite indexes (BODE, U-BODE, ADO) predict mortality in the population of patients with chronic obstructive pulmonary disease (COPD) as large. However, patients attending the specialized clinics of tertiary referral hospitals are often old and suffer severe or very severe airflow limitation. We aimed to compare the prognostic value of FEV1, BODE, U-BODE and ADO indexes in patients attending the outpatient clinics of Hospital de Cruces, a tertiary referral hospital in Bilbao (Spain). Patients from two outpatient clinics were included. FEV1, BODE, U-BODE and ADO were values determined at recruitment and patients were followed up for a mean of 4.5 years.

We studied 106 patients (70.5±8.9 yrs; FEV1 44.4±19.9% of ref., 35 of whom (33%) died during follow-up. In this population, FEV1 did not predict mortality, whereas BODE (p=0.001), U-BODE (p=0.000) and ADO indexes (p=0.003) did. BMI did not discriminate survival significantly but dyspnea (p=0.003), distance walked (p=0.000) and age (p=0.002) did.

In patients attending the outpatient clinic of a tertiary referral hospital, FEV1 is not a good prognostic marker, at variance to age, dyspnea, walked distance, ADO, BODE and U-BODE indexes.

P2246 Evaluation of treatment with fixed dose combinations in asthma patients in primary care in Sweden by using mannitol challenge test
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Background: The mannitol challenge test is an indirect bronchial challenge test suitable for use in a primary-care setting. The test is most often used to diagnose asthma. In this pilot study the test was used to evaluate the effectiveness of ongoing treatment with ICS/LABA combination therapy in patients with asthma.

Objectives: To explore the prevalence of optimal treated asthma patients in primary care in Sweden. The hypothesis was that not all patients are optimal treated.

Methods: Male and female patients, 18-65 years with asthma, who were treated with a fixed dose combination (budesonide/formoterol or fluticasone/salmeterol) were included in the study. The subjects performed a mannitol challenge test (direct FOT), followed by an inhalation of a β2-agonist. A new spirometry (reversibility test) was performed 15 minutes later. The explorative end-point was response or negative response of mannitol challenge test and/or a reversibility of ≥15%.

Results: The preliminary result of this pilot study (100 subjects) shows that an unexpectedly, surprisingly high proportion of the asthma patients had a positive response, either as a direct fall of FEV1 ≥15% in the mannitol challenge test and/or a reversibility of ≥15%.

Conclusion: The result of this study indicates that a large proportion of asthma patients in primary care, who are currently treated with fixed dose combination therapy, may not be optimally treated. Further research is needed to support these findings and to understand the reasons.

P2247 Difference of respiratory reactance between mild and moderate COPD by forced oscillation technique using a MostGraph-01
Yasuhiro Yamanchi, Tadashis Koyama, Tsukasa Jo, Masafumi Horie, Yusuke Mikami, Takahide Nagase. Respiratory Medicine, The University of Tokyo, Japan

Background: COPD is characterized with persistent airflow limitation caused by airway inflammation and parenchymal emphysema. The Forced Oscillation Technique (FOT) can detect the lung impairment by measuring respiratory impedance during tidal breathing without special maneuver of respiration. Respiratory reactance and resistance (Xrs) dynamically change during tidal breathing in COPD patients. We evaluated the difference of the Xrs in respiratory cycle between mild and moderate COPD.

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 cycle was measured by FOT using MostGraph-01, which was manufactured in Japan CHEST Company. The Xrs during inspiratory and expiratory phase during tidal breathing was evaluated at 4 Hz of oscillatory frequency. Comparisons of Xrs between both groups were performed using the Student’s t-test.

Results: The mean Xrs at 4 Hz (X4) in respiratory cycle were similar in mild and moderate groups. There were also no significant differences between inspiratory X4 (inx4) and expiratory X4 (ex4) in both groups. However, the ratio of inx4 to ex4 in mild COPD was significantly lower than that in moderate COPD (p=0.01).

Conclusion: The ratio of inx4 to ex4 during tidal breathing in mild COPD was lower than moderate COPD. During tidal breathing, the Xrs changes in inspiratory and expiratory phase and might be influenced by airway obstruction and parenchymal emphysematous change. The measurement of Xrs during tidal breathing might be useful property to distinguish the severity of COPD.
**Methods:** We reviewed all tests in our Trust between 2009 and 2011, compared baseline spirometry between positive and negative tests, and looked at immunological evidence of atopy. We reviewed clinic letters for change in diagnosis or management, as well as symptomatic improvement and whether patients were discharged from follow-up (representing clinical stability).

**Results:** Tests were performed on 177 patients between April 2009 and October 2011. The positive and negative groups were compared in terms of spirometry and immunological evidence for atopy (total IgE and IgE to inhaled allergen mix and aspiragel). The test was positive in 40 patients (22.6%). Of these, immunological evidence of atopy was greater than in those with negative tests (mean total IgE 275 vs. 132, IgE to IAP 5.48 and 4.73, IgE to aspiragel 0.6 and 0.25 respectively). Baseline spirometry tended towards more airflow obstruction in the positive group though the means were both within normal range (89% and 97% predicted). Of the 126 patients for whom we had data the manntol challenge resulted in changes in treatment and improved symptoms in 115 (91.2%).

**Conclusion:** Bronchial provocation testing is useful in identifying those with AH, and for guiding treatment leading to symptomatic improvement.

**P2249**

**Best time for evaluating the response to bronchodilators**

**Abouda Maher, El Goul Jamel, Youngui Ferdaous, Triki Miriam, Charfi Med**

**Ridha. Pneumology, FSI, La Marsa, Tunis, Tunisia**

**Introduction:** There is no clear consensus on the time of interpretation of the bronchodilator effect. The interval between administration of bronchodilator type β2-agonist short-acting and the practice of post bronchodilator spirometry remains a controversial issue. Our objective was to define the optimal time of bronchodilator responsiveness in assessing the reversibility or otherwise of an obstructive respiratory disorder (ORD).

**Materials and methods:** Analytical study prospectively over a period of 8 months performed in the pneumology service of FSI Hospital Security. The study included patients with ORD defined by an FEV/FVC <0.7 and who had consulted outside of an exacerbation. Flows and expiratory volumes (FEV, FVC) were measured before and after bronchodilator in the 5th, 10th, 15th, 20th and 30th minute. The response to BD was expressed in absolute and percentage change from baseline.

**Results:** 126 patients were included in the study, mean age 54±15 years with a majority of men. Our study was conducted in patients with asthma and COPD whose airway obstruction was moderate (FEV > 2 liters, or >62% of predicted). (1) The maximum response after bronchodilator occurred at the 20th and 30th minutes respectively for FVC and FEV (2) The number of reversible patients was guideline defining. (3) The maximum number of reversible patients was obtained in the 20th minute with a significant difference compared to that observed at the 5th and 10th minute.

**Conclusion:** The interpretation of the response to bronchodilator in the 20th minute after was the ideal time to assess the reversibility of ORD.

**P2250**

**Small airway dysfunction by impulse oscillometry system (IOS) in asthma.**

**Relationship with spirometry, bronchodilator response and disease control**

**Roberta Pisi, Panagiota Tzani, Marina Aiello, Enrico Martinelli, Emilio Marangio, Dario Olivieri, Alfredo Chetta. Clinical Sciences Dpt, Respiratory Disease Unit, University Hospital, Parma, Italy**

**Rationale:** Small airways are relevant to the pathophysiology of asthma.

**Objective:** We investigated the relationship between small airway function, as assessed by IOS and spirometry, bronchodilator response, disease control and fractional exhaled nitric oxide (FeNO) values, in asthmatic patients.

**Methods:** We studied 38 patients with asthma (24 F, age range 16–70 yr). The fall in resistance from 5 to 20 Hz (R5–R20) and reactance at 5 Hz (X5) in kPa s l–1 by IOS and spirometry at baseline and after 400 mg of salbutamol were measured. Asthma Control Test (ACT) and FeNO (in ppb) were also recorded.

**Results:** R5–R20 and X5 were significantly related to spirometry, with FEF25-75 < 80% predicted (p < 0.01). The maximum response after bronchodilator occurred at the 20th and 30th minutes respectively for FVC and FEV. (2) The number of reversible patients was guideline defining. (3) The maximum number of reversible patients was obtained in the 20th minute with a significant difference compared to that observed at the 5th and 10th minute.

**Conclusion:** The interpretation of the response to bronchodilator in the 20th minute after was the ideal time to assess the reversibility of ORD.

**P2251**

**Comparison of SAPALDIA and ECCS lung function normal values in a Swiss hospital setting**

**Jochen Küttner1, Florent Bary1, Andreas Bloch1, Lukas Kern2, Tino Schneider1, Martin Brutsche1, 1Pneumologie, Kantonsspital St. Gallen, St. Gallen, Switzerland; 2Pneumologie, Zuger Kantonsspital AG, Baar, Switzerland**

The SAPALDIA survey observed better lung function in healthy volunteers than the common ECCS normal values (ECCS) predicted. We thus introduced the SAPALDIA normal values (SAP) for lung function interpretation at the Kantonsspital St. Gallen. We currently analyzed the distribution of FVC and FEV1 in non-pulmonary patients with a normal lung function comparing SAP and ECCS (so far 379 lung functions). Data was analyzed using descriptive statistics, Bland-Altman (BA) analysis and linear regression. Estimated bias and precision were calculated.

For FEV1 we observed a significant difference between ECCS and SAP only in elderly men (>59 y.o.) (7±336 vs. 12±336 ml/s). When comparing FVC using SAP, the Bland Altman analysis revealed a bias, which was significantly lower using ECCS (e.g. in men bias of SAP was 0.33 l (0.27-0.39), bias of ECCS was 0.18 l (0.11-0.24), (fig.1, lower panels).

In summary, SAP tended to overestimate FVC and FEV1 in elderly men compared to ECCS. However, absence of a pulmonary consultation in our population does not exclude a slight impact of the underlying disease on lung function. We consider SAP for FEV1 and FVC appropriate for the measurement of lung function of our population. Cut-off values require special attention especially in elderly.

**P2252**

**Prevalence of hyperinflation and its reversibility in asthma patients with poorly controlled disease or significant dysnea**

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**Introduction:** Inflammation in asthma involves proximal and distal airways. The latter may induce a significant hyperinflation (HI).

**Aim:** To evaluate the prevalence of HI by body plethysmography in asthmatic patients with poorly controlled disease and/or significant dysnea.

**Methods:** In 324 patients (age 49±17, FEV1 75±18% pred) insufficient asthma control was defined by an ACT score < 20 (n = 302) or a significant dysnea by a MRC score ≥ 1 (n=22).

HI was defined by either a RV > pred + 1.64 RSD (RV-HI) or a FRC > 120% pred (= FRC-HI). HI reversibility after bronchodilator was defined by a decrease of RV > 20% or a reduction of FRC > 10% from baseline. Change in dysnea and chest tightness were evaluated by a VAS. Results: HI was found in 49% (RV-HI) and 47% (FRC-HI) of cases. Prevalence of HI was higher in patients with a FEV1 < 60% pred than in those with a FEV1 > 80% pred: 78% for RV-HI and 70% for FRC-HI, vs 34% and 40%, respectively. ACT score was lower in patients with FRC-HI (13±4±4 vs 14±6±4; p = 0.004). Post-bronchodilator change was -10±13% for FRC, and -12±21% for RV. HI reversibility was obtained in 59% of cases with RV-HI and 47% of cases with FRC-HI. Chest tightness decrease after bronchodilator was greater in patients with...
baseline FRC-HI (-44±25 vs -37±24 mm, p = 0.02). Dyspnea improvement was higher in those with baseline RV-HI (-45±26 mm vs -38±23, p = 0.02).

**Conclusion:** Hypereventilation is frequent in poorly controlled asthma, including patients with normal FEV1, suggesting an involvement of distal airways. It appears reversible in more than half of cases.

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### P2253

**Sprirometry and home oxygen in COPD patients with and without a history of illicit drug smoking**

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Respiratory, Royal Liverpool University Hospital, Liverpool, United Kingdom

Our 960 bed inner city hospital has 3 full time COPD nurses providing a 7-day a week service reviewing patients admitted with COPD exacerbations. They are employed with a view to reducing length of stay and preventing re-admissions. The team audit their work prospectively. Several patients have recurrent admissions with exacerbations of COPD. We looked at the database from January 2009 to September 2011 and compared spirometric confirmation of COPD and home oxygen prescription amongst four groups of patients: Ex-tobacco smokers and active tobacco smokers with and without a history of illicit drug smoking.

**Results:**

<table>
<thead>
<tr>
<th>No history of drug use</th>
<th>History of Drug Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age (yrs)</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>53.9</td>
</tr>
<tr>
<td>Number of Admissions</td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>252</td>
</tr>
<tr>
<td>Home oxygen (%)</td>
<td></td>
</tr>
<tr>
<td>241 (22)</td>
<td>59 (23)</td>
</tr>
<tr>
<td>Spirometry (%)</td>
<td></td>
</tr>
<tr>
<td>489 (44)</td>
<td>118 (47)</td>
</tr>
</tbody>
</table>

**Conclusion:** There were no significant differences in the proportion of patients that had documented spirometry or a home oxygen prescription amongst those with and without a history of illicit drug smoking. A greater proportion of ex-smokers with a history of illicit drug smoking had a home oxygen prescription. This may reflect more severe disease which may be caused by the additional damage caused by drug smoking.

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### P2254

**Assessment of ventilation heterogeneity by impulse oscillometry in patients with mild asthma**

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Ventilation heterogeneity is an independent determinant of airflow hyperresponsive-ness (AHR) in asthma, and its measurement is complex and technically difficult. Impulse oscillometry (IOS) is increasingly used to obtain information on the state of the respiratory system. In this study, we determined the clinical validity of IOS as a novel and simple method for the assessment of ventilation heterogeneity in asthma.

Serial measurement of resistance at 5 Hz (R5) or 20 Hz (R20) by IOS was performed in 23 mild asthmatic patients and 28 normal control subjects; the measurements were made at baseline, after methacholine (maximal dose) provocation test for asthma and subsequent salbutamol administration. Further, exhaled nitric oxide (eNO) levels were examined and pulmonary function test was also performed. The baseline R5, but not R20, was significantly higher in asthmatic patients than in controls. Both R5 and R20 were not significantly correlated with the degree of airflow obstruction and eNO levels. However, R5 was significantly correlated with the severity of AHR (r = -0.55, P = 0.01), whereas R20 was not.

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### P2255

**Heterogeneity of small airways flow and hyperinflation are markers of a persistent obstruction phenotype in severe non-controlled asthmatics**

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Persistent functional impairment in some severe asthmatics, even after maximal treatment, is usually linked to inflammation, which does not explain all asthma limitations and seems to be determined by small airways structural changes too.

**Objective:** Evaluate functional mechanisms related to persistent airflow obstruction (PAO) after an intensive therapeutic regimen in severe asthmatics.

**Methods:** Non-controlled severe asthmatics received high inhaled corticosteroid dose (ICSs) plus LABA for 12 weeks and oral corticosteroid (OC) in the first two weeks, after which they were classified into PAO by an FEV1 after BD< 80% plus FEV1/FVC < 0.70. Complete airway reversibility were labeled as reversible disease.

**Results:** All PAO values, including Slope of Phase III of the single breath nitrogen washout test (dN2), became different after OC and did not return to normal. ACQ in NPAO decreased to near normal values (1.75±0.94).

**Conclusion:** Persistent obstruction phenotype in severe asthmatics showed a high heterogeneity of airflow measured by dN2 and early airway closure due to high resistance (R5), which might be a novel and simple method for the assessment of ventilation heterogeneity in asthma.

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### P2256

**Change in pulmonary function abnormalities in sarcoidosis over time: A review of 75 cases**

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Airflow obstruction is common on initial pulmonary function tests (PFTs) in Sarcoidosis. Little has been published about change in PFTs over time, or with treatment. We examined PFT change in patients diagnosed with Sarcoidosis over a 14 year period. 75 patients were included. Median follow-up was 5.1 years. Patients were divided into those treated prior to follow-up (n=39) and those not (n=36). Results are shown in table 1.

Treated patients tended to have greater deterioration of their PFTs. The difference was non-significant, except for a lower decline in FEV1/FVC ratio in those untreated. Previous research (Miller et al. Chest 2011; 139:52-59) suggests fixed ratio values are less accurate than percentile predicted; here, there was no statistical difference in percentile change between groups. Absolute FEV1 and FVC values declined in both groups, though less in those untreated. Both groups showed greater than expected annual decline in FEV1.

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### Abstract P2256 – Table 1. Absolute and centile values (baseline, follow-up and within-group differences)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Presentation</th>
<th>Follow-up</th>
<th>Within-group difference</th>
<th>Between-group mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Treated</td>
<td>Untreated</td>
<td>Treated</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.83</td>
<td>2.61</td>
<td>2.77</td>
<td>2.38</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.66</td>
<td>3.40</td>
<td>3.65</td>
<td>3.31</td>
</tr>
<tr>
<td>FEV1/FVC Ratio</td>
<td>77.4%</td>
<td>77.2%</td>
<td>76.2%</td>
<td>72.1%</td>
</tr>
<tr>
<td>FEV1 (centile)</td>
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<td>25.5</td>
<td>50.9</td>
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<tr>
<td>FVC (centile)</td>
<td>46.1</td>
<td>32.7</td>
<td>58.8</td>
<td>58.8</td>
</tr>
<tr>
<td>Ratio (centile)</td>
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<td>35.7</td>
<td>34.7</td>
<td>28.5</td>
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1*L/yr change.
P2257
Lung clearance index is a reliable and sensitive measure of airways disease in bronchiectasis
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Introduction: In bronchiectasis (BE), there is a need for a sensitive outcome measure that is responsive to interventions, particularly in those with mild disease. FEV1 is insensitive to small airways disease and is often within normal range in BE. Lung clearance index (LCI) is a measure of ventilation inhomogeneity derived from multiple breath washout (MBW).

Objective: To assess intra and inter-visit repeatability of LCI and determine the relationship between FEV1 and LCI in stable BE.

Methods: Inclusion criteria: HRCT diagnosis of BE within 5 years; clinically stable (>4 weeks no infective symptoms); no features of CF. Participants attended for 2 visits, 2-4 weeks apart. At each visit they performed MBW in triplicate, using 0.2% SF6 and a modified InnocorTM device. LCI was derived from the mean of at least 2 acceptable washouts. Spirometry was performed at ATS/ERS standards.

Results: 30 patients (14M/16F) attended for 2 visits. The mean (SD) age was 56.6 (14) yrs. Mean (SD) FEV1% predicted was 84.8 (20.7), range (40-117). Mean (SD) LCI was 9.2 (1.7) on visit 1 and 9.3 (1.9) on visit 2 (normal <7.5). The intra- and inter-visit intraclass correlation coefficient was 0.94. LCI negatively correlated with FEV1 (r=-0.73, p<0.001) and FEF25-75 (r=-0.84, p<0.001). Sensitivity of LCI, FEV1 and FEF25-75 for the diagnosis of bronchiectasis by CT was 83%, 40% and 73% respectively.

Conclusions: This is the first report of LCI in BE. LCI has good intra and inter-visit repeatability. Across a range of FEV1 there is a strong relationship between LCI and FEV1. LCI is a more sensitive test of lung function than FEV1 and FEF25-75, and is abnormal in the majority of people with BE who have a normal FEV1.

P2258
Managing asthma in the outpatient clinic - Can the FEV1/FVC indicate when to do a reversibility test
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Background: Testing for reversibility to SABA often constitutes the first step of a diagnostic assessment of asthma. However, patients with a normal or near-normal lung function often do not have significant reversibility, and performing reversibility testing in these patients may not be cost-effective.

Aims: To compare the predictive value of the FEV1/FVC ratio using lower limit of normal (LLN) for predicting significant reversibility to SABA, and to define optimum cut-points that might be applied clinically.

Methods: The MAPoAti study is a retrospective observational study of all patients consecutively referred to a tertiary hospital specialist clinic over a 12-month period, on suspicion of asthma (n=221).

Results: In total, 122 subjects (55%) had a reversibility test performed, among whom 28 (23%) had a significant response to beta-2-agonist, defined as an increase in FEV1 of 12% or more, and at least 200 mL. The area under the curve of the FEV1/FVC % of the LLN for predicting reversibility was 0.76 (p<0.001). The FEV1/FVC ratio was above the LLN in 77% of newly referred asthma patients, including subjects who had a reversibility test performed (94/122 (77%)). Only 14% of subjects with an FEV1/FVC above the LLN had significant reversibility, compared to 54% of subjects with an FEV1/FVC ratio below the LLN.

Conclusion: Absence of significant airflow obstruction at rest was associated with a low likelihood of reversibility to beta-2-agonist. The majority of subjects referred for specialist assessment on the suspicion of asthma did not have airflow obstruction. In these subjects, alternative diagnostic strategies may be more cost-effective.

P2259
The prediction of airway wall thickening by computer aided lung sound analysis
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Computer Aided Lung Sound Analysis (CALSA) has been used to detect and analyse added lung sounds to aid diagnosis of many respiratory diseases. The wall area of the main bronchi, expressed as a percentage of the cross-sectional area of each branch, is a biomarker of chronic airway inflammation which is raised in COPD. The objective of this study was to explore the possible relationship between characteristics of crackles measured by CALSA and percentage of wall area of the main bronchi measured by High Resolution Computed Tomography (HRCT), and hence the possibility of using crackles as a biomarker of COPD. 26 participants (9 healthy non-smokers, 9 healthy smokers and 8 COPD) were recruited. Lung sound data were recorded using a digital stethoscope. HRCT scans were conducted using a Siemens Sensation 64 CT scanner and the resulting data were analysed using the Pulmonary Workstation 2 (Vida Diagnostics, Iowa, USA) software to give measurements of airway geometry. The results showed that the percentage of wall area at the right upper bronchus correlated with the two cycle duration of crackles (r=0.39, p=0.025) recorded at the right upper lobe (RUL), the number of crackles per breathing cycle (NCpB) at RUL (r=0.49, p=0.005) and NCpB at right lower lobe (r=0.49, p=0.006). Additionally, the NCpB at RUL was found to significantly predict the percentage of wall area at the right upper bronchus (adjusted R²=0.20, R²=0.24, p<0.010). These initial results suggest NCpB might be useable to predict changes in percentage of wall area caused by the chronic inflammation of the main bronchi, though a larger sample needs to be examined. This suggests that crackles could possibly be used as a biomarker of COPD.

253. Inflammation in airway diseases: diagnosis and management

P2260
Additive role of exhaled NO and blood eosinophil count to predict wheezing in a random population sample
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The fraction of nitric oxide in exhaled air (FeNO) and blood eosinophil count (B-Eos), markers of local and systemic eosinophil activation, respectively, are increased in asthma. Little is known about the relation to reported wheezing in a random population sample or the additive value of these two methods. FeNO (NIOX Mino) and B-Eos were measured in 12,408 subjects aged 6-79 years from the National Health and Nutrition Examination Survey 2007-08 and 2009-10. Current wheezing, hay fever and smoking habits were questionnaire-assessed. Subjects with wheezing had higher FeNO and B-Eos than subjects without wheezing (p<0.001). Slightly increased FeNO (25-50 ppb) and high FeNO (>50 ppb) related to a higher wheezing prevalence than normal FeNO (14% and 25% vs 12% for normal FeNO, p=0.001). Slightly increased B-Eos (300-500 Eos/mm3) and high B-Eos (>500 Eos/mm3) related to a higher wheezing prevalence than normal B-Eos (17% and 22% vs 11% for normal B-Eos, p<0.001). The risk of wheezing increased with increased B-Eos for subjects with high FeNO and, similarly, with increased FeNO for subjects with high B-Eos (Table).

Risk of wheezing (odds ratios) with increased FeNO and B-Eos

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<tr>
<th>Normal B-Eos</th>
<th>Intermediate B-Eos</th>
<th>High B-Eos</th>
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<tr>
<td>FeNO</td>
<td>1</td>
<td>1.41</td>
</tr>
<tr>
<td>Intermediate FeNO</td>
<td>1.29</td>
<td>1.81</td>
</tr>
<tr>
<td>High FeNO</td>
<td>1.81</td>
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Adjusted for gender, age, BMI, smoking and hay fever.

In conclusion, the prevalence of wheezing increased in this random population sample with increased FeNO and blood eosinophil count and the predictive values of these biomarkers for wheezing is additive. The clinical importance of these findings in asthma with regard to phenotyping and individualized treatment has to be determined.

P2261
The effect of long-term macrolides therapy for acute exacerbation of chronic obstructive pulmonary disease: A meta-analysis
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Introduction: Chronic obstructive pulmonary disease (COPD) exacerbations are associated with frequent hospital admission reduction of lung function, and decreased quality of life. Macrolides have airway antiinflammatory actions and may reduce the frequency of COPD exacerbations. Methods: We searched PubMed and Embase databases to identify randomized
Significant differences were observed between the groups in terms of age, desaturator (n=47) and non-desaturator (n=177) groups.

Long-term macrolide therapy in patients with COPD can decrease macrolides (RR=1.35, 95%CI(1.09, 1.67), p=0.007).

Five studies reported adverse events, and adverse events were more frequent with patients with at least one exacerbation( RR=0.50, 95%CI (0.27, 0.90), P=0.02). Five studies reported adverse events, and adverse events were more frequent with macrolides (RR=1.35, 95%CI(1.09, 1.67), p=0.007).

Conclusions: Long-term macrolide therapy in patients with COPD can decrease exacerbations, but the safety is not sure.

The CT emphysema index is a predictor for exertional desaturation in COPD patients without resting hypoxemia.

Results: A total of 224 subjects were selected from the Korean Obstructive Lung Disease cohort. Exertional desaturation was defined as a post-exercise oxygen saturation (SpO2) of >90% and a ≥4% decrease. The cohort was divided into desaturator (n=47) and non-desaturator (n=177) groups.

Conclusions: In patients with COPD, exertional desaturation possibly occurs in parallel with an increase in the CT emphysema index. Exertional desaturation may be a manifestation of emphysema phenotype, and COPD patients with exertional desaturation are associated with a more rapid decline in lung function and poorer health-related quality of life.

Managing asthma in the outpatient clinic: Is the diagnosis of asthma confirmed objectively according to guidelines?

Risk factors associated with persistent airflow limitation in difficult asthma.

Background: GINA guidelines recommend that a diagnosis of asthma is confirmed by an objective measurement of lung function or the presence of airway hyperresponsiveness. However, currently no diagnostic flowchart exists on asthma, and objective tests are used inconsistently.

Methods: The MAPOut I study is a retrospective observational study of all patients consecutively referred to a tertiary hospital specialist clinic over a 12-month period, on suspicion of asthma (n=221).

Data on lung function, peak flow, reversibility to beta2-agonist and airway hyperresponsiveness (AHR) was collected.

The prevalence of bronchiectasis among the asthma patients was 2.2%.

Adherence to asthma treatment: Can it be improved in general practice?

Background: Good treatment adherence is pivotal in maintaining well-controlled asthma, along with the right diagnosis and the right treatment.

Conclusion: The overall treatment adherence improved significantly when a systematic asthma management approach was introduced and applied by dedicated health care staff.

Risk factors associated with persistent airflow limitation in difficult asthma.

Background: Bronchiectasis and asthma are different disease. However, some patients have both diseases. There are insufficient data for the effect of bronchiectasis on asthma exacerbations.

Methods: We investigated 2270 patients having asthma in our hospital. Fifty patients had bronchiectasis and asthma. These patients were compared with fifty age and gender matched patients having asthma only. We evaluated frequency of asthma exacerbations (steroid use, emergency room (ER) visit and hospitalization) in each group.

Results: The prevalence of bronchiectasis among the asthma patients was 2.2%. Follow up duration of each group was 51.9±35.2 months for asthma with bronchiectasis and 53.8±29.8 months for pure asthmatics. The number of asthma exacerbations/year (1.04±1.15 vs 0.35±0.42, p=0.004), steroid use/year (0.4±0.54 vs 0.26±0.36, p=0.006), ER visit/year (0.46±0.84 vs 0.26±0.36, p=0.001) and hospitalization/year (0.7±1.44 vs 0.1±0.17, p=0.04) due to asthma exacerbation was higher in asthma with bronchiectasis vs pure asthma.

Conclusion: The number of asthma exacerbation, steroid use, and ER visit due to asthma exacerbation was higher in asthma with bronchiectasis than pure asthma.

Risk factors associated with persistent airflow limitation in difficult asthma.

Introduction: The clinical manifestations of difficult asthma are heterogeneous. Some patients with difficult asthma develop irreversible airflow obstruction, which is associated with poor outcomes.

Objective: The aim of the study is to determine clinical characteristics associated with persistent airflow limitation in difficult asthma.

Methods: We retrospectively analyzed 48 patients with difficult asthma between 2005 and 2010. Twenty patients (8 female, 12 male) with persistent airflow limitation (post bronchodilator FEV1/FVC ratio < 70%) were compared to 28 patients (13 female, 15 male) with normal post bronchodilator FEV1/FVC ratio. Patients with chronic obstructive pulmonary disease and bronchiectasis were excluded.

Results: There was no significant difference between the two groups in age (51 vs 45 years, p=0.17), sex (p=0.66), age of asthma onset (55 vs 32 years, p=0.07), number of hospitalizations (p=0.39) and frequency of exacerbations (p=0.74).

Conclusion: The most frequent episode of asthma exacerbation was acute asthma exacerbation. Persistent asthma exacerbations were more frequent in patients with normal FEV1/FVC ratio (15% vs 35%). But, the difference was not significant (p=0.41).

Gastroesophageal reflux was found in 25% of patients in both groups.

Risk factors associated with persistent airflow limitation were as follows: longer duration of asthma (22 vs 9.5 years, p < 0.001), current or past smoking (50% vs 21%, p=0.038) and absence of allergy (69% vs 33%, p=0.026). Dust mite sensitization was significantly more frequent in patients with normal FEV1/FVC ratio (26% vs 61%, p=0.33).

Conclusion: Smoking, longer disease duration and absence of sensitization seem to be related to persistent airflow limitation in Tunisian patients with difficult asthma.
P2267
Can we achieve GINA guidelines described asthma control in a developing country?
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Introduction: In Pakistan, 5% of adult population suffer from asthma. Poor disease control accounts for morbidity and recurrent hospitalization. Prospective studies assessing asthma control in Pakistan are lacking.

Aims & Objectives: To assess asthma control and factors predicting good asthma control.

Methods: Consecutive 50 asthmatic patients were studied in this prospective, interventional study from April to December, 2010. Diagnosis was confirmed by a rise in FEV1 of ≥12% after bronchodilator. Patients were assessed during intervention period at weeks 0, 4 and 8 and finally after 6 months. Data was analysed using SPSS version 17.

Results: Mean age was 43 years with predominant females (66%). 50% were in lower social class and 58% had family history of asthma. Majority belonged to mild (42%) or moderate (48%) persistent varieties of asthma. At initial assessment 24% used inhalers correctly and 52% required treatment modification according to GINA guidelines. At completion of intervention period 70% had well controlled asthma, 60% used inhaler correctly and 66% were compliant with treatment. At completion of non-interventional period (after 6 months) only 49% had well controlled asthma, 44% used inhalers correctly and 50% were compliant with treatment. A linear regression analysis recognised correct inhaler technique and treatment compliance as significant predictors of good asthma control while age, gender, social class, educational level, severity and family history of asthma were not of any significance in this regard.

Conclusions: GINA guidelines stated asthma control is achievable in our setting provided repeated patient education, correct inhaler technique and compliance to medical therapy are ensured.

P2268
Long term inhalatory therapy in asthma – Achieving control of the disease
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Objective: Evaluation of long term inhalatory therapy in asthma and achieving control of the disease using asthma control test.

Methods: This was a prospective study recruiting ambulatory patients aged ≥12 years with asthma at the Pneumology Hospital Oradea between December 2011 and January 2012. We evaluate the effectiveness of long term inhalatory treatment of the disease with ACT as a means of detecting GINA defined uncontrolled, partially controlled and controlled asthma (uncontrolled and partially controlled asthma are together labelled as ‘not controlled’ according to GINA). Patients with the following were included in the study: hospitalized for asthma and ambulatory patients with asthma. The questionnaire used was ACT Romanian and English version for adults from www.asthmacontroltest.com. Eligible patients answered and submitted the questionnaire to the investigator, patients then performed Spirometry tests followed by interviews with a pulmonologist who evaluated their asthma control and provided treatment modifications as required.

Results: A total of 60 patients were included in the study of mean age 55 years. Females comprised of 55% of the participants and 45% male participants. A mean ACT score was 15.05, in which GINA stage 1 and 3 are prominent 35%, but in general patients are unequally distributed among the four stages. Most of the patients were using preventive medication; the majority had uncontrolled asthma according to both GINA and ACT criteria and were stepped up on treatment after their visit.

P2269
Comparing COPD in Malta, to other European hospitals: Results from the ERS COPD audit
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Background: Proper management of COPD can reduce exacerbations, which in turn reduces disease-related mortality.

Aim: To find out how management of COPD exacerbations in Malta contrasts with other countries.

Methods: A total of 422 European hospitals took part. Every COPD patient admitted with an exacerbation to our hospital over 8 weeks, was included (n=112). The ERS COPD audit proforma and web tool was used. Data was processed by the Data Analysis Team. The authors take full responsibility for any inferences made in this abstract.

Results: The median length of stay was 5 days, while the European Median (EM) was 8 days; there is no early supported discharge programme locally (31.8% of European hospitals run this). The 90-day readmission rate was 47.6% locally vs. 35.1% EM. In Malta there is no respiratory ward (81.7% EM), no specialist COPD ward (61.8% EM), nor respiratory nurse specialists. There are 4 respiratory teams (EM 80%). On admission, only 48.2% had spirometry results available (59.6% EM). 6.4% needed IV (12.5% EM), but 91.1% of patients improved before IV was needed (40% EM). On discharge 15.5% were given LTOT (30.4% EM), the PaO2 our patients had on admission was 66.9mmHg vs. 59.4mmHg EM. 49.1% of our cases satisfied GOLD criteria to be discharged on LAMA (1.8% vs. 59.8% EM) or ICS + LABA (12% vs. 69.5% EM). 45.5% of our patients were on antibiotics on discharge (11.9% EM). The 90-day mortality was 7.6% (6.1% EM). Still, this was COPD-related in only 37.5%.

Conclusions: In Malta management of COPD needs to be optimised by establishing and adhering to guidelines. Specialised care is recommended as well as re-auditing at a later stage.

P2270
Clinical features of alpha one antitrypsin deficiency in COPD
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Setting: About 1-3% of patients with diagnosed chronic obstructive pulmonary disease (COPD) are predicted to have alpha1-antitrypsin deficiency (A1ATD).

Objective: To clinically evaluate and increase recognition of AATD in patients with COPD.

Material and methods: Sixty COPD patients were diagnosed on the basis of clinical and pulmonary function tests. They fulfilled the inclusion criteria and divided into group (A) COPD below 40 years (30 cases) and group (B) COPD above 40 years (30 cases). All patients were subjected thorough history taking, radiological examination, blood gas analysis and quantitative measurements of serum alpha-1 antitrypsin by radio-immunoassay.

Results: Mean age of group A&B were (44.17±2.75, 61.87±6.04) respectively with (p value <0.001). The mean serum level alpha 1 antitrypsin in group A&B were (185.03±23.00 with only one case deficient(177.53-94) with only four cases deficient) respectively without statistical significance. There is significant relationship between the age of the patient and A1ATD, where in deficient patients mean age 39.63±13.66, and in normal patients mean age 50.18±12.06) with (P value 0.02). There is also significant relationship between family history and A1ATD, where in deficient patients 50%of cases (4 cases) had positive family history, in contrast to 11.61% of cases(13 case) of normal patients (p value 0.03).

There is a significant difference in ages between deficient and normal group as regards gender distribution, smoking history, symptomatic presentations, physical signs, radiological picture, pulmonary function tests and blood gas parameters.

Conclusion: Emphysema at an early age, non smoker with positive family history are clinical features suggestive for A1ATD.

P2271
Chronic kidney disease (CKD) – A forgotten co-morbidity in COPD
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Background: CKD is a less recognized co-morbidity in COPD and its impact on exacerbations and mortality has been under reported.

Objectives: To look at the prevalence of CKD in patients admitted to hospital with exacerbation of COPD. Secondly, to compare the length of stay (LOS) in hospital and all cause mortality between the CKD and non-CKD cohort.

Methods: We included all patients admitted to hospital with a COPD exacerbation from 1st January 2010 to 31st December 2010. CKD was defined as eGFR<60ml/min/sq.m for at least 3 months. Data was analysed by independent sample t-test, chi-square and Mann Whitney U test using online tool Vassar stats and significance reported at p≤0.05.

Results: 161 patients (56% females) were admitted each with FEV1/FVC ratio<0.7 and median FEV1 36% predicted. Spirometry and BMI data were analysed on 113 patients (CKD n= 90, non-CKD n=23) as records for 48 patients could not be obtained. The prevalence of CKD was 18.6% (n=30). CKD group, was older (mean age 75.8 yrs vs 69.2 yrs; p=0.001), included more males (45% vs 43%), had higher Body Mass Index (30 vs 23.8 kg/m²; p= 0.002), had better FEV1 (46 vs 35.5% predicted; p= 0.02) and longer LOS (8 vs 6 days; p= 0.042). There was no significant difference in mortality between the two groups (n= 7 vs n=30; p=0.84).

Conclusion: CKD is prevalent in COPD and has a significant effect on the LOS during exacerbations; however it does not contribute to increased one year mortality. Hence, more work is required in this field.

References:
[1] ICD code J44.1

P2272
Characteristics of αz alpha one antitrypsin deficiency patients on the Irish national registry
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Rationale: Alpha-1 antitrypsin (AAT) is produced by hepatocytes, and is the
most important antiprotease in the lung. AAT deficiency (AATD) is a hereditary disorder resulting from mutations in the AAT gene. Individuals with this deficiency classically present with lung disease in adulthood. WHO guidelines advocate a targeted strategy in screening COPD, non-responsive asthma, cryptogenic liver disease patients and relatives of known AATD patients.

**Methods:** The most common AAT phenotype associated with lung disease is ZZ. A chart review of AATD patients on the National Alpha-1 Registry was performed on ZZ patients (n=100). Our registry collects data on pulmonary function tests, GOLD guidelines, initial reason for screening, complications, and smoking history. The mean age of symptom onset was 37.6 ± 3.9 years; the interval between symptom onset and diagnosis was 6.2 years. The mean number of physicians seen prior to diagnosis was 2.6 ± 0.3. Symptomatically screened ZZ individuals mean age of symptom onset was 36.2 ± 3.0 years; mean age of diagnosis was 44.3 ± 1.9 years (range 6-60). The interval between onset of symptom and diagnosis was 6.2 ± 2.8 years (range 4-60). We evaluated the longitudinal changes in FEV1 in asthmatic outpatients during a 10 year follow-up period (P value 0.01, 0.004, 0.001, 0.001). The mean decrease in FEV1 in symptomatic smokers was 21.4% and in asymptomatic smokers was 10.5%. We recorded the changes in FEV1 variability at 3 months. FEV1 variability at the 1st year was computed. Short term treatments with oral steroids (OS) were used as needed. The best FEV1 measures at 1st, 5th and 10th year were evaluated and normalized for the subject’s height at third power (FEV1/HT3). The slopes FEV1/HT3 vs time during the 1st and 2nd periods were evaluated. We evaluated the effect of body mass index, baseline FEV1, age at enrolment, age of disease onset, disease duration, allergic sensitization, number of OS courses, and FEV1 variability on FEV1 decay slopes. Median FEV1/HT3 slope values were -0.013 and -0.014 (±0.001) for the 1st and 2nd period, respectively (P<0.0001). No correlation was found between the slopes of the two periods. 1st period slopes were correlated to FEV1 variability (P<0.0001), but such correlation was not found for 2nd period slopes. Negative relationship between 1st period slopes and long term reversibility was found (P=0.006). Subjects with disease duration ≤5 years had steeper 1st period slopes (P=0.04). A relationship was found between 1st period slopes and the number of OS courses (P=0.012). In conclusion, FEV1 decay in treated adult asthmatics is not constant. In particular, it drops down over time, and is influenced by some subjects’ clinical and functional characteristics.

**P2276**

**Computer aided lung sound analysis in smokers**

Mohammad Alzahra1, Anne Bruton2, Anna Barney3

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Computer technology was used to record and analyse lung sounds in two groups of healthy young subjects (smokers and non-smokers).

**Introduction:** Tobacco smoking is known to have adverse effects on human health. It is believed that smoking in early life has a substantial role in the development of chronic lung disease, but it is not yet known when the first measurable effects of smoking can be detected. Computer aided lung sound analysis (CALSA) permits the quantification of lung sounds, which may change in response to smoking. We found that smoking significantly affected lung sound recordings when compared to non-smokers. We compared the lung sound recordings of smokers and non-smokers.

**Method:** Sixty male subjects (30 smokers and 30 non-smokers) aged 26.8 ± 4.7 years were recruited from a staff population. Lung sound recordings were made using a digital stethoscope, following published guidelines. Lung sounds were recorded on a computer with Matlab software. Using signal processing techniques, one characteristic of the crackles was measured (namely the two cycle deflection (2CD)) at each anatomical recording site. Statistical analysis was used to quantify differences in crackles between smokers and non-smokers.

**Findings:** Sixty sets of data have been analysed. The 2CD per site data revealed some statistically significant differences at both anterior sites (anterior left: F(2,57)=7.87, P=0.02, anterior right: F(2,57)=9.51, P=0.00) and both lateral sites (middle left: F(2,57)=4.2, P=0.02, middle right: F(2,57)=9.51, P=0.002).

**Conclusion:** The hypothesis that crackle’s 2CD differ between asymptomatic smokers and non-smokers has been supported.

**P2277**

**Clinical features of alpha one antitrypsin deficiency in non cystic fibrosis bronchiectasis**

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**Setting:** It’s important to identify manifestation of alpha-antitrypsin deficiency (AATD) in bronchiectasis to improve patients care and outcome.

**Objective:** To clinically evaluate AATD in patients with non cystic fibrosis bronchiectasis.

**Material and methods:** Patients with non cystic fibrosis bronchiectasis were diagnosed clinically and confirmed radiologically. They fulfilled the inclusion criteria and divided into group (A) bronchiectasis with hyperinflation (30cases) and group (B) bronchiectasis without hyperinflation (30 cases). All patients were subjected to history taking, pulmonary function tests, and quantitative measurements of serum A1AT by radio-immunoassay. It's important to identify manifestation of alpha1-antitrypsin deficiency (AATD) in bronchiectasis to improve patients care and outcome.

**Results:** Mean age of both groups was (50.5±6.8) and (36.8±7.5) respectively (P=0.001). There were significant difference in gender distribution (P=0.006), and smoking history (P=0.001). Haemoptysis presented in 12 cases (40%), and 20 cases (66.67%) in both groups respectively (P=0.04). Dyspnea presented in 27 cases (90%) and 19 cases (63%) for group A&B with (P=0.02). There were no significant difference in sinusitis, hepatological symptoms, clubbing and family history. There were significant differences compared to normal lung sounds, radiological findings and spirometric tests (P value 0.01, 0.004, 0.001, 0.001).
Conclusion: A LATD is seldom found in patients with bronchiectasis even with concomitant hyperinflation. Inheritance could influence an individual risk of a LATD for developing bronchiectasis.

P2278
Clinimetric properties of outcome measures in bronchiectasis
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1Centre for Infection and Immunity, Queen’s University Belfast, United Kingdom; 2School of Health Sciences, University of Ulster, Belfast, United Kingdom

Introduction: In bronchiectasis (BE) there is demand for researchers and regulatory bodies to use robust outcome measures (OM) in clinical trials which have evidence of validity, reliability and responsiveness.

Aim: To explore the evidence for clinimetric properties of commonly used outcome measures in BE.

Methods: A systematic search of key databases (2000-2010) to identify studies in adults with BE which included the following OM; HRCT, FEV1, Quality of life (Qol), exacerbations (PEX), sputum volume/colour and sputum inflammatory markers (IL-8 and elastase). Data relating to clinimetric properties was extracted.

Results: 68 papers met the inclusion criteria. There was good evidence for all components of validity for HRCT, FEV1, Qol, and with exception of predictive validity for sputum volume/colour and sputum inflammatory markers. There was minimal evidence for validity for PEX. The majority of RCTs in BE included FEV1 (n=9/11) as a key OM however none were able to demonstrate a treatment effect with FEV1. Other research designs (e.g. crossover/cohort studies) were also unable to demonstrate a treatment effect with FEV1. A small number of RCTs (n=5) included the other OMs and some of these studies were able to demonstrate a significant treatment effect (Qol, n=2/4, PEX n= 2/4, sputum/colour/n=1/5 and sputum inflammatory marker n=1/5). Other research designs were also able to demonstrate a treatment effect with these outcomes. There are a small number of studies demonstrating test-retest reliability of these OM.

Conclusions: FEV1 is considered to be the primary outcome in clinical trials however current evidence in BE suggests that FEV1 may not be responsive and other outcome measures should be considered.

P2279
PCD – As serious as CF in every day lung clinic?
Annika Halling1, Dept. Women’s and Child Health, Uppsala University, Uppsala CF Centre, Uppsala, Sweden

Background: Cystic fibrosis, CF, and Primary cilia dyskinesia, PCD, have very different genetic background, but present very similar in clinic with vicious mucus, bacteria, bronchiectasis and negatively affected lung function. Our regimen involves mucolytica, inhalations, airway clearance and anti-bacterial treatment regardless of diagnosis, but in all cases individualized.

Aim of study: To see whether PCD patients as a group were as affected as CF patients.

Patients: All patients, CF and PCD, seen regularly at our clinic were compared as a whole group and also in an age and gender matched subgroup of 21 pairs.

Results: When comparing lung function in the two groups, FEV1 (in percentage of expected for age and length) showed, to our surprise, to be worse for the PCD group, both in the main group and in the subgroup. The bronchiectases are evaluated separately and will be presented at the Congress. There were more, but not exclusively, pseudomonas infections in the CF group – an expected finding.

Conclusions: We studied 69 patients (44F, 25M); mean age of 60 (SD 14.2). Mean FEV1 % predicted was 69% (SD 30.2), 24 patients (35%) had chronic P. aeruginosa infection.

P2280
Relation between COPD assessment test (CAT™) and quality of life in COPD patients
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The aim was to investigate the relation between COPD assessment test (CAT™) and pulmonary function tests(PFT), BODE index, and St. George Respiratory Questionnaire (SGRQ).

Patients: 100 patients diagnosed by GOLD criteria were included to the study. A Questionnaire that include sociodemographic findings as well as CAT, PFT, SGRQ, and BODE index were assessed for each patient.

Exacerbation number in a year and hospitalization in a year was related with all the parameters above.

Conclusion: There was no relation between CAT and quality of life in COPD patients and also correlation between these parameters and disease stage were observed. CAT can be used as simple, practical test when PFT were unavailable or there was no enough time to apply quality of life questionnaire.

P2281
The impact of airflow obstruction, P. aeruginosa infection and psychological factors on cognitive function in bronchiectasis patients
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Introduction: Bronchiectasis is a chronic lung systemic disease; whilst acute sepsis is associated with cognitive dysfunction, there is little data for chronic lung sepsis. We have compared cognitive function to relevant factors, e.g. airflow obstruction and P. aeruginosa infection.

Methods: Adult Bronchiectasis patients from clinic (3 months) were screened. Cognitive function was determined by the Cognitive Failures Questionnaire (CFQ), a self-reported measure; poor memory has a high score and >40 is abnormal. We recorded airflow limitation (FEV1), MRC dyspnoea (MRCD) and P. aeruginosa infection. The Hospital Anxiety and Depression Scale assessed anxiety (HADS-A) and depression (HADS-D). Fatigue was measured by Fatigue Impact Scale (FIS); abnormal >40.

Results: We studied 69 patients (44F, 25M); mean age of 60 (SD 14.2). Mean FEV1 % predicted was 69% (SD 30.2), 24 patients (35%) had chronic P. aeruginosa infection.

Conclusion: Cognitive dysfunction may be a co-morbidity in Bronchiectasis patients and is associated with anxiety, depression and fatigue. However, it does not appear to be related to objective markers of disease severity.
Table 1

<table>
<thead>
<tr>
<th>PCG</th>
<th>Partially</th>
<th>WCG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.7±14</td>
<td>51.7±16</td>
<td>44.2±16</td>
</tr>
<tr>
<td>BMI</td>
<td>28.9±6</td>
<td>29.6±6</td>
<td>27.1±5</td>
</tr>
<tr>
<td>% Severe asthma</td>
<td>64</td>
<td>62</td>
<td>32</td>
</tr>
<tr>
<td>FEV1%</td>
<td>64.5±20</td>
<td>76.8±17</td>
<td>82.8±18</td>
</tr>
<tr>
<td>No. exacerbations</td>
<td>4±3</td>
<td>2±4</td>
<td>8±6</td>
</tr>
<tr>
<td>Dispana MRC</td>
<td>1.12±0.8</td>
<td>1.9±0.8</td>
<td>3±0.05</td>
</tr>
<tr>
<td>CRP</td>
<td>9.2±12</td>
<td>3±1.9</td>
<td>3±1.7</td>
</tr>
<tr>
<td>NO</td>
<td>24.2±8.5</td>
<td>26±10</td>
<td>15.9</td>
</tr>
<tr>
<td>SGRQ</td>
<td>60.8±16</td>
<td>55±15</td>
<td>37±11.4</td>
</tr>
<tr>
<td>Activity</td>
<td>7±8.22</td>
<td>65.3±22</td>
<td>36.2±20</td>
</tr>
<tr>
<td>Symptoms</td>
<td>61.8±18.9</td>
<td>56±12</td>
<td>43.8±11.8</td>
</tr>
<tr>
<td>Impact</td>
<td>54±16</td>
<td>49.2±18</td>
<td>35.4±11</td>
</tr>
</tbody>
</table>

Conclusions: The difference between the three groups was at the expense of that between PCG and WCG. PCG presented severe course of disease, worse lung function, hyperventilation, some degree of inflammation, increased number of exacerbations and poorer QOL. There was no relationship between worse asthma control and nutrition.

P2283
New GOLD 2011 guidelines: Is there an improvement?
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Background: The new revision of GOLD report 2011 has established new assessment of COPD based on the patient’s level of symptoms, spirometric classification and exacerbation history.

Aims: To compare and establish the differences between the classification of COPD patients using the guidelines of GOLD report 2010 and 2011.

Methods: A prospective study with a group of consecutive COPD patients from our outpatient clinic was performed. They were assessed according to GOLD 2011 by answering COPD Assessment Test (CAT) and Modified British Medical Research Council (mMRC) Questionnaire; by a spirometric evaluation in the same day and by the history of exacerbations of the previous year. This data was compared with the GOLD 2010 COPD assessment of the same patients.

Results: 45 patients were included (mean age 62.3 (±9); 73% male). The results are as below:

<table>
<thead>
<tr>
<th>2010 GOLD CAT ≥10 mMRC ≥2</th>
<th>2011 GOLD stage (%) grade group ≥2</th>
<th>2011 GOLD Risk Exacerbations 2010 COPD stage (%) grade group ≥2</th>
<th>assessment (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=8)</td>
<td>38</td>
<td>25</td>
<td>1 (n=8)</td>
</tr>
<tr>
<td>2 (n=12)</td>
<td>92</td>
<td>75</td>
<td>2 (n=12)</td>
</tr>
<tr>
<td>3 (n=12)</td>
<td>83</td>
<td>75</td>
<td>3 (n=12)</td>
</tr>
<tr>
<td>4 (n=13)</td>
<td>100</td>
<td>100</td>
<td>4 (n=13)</td>
</tr>
</tbody>
</table>

In GOLD 2010 classification 92% stage 4 patients had chronic respiratory failure; of those 62% were GOLD grade 3 in the 2011 spirometric assessment.

Conclusions: GOLD 2010 stage 4 patients were the group with greater exacerbation history. With exception for GOLD 2010 stage 1 patients, which were mainly assessed as group A in the 2011 GOLD classification, the remaining patients were mostly placed in the groups with greater symptomatic impact (B and D), which was better assessed by CAT. This shows the burden of disease in patient’s life and the need of a better treatment management, which is one of the goals of the 2011 GOLD assessment.

P2285
Impact of cognitive dysfunction and neuro-psychiatric symptoms over quality of life in stable COPD patients
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Background: Extrapulmonary manifestations in COPD contribute to its morbidity. Aims: To assess quality of life, cognitive functions and neuro-psychiatric symptoms in COPD patients and to analyze if quality of life is influenced by cognitive dysfunctions or neuro-psychiatric symptoms.

Methods: 200 stable COPD patients and 50 healthy volunteers [HV] were included. St George Respiratory Questionnaire (SGRQ) was used to assess quality of life. PGI Memory Scale Questionnaire (PGIQMS) was used to assess cognitive functions under 10 subsets: remote & recent memory, mental balance, attention and concentration, delayed recall, immediate recall, retention for similar & dissimilar pair, visual attention, and recognition. Symptom Check List 80 Questionnaire (SCL-80) was used to assess neuro-psychiatric symptoms under 9 subcales: depression, anxiety, interpersonal sensitivity, somatisation, phobic anxiety, obsessive compulsive neurosis, anger hostility, paranoid ideation, and additional symptoms.

Results: SGRQ scores in COPD patients for symptom, activity, impact subcategories were 28.7±4.8, 33.4±2.8 and 23.4±7.6, respectively. SGRQ scores in HV subjects for these subcategories were 2.9±4.9, 1.1±2.6 and 0.8±1.8, respectively. 105 COPD patients had PGIMSQ scores suggestive of cognitive impairment. 138 COPD patients had one or more neuro-psychiatric symptom. The SGRQ scores were correlated with remote memory, recognition, immediate & delayed recall, depression, verbal retention for dissimilar pair, retention for similar pair, visual retention.

Conclusions: Many COPD patients have cognitive dysfunctions and neuro-psychiatric symptoms that have significant impact over their quality of life.

P2286
The performance of COPD assessment test (CAT) in mustard lung patients
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Introduction: Mustard lung is a form of chronic obstructive pulmonary disease (COPD) due to sulfur mustard exposure. Health-related quality of life (QOL) is an important part of management in mustard lung patients. The properties of COPD assessment test (CAT), in COPD patients have been well documented. The aim of this study was to determine the role of CAT in evaluating the QOL in mustard lung patients.

Methods and materials: Eighty- six consecutively patients with stable COPD with all levels of severity were enrolled into this study. The QOL was evaluated by CAT and ST George Respiratory Questionnaires (SGRQ). Also standard spirometry, 6 minute walk test (6MWT), and pulse oxymetry were performed in patients. Severity of COPD was evaluated by GOLD (Global initiative for chronic Obstructive Lung Disease) and BODE (body mass index, obstruction, dyspnea, exercise) index.

Results: The mean age of the patients was 47.30 (±7.0) SD years. The mean CAT score was26.0±3.8. Thirty-five (43%) patients were in CAT stage 3. There was statistically significant correlation between CAT with SGRQ (p=0.001) and BODE index (p=0.001) respectively. Also statistically significant inverse correlation was found between CAT score with FEV1 (p=0.03) and 6MWT (p=0.001) respectively. There was statistically significant difference in mean CAT score between patients in GOLD stage ≥3 and those with < (p=0.02).

Conclusion: The findings of this study revealed that CAT questionnaire as a simple tool for assessment of QOL in mustard lung patients is valuable and can be used in clinical practice.

P2287
The relationship between COPD assessment test (CAT) scores and severity of airflow obstruction in stable COPD patients
Hassan Gholami Marali, Sadeq Sadehieh-ahari, Shahrzad Mohammadzadeh Lari1, Arad. Internal Medicine, Ardabil University of Medical Sciences, Ardabil, Islamic Republic of Iran

Background: COPD is a major cause of morbidity in smokers. The COPD as-
and community services resulting in a reduction length of hospital stay with low readmission rates.

P2290
Assessment of cognitive functions in stable COPD patients using PGI Memory Scale and to analyze for their correlation with patients' characteristics and BODE index
Prem Parkash Gupta 1, Hitesh Khurana 2, Sachin Bansal 1, Dipi Agarwal 1 1TB & Respiratory Medicine, PGIMS, University of Health Science, Rohtak, Haryana, India; 2Psychiatry, PGIMS, University of Health Science, Rohtak, Haryana, India; 3Physiology, PGIMS, University of Health Science, Rohtak, Haryana, India

Background: COPD is a multisystem disorder with significant extra-pulmonary manifestations.
Aims: To assess cognitive functions in stable COPD patients using PGI Memory Scale Questionnaire [PGIM-SQ] and to seek for any correlation with patients' characteristics and BODE index variables.
Methods: We included 200 stable COPD patients and 50 healthy volunteers (HV).
Their baseline characteristics and BODE index variables were assessed. PGIM-SQ was used to assess cognitive functions under 10 subsets (shown in Table 1).
Results: The age of subjects in COPD Group was 61.3 ± 7.4 year, and of those in HV group was 59.76 ± 7.21 year. 105 COPD patients (52.5%) were having PGIM-SQ scores beyond ± 3 SD of HV scores. PGIM-SQ scores are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>PGIM-SQ Subsets</th>
<th>COPD group</th>
<th>HV group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote memory [6]</td>
<td>3.56 ± 1.12</td>
<td>4.64 ± 0.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recent memory [5]</td>
<td>3.96 ± 0.49</td>
<td>4.30 ± 0.46</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mental balance [9]</td>
<td>6.48 ± 1.56</td>
<td>8.08 ± 0.88</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Attention and concentration [15]</td>
<td>9.68 ± 3.07</td>
<td>13.08 ± 0.72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Delayed recall [10]</td>
<td>6.06 ± 1.35</td>
<td>7.40 ± 0.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Immediate recall [12]</td>
<td>7.24 ± 1.09</td>
<td>8.54 ± 0.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Verbal retention for similar Pair [5]</td>
<td>3.68 ± 0.74</td>
<td>4.16 ± 0.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Verbal retention for dissimilar Pair [15]</td>
<td>9.52 ± 1.56</td>
<td>7.22 ± 0.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Visual Retention [13]</td>
<td>6.04 ± 1.44</td>
<td>7.62 ± 0.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recognition [10]</td>
<td>5.48 ± 1.13</td>
<td>6.30 ± 0.46</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Conclusion: We observed a global decline of cognitive functions in COPD group and observed their significant correlations with age, duration of illness and BODE index variables.

P2291
An analysis for neuro-psychiatric symptoms in stable COPD patients and to assess for their correlation with patients' characteristics and BODE index
Prem Parkash Gupta 1, Hitesh Khurana 2, Sachin Bansal 1, Dipi Agarwal 1 1TB & Respiratory Medicine, PGIMS, University of Health Science, Rohtak, Haryana, India; 2Psychiatry, PGIMS, University of Health Science, Rohtak, Haryana, India; 3Physiology, PGIMS, University of Health Science, Rohtak, Haryana, India

Background: COPD is known to have significant extra-pulmonary involvement that contributes to COPD morbidity.
Aims: To assess neuro-psychiatric symptoms in stable COPD patients using Symptom Check List 80 Questionnaire [SCL-80] and to seek for any correlation between these symptoms and COPD severity.
Methods: We included 200 stable COPD patients and 50 healthy volunteers (HV).
The COPD subjects had a smoking history > 20 pack years. SCL-80 was used to assess neuro-psychiatric symptoms under 9 subscales (table 1).
Results: The age of subjects in HV group was 59.76 ± 7.21 year, and of those in COPD Group was 61.37 ± 7.4 year. 138 COPD patients (69%) had neuro-psychiatric symptom(s) detected using SCL-80. A total of 78 (39%) patients had a global decline of neuro-psychiatric symptoms in stable COPD patients with significant correlation with patients' characteristics and BODE index variables.

Table 1

<table>
<thead>
<tr>
<th>SCL-80 scores (n=120)</th>
<th>COPD group</th>
<th>HV group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatisation (38)</td>
<td>13.04 ± 7.83</td>
<td>2.46 ± 1.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depression (52)</td>
<td>13.23 ± 8.16</td>
<td>2.46 ± 1.43</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anxiety (46)</td>
<td>9.64 ± 3.71</td>
<td>26.0 ± 4.44</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Phobic anxiety (28)</td>
<td>6.14 ± 0.98</td>
<td>0.08 ± 0.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Obsessive compulsive (40)</td>
<td>10.18 ± 0.69</td>
<td>0.08 ± 0.27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hostility (24)</td>
<td>1.01 ± 0.70</td>
<td>0.02 ± 0.49</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Conclusion: SCL-80 scores (n=120) of COPD patients and 50 healthy subjects (HV) were compared to assess the significant cognitive differences and neuropsychiatric symptoms in stable COPD patients with significant correlation with patients' characteristics and BODE index variables.
scores had positive correlations with SCL-80 scores. FEV1 and distance walked in six minute had inverse correlations with SCL-80 scores.

Conclusions: 60% stable COPD patients had neuro-psychiatric symptoms detected using SCL-80, and the SCL-80 scores had significant correlations with age, smoking pack years, duration of illness and BODE index variables.

P2292
Cross-sectional analysis of the Belgian Severe Asthma Registry
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The Belgian severe asthma registry (BSAR) is a secured web-based registry encompassing demographic, clinical, functional and inflammatory data of severe adult asthmatics as defined by the ATS, raising awareness on severe asthma, studying its natural history, identifying phenotypes, and offering tools to optimize care.

Methods: The cross-sectional analyses of the BSAR included 229 refractory asthmatics from 7 Belgian centers, followed up by respiratory physicians for at least one year prior to inclusion.

Results: Severe asthma was more frequent in women (56%), was associated with atopy (69%) and started early (71%) before age 40; 10% were current smokers and 32% ex-smokers. In addition to high doses of ICS+LABA, 48% of patients received LTRA, 21% anti-IgE and 21% oral corticosteroids. Despite impaired flow rates (mean FEV1<70% pred; PEFV<63%), KCO was well preserved (98% pred).

Eosinophilic asthma (sputum Eos<3%) was the predominant phenotype (60%, n=45) while neutrophilic (sputum Neu≥76%) and paucigranulocytic asthma were 22% and 13% respectively. The median FEV1 was 222pp (4250/25ppb) and the fraction of patients with FEV1<50ppb was 13% (n=155). Comorbidities included chronic rhinosinusitis (35%), nasal polyposis (21%), oesophageal reflux (36%), obesity (34%). Sputum neutrophilic (sputum Neu≥76%) and eosinophilic (sputum Eos≥3%) asthma was impaired (85% had ACT<20 and 87% had AQLQ<0.75) and average AQLQ was 4.39.

Conclusion: In the BSAR, severe asthmatics are characterized by airflow limitation, frequent comorbidities, poor asthma control and quality of life. Paucigranulocytic asthma represents a rare phenotype while a high proportion of severe asthmatics have uncontrolled eosinophilic airway inflammation.

P2293
Impact of short term supervised breathing exercises added to regular medications over nocturnal symptoms, requirement of rescue medication and spirometric variables in asthma patients
Dipti Agarwal1, Sushma Sood 1, Prem Parkash Gupta 2. 1. Dept of Physiology, PGIMS, University of Health Sciences, Rohtak, Haryana, India; 2. Dept of TB & Respiratory Medicine, PGIMS, University of Health Sciences, Rohtak, Haryana, India

Background: Breathing exercises have been described to be useful in asthma management by a few workers.

Objectives: To assess efficacy of breathing exercises (Pranayamas) in asthma patients on optimal medications using spirometric indices, nocturnal symptoms parameters and requirement of rescue medication.

Methods: 60 stable asthma patients (34 females), on optimal regular medications as per GINA guidelines for ≥ 3 months, were enrolled. All subjects continued their respective medications during study period and, in addition, performed seven breathing exercises (BEs) for a period of 3 months initially under full and thereafter, after intermittent supervision at Yoga centre in our Institute. Spirometry, nocturnal symptoms and requirement of rescue medicine (salbutamol, given via an MDI) were assessed before and after study period.

Results: The mean age of asthma patients was 25.45±5.41 years. After study period, mean FEV1 increased from 2.92+0.338 L to 2.74±0.343 L and mean PEF increased from 238.82±51.12 L/min to 336.23±51.47 L/min; all increases were statistically significant. The mean days with nocturnal symptoms/week decreased significantly from 1.417±0.619 to 0.067±0.362. The requirement of rescue medication decreased significantly from 6.23±2.95 to 0.90±1.25 puffs/week.

Conclusions: Breathing exercises, when added to regular medications, observed to be beneficial in stable asthma patients leading to significant improvements in spirometric parameters and significant reduction in nocturnal symptoms as well as requirement of rescue medicine.

P2294
The German severe asthma register
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Patients with severe persistent asthma represent the highest unmet medical need among the asthmatic population today.

To improve the understanding of more severe disease progresses in pediatric and adult asthma the German Asthma Net (GANE v.) launched a National Severe Asthma Register in December 2011. Enrolled patients undergo detailed clinical and physiologic evaluations, including patients' medical history, allergy, lung function, lung inflammation, blood testing as well as past and concomitant medication and comorbidities. As of February 20, 2012 six participating centers joined the program and recruited 93 subjects (mean age ± SEM 49±1.1 years, 63% female. FEV1 2.0±0.1 L (65 ±5±1.2%), 97% uncontrolled or partly controlled asthma according to GINA, 54% allergic asthma, 46% on oral corticosteroids, 39% on omaluizumab, eNO 51±6 ppb, 3±4±6±4 exacerbations during the last 12 months). Recruitment of a larger number of subjects with severe asthma, including children, is ongoing and will allow further characterization of clinical, physiologic, cellular and biochemical factors related to severe disease in a longitudinal assessment to identify parameters that improve diagnosis, phenotyping, management and treatment of this heterogeneous condition. In addition, the German Severe Asthma Register may help to confirm and extend results obtained in similar databases, including U-BIOPRED and SARPI.

P2295
Factors affecting quality of life in children, adolescents and adults with primary ciliary dyskinesia
Neil Botting1, Andrea PannuGalvin2, Fiona Copeland3, Jane Lucas1. 1. PCD Group, Faculty of Medicine, University of Southampton, United Kingdom; 2. Paediatrics and Child Health, University of Cork, Ireland; 3. PCD Family Support Group, Milton Keynes, United Kingdom

Background and objective: Primary Ciliary Dyskinesia (PCD) is a rare autosomal recessive disorder associated with chronic pulmonary disease, rhinosinusitis, sinusitis, otitis media and often infertility. For example in adolescents, ‘embarrassment from having a runny nose’ had the highest mean score (4.11), whilst ‘physical problems from symptoms of PCD’ was less of an issue (2.56). Lack of understanding about PCD by others was highly relevant for all age groups, but particularly children, whose classmates did not understand (4.43). PCD was reported to have little impact on social life in all ages.

Conclusions: Patients of all age groups reported emotional consequences and embarrassment from PCD. Adults reported physical symptoms to be more relevant than in children or adolescents. The prototype questionnaire with the most relevant items is nearing completion. Cross-sectional and longitudinal validation will be conducted in UK, Ireland and USA.

P2296
Determinants of asthma control and quality of life in stable asthma
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Asthma control and quality of life are poorly associated with traditional asthma biomarkers. In the present study we evaluated two new cough provocation tests in this respect.

Asthma Control Questionnaire and Leicester Cough Questionnaire were completed by thirty-six stable asthmatics. Cough provocation tests with hypertonic saline (Koskela HO et al Clin Exp Allergy. 2008 Jul;38(7):1100-7) and isotonic hypopnoea of dry air were performed (Purokivi M, et al. Cough. 2011;7(1):8), as well as spirometry, ambulatory peak expiratory flow (PEF) monitoring, and exhaled nitric oxide measurement (eNO).

Leicester Cough Questionnaire score correlated closely with cough responsiveness to hypertonic saline and isotonic hypopnoea of dry air (Rs = 0.66, p<0.001
and Rs = 0.49, p<0.002, respectively). Asthma Control Questionnaire also correlated with the cough responsiveness to these challenges (Rs = 0.52, p<0.001 and Rs 0.43, p<0.08, respectively). FEV1 (%predicted), diurnal PEF variation and ACQ did not correlate with cough-related quality of life but showed some association with asthma control. There was a significant correlation between Leicester Cough Questionnaire and Asthma Control Questionnaire (Rs = 0.54, p<0.001.

Asthma control and cough-related quality of life are more closely associated with cough sensitivity to the investigated cough provocation tests than to eNO and traditional indices of bronchial obstruction. Cough is a major contributor to poor asthma control.

P2297
The inhaled corticosteroids questionnaire shortened version (ICQ-S): A brief patient-rated scale for monitoring inhaled corticosteroid side effects in clinical practice
Juliet Foster1, Siebrit Schokker2, Robbert Sanderman3, Dirkje Postma4,5

Methods: At days 0 and 14, adults with doctor-diagnosed asthma and prescribed an ICS inhaler, completed the ICQ, ICQ-S, 6-minute ACQ and AQOL(y). The intraclass correlation coefficient (ICC) between day 0 and 14 ICQ-S assessed test-re-test reliability. Cronbach’s alpha (coefficient) and item-total correlations tested the internal consistency of ICQ-S. Associations (Spearman’s rho) between the ICQ-S total score and relative associations of the ICQ and ICQ-S with the AQOL(y) assessed criterion validity. Patients reported duration and perceived difficulty (1=very difficult, 5=very easy) of ICQ-S completion.

Results: 62 patients (female 63%, mean age 54 (SD 13) yrs., mean ACQ 0.79 (SD 0.83), median ICS dose 1000 μg (IQR 500,1000)) were eligible. The ICC between day 0 and 14 ICQ-S scores was 0.90, u coefficient was 0.90 and all item-total correlations were rho>0.2. ICQ and ICQ-S were strongly associated (rho=0.80) and 81% patients completed the ICQ-S within 5 minutes and 97% reported that it was not difficult to fill in.

Conclusion: The ICQ-S is a patient-friendly tool which retains the reliability and validity of the original ICQ scale but is brief enough for monitoring/managing inhaled steroid side effects in clinical practice.

P2298
A study of neuromuscular dysfunction in patients with chronic obstructive pulmonary disease
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Methods: This was a prospective study, which included 20 inpatients with severe chronic obstructive pulmonary disease (COPD) and 15 healthy subjects as a control group. All patients subjected to clinical assessment. All subjects were subjected to respiratory functions tests, blood gases, X-ray chest and computed tomography. The levels of CD4 + CD25high peripheral blood was measured using fluorescence-activated cell sorting.

Results: 20 patients (female 70%, mean age 70 (SD 13) yrs., mean FEV1=80,7 (SD 11)%) and 15 healthy (30,0 (28,0:35,0) yrs.) were eligible. The ICC between post-bronchodilator FEV1 and post-bronchodilator FEV1/FVC was 0.90, Rs 0.43, p=0.008, respectively. FEV1 (%predicted), diurnal PEF variation and ACQ did not correlate with cough-related quality of life but showed some association with asthma control. There was a significant correlation between Leicester Cough Questionnaire and Asthma Control Questionnaire (Rs = 0.54, p<0.001).

Asthma control and cough-related quality of life are more closely associated with cough sensitivity to the investigated cough provocation tests than to eNO and traditional indices of bronchial obstruction. Cough is a major contributor to poor asthma control.

P2299
The relationship between radiologic findings and lung function impairment in chronic obstructive pulmonary disease
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Objectives: To evaluate the presence of peripheral neuropathy and myopathy in chronic obstructive pulmonary disease (COPD) patients. Replicated emerging pulmonary symptoms: cough, breathlessness, and fatigue, may be associated with bronchiectasis and emphysema. The patients with more severe airflow obstruction (group II) during remission had more severe respiratory function status during exacerbation comparing to group I patients.

Conclusions: Our study showed that relationship between radiologic findings and lung function impairment in COPD is variegated. Determination in DLCO values could be supported emerging pulmonary symptoms: cough, breathlessness, and fatigue, may be associated with bronchiectasis and emphysema. The patients with more severe airflow obstruction (group II) during remission had more severe respiratory function status during exacerbation comparing to group I patients.

255. Asthma and COPD: understanding through mechanisms

P2300
T-reg cells levels in smoking and non-smoking patients with asthma
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Backgroumd: Tobacco smoking is associated with severity of asthma, response to basis therapy and control achievement. Cigarette smoke reduces the pool of T- regulatory cells in healthy smokers but the role of T-regs in the development of allergic diseases still unclear.

Objective: To assess the level of CD4 + CD25high T-reg in healthy and asthmatic with different status of smoking.

Materials and methods: Were enrolled 55 patients with asthma: mild asthma (n=14, (35.2 (32.0:40.0) years), mean FEV1=100,9 (94,3:111,5%), moderate asthma (n=20), (35,4 (30,6:50,6) years), FEV1=80,24 (72,4:89,5%), severe asthma (n=21), (45,0 (41,0:49,0) years), FEV1=66,6 (48,9:70,7%), and 17 healthy (30,0 (28,0:35,0) years), FEV1=104,0 (98,0:111,0%). Peripheral blood mononuclear cells were isolated in Ficoll density. To study the phenotypic characteristics of regulatory T cells was assessed variation of CD markers (CD4 + , CD25 + ) by flow cytometry (FACAFCalibur Becton Dickinson, USA) using appropriate monoclonal antibodies. Results and discussion: The levels of CD4 + CD25high peripheral blood was lower in smokers (0.84 (0.59:2.09%) compared with non-smokers (2.07 (1.20:2.92%) (p<0.05). In current smokers patients and patients with history of smoking the levels of CD4 + CD25high peripheral blood were lower (0.62 (0.22:0.94)) compared with non-smokers (2.20 (0.73:3.47) (p<0.05). A negative correlation between pack-years and the level of CD4 + CD25high (r = -0.51; p<0.05) in healthy volunteers was shown.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group B</th>
<th>Group C</th>
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<td>94.00±7.44</td>
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<td>58.1±4.6</td>
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<td>PaO2</td>
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<td>PaCO2</td>
<td>56±90</td>
<td>48±11</td>
<td>37±50</td>
</tr>
</tbody>
</table>

*Significant at p<0.01
Conclusion: Cigarette smoke may have an independent influence on asthma course not only as trigger (irritant) but also as factor that leads to reducing the population of CD4+ CD25high Treg and inadequate suppression of Th2-response.

P2301
Peripheral Thelper1/Thelper2/Thelper17/regulatory T cell imbalance in asthmatic pregnancy
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Asthma and pregnancy show bilateral clinical interactions with mostly unknown mechanisms. Healthy pregnancy is characterized by a sensitive balance of Th1/Th2/Th17/regulatory T cell and compromised immune tolerance characterizing asthmatic pregnancy. The aim of this study was to describe the prevalence of these cell subtypes in asthmatic pregnancy.

The prevalence of Th1, Th2, Th17 and Treg lymphocytes was identified by cell surface and intracellular marker staining in 24 healthy non-pregnant (HNP), 23 healthy pregnant (HP), 15 asthmatic non-pregnant (ANP) and 15 asthmatic pregnant (AP) women using flow cytometry. HP and ANP were characterized by increased Th2/Th1 ratio compared to HNP, but no further increase was observed in AP. Healthy pregnancy increased Treg cell level by 1.03% compared with HNP data (4.64% vs. 2.98%; p<0.05), and this pregnancy-induced elevation was absent in AP women (2.52% vs. HP; p<0.05). Th17 cell prevalence was similar in the HP and HNP groups (2.78% vs. 3.17%; p>0.05). Asthma increased Th17 prevalence in non-pregnant patients (3.81% vs. HNP; p<0.05), and this asthma specific increase of Th17 cell prevalence was also observed in AP patients (AP vs. HP: 3.44% vs. 2.78%; p<0.05). As a result, Th1/Th7/Treg ratio was decreased in HP, but not in AP women, compared with HNP data.

Peripheral Thelper1/Thelper2/Thelper17/regulatory T cell imbalance may play a role in the interrelationship and compromised immune tolerance characterizing asthmatic pregnancy.

P2302
Activin-A induces human regulatory T cells that control allergic asthma
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Activin-A is a cytokine involved in essential biological processes. Our previous studies have uncovered activin-A as a controller of experimental asthma through the induction of mouse regulatory T cells (Tregs). Here we studied the role of activin-A in the induction of human Tregs in patients with allergic asthma.

Our data reveal that activin-A greatly inhibits human T cell proliferation and Th2 cytokine release. Activin-A treated T cells remain hyporesponsive after allergen restimulation and do not express effector cytokines. Still, they express significantly increased amounts of immunosuppressive IL-10. Notably, activin-A-treated T cells restimulation and do not express effector cytokines. Activin-A-treated T cells remain hyporesponsive after allergen restimulation and do not express effector cytokines. Activin-A-treated T cells also restrain Th2 responses in the bronchoalveolar lavage (BAL) of severe asthmatics. Using a humanized model of asthma, we show that, co-transfer of act-A+Tregs with human T effectors confers protection against asthma in vivo, as shown by greatly decreased airway hyperresponsiveness, BAL, lung inflammation and Th2 responses in the lungs and draining lymph nodes. Our data reveal that activin-A generates IL-10-producing Tregs that suppress human allergen-driven responses and protect against asthma. Our findings may facilitate the use of act-A+Tregs in adoptive-transfer therapies as re-establishing tolerance in asthma.

P2303
4-1BBL mediated balance of Th17/Treg in patients with allergic asthma
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Peripheral blood CD4+ T cells were stimulated with a clinically-appropriate allergen extract. Neutrophil functions were measured with flow cytometry. The s4-1BBL concentrations of patients with asthma (202.47±60.68 μg/L) were decreased than controls (298.29±46.32 μg/L; p<0.01). The m4-1BBL on monocytes of patients with asthma (2.99±1.55%) was decreased than the controls (9.06±6.79%; p<0.01). The supernatant concentrations of TGF-β (655.81±476.26 ng/mL) and IL-17 (5201±4143.74 pg/mL) in PBMCs stimulated with allergen extract (410.50±363.03 ng/L, IL-17: 8377±3839.98 ng/mL, both p<0.05). There was a lower proportion of Th17 cells (1.298±0.53% vs 1.536±1.01%) and a higher proportion of Treg cells (3.45±1.03% vs 2.76±0.97%) in the 4-1BBL mAb group than isotype control, but no difference between the two groups (p>0.05).

Conclusions: Both s4-1BBL and m4-1BBL decreased in peripheral blood of patients with allergic asthma. In vitro agonistic 4-1BB antibody stimulation enhanced TGF-β but inhibited IL-17, which might be due to the ability of s4-1BBL to decrease TGF-β. The balance between Th17/Treg may restore Th17/Treg balance in allergic asthma more likely by changing the function of Th17 and Treg cells.

P2304
Efficacy of basis therapy and level of immunoregulatory T-cells (T-regs) in COPD
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Conclusions: COPD is heterogeneous disease with variable clinical and radiographic signs, different response to therapy and rate of decline in lung function and survival of patients. The levels of T-cells could influence on the efficiency of the basis therapy of COPD.

Aim and objectives: Compare the data of COPD clinical course dynamics during basic therapy and levels of inducible (CD4+FOXP3+) T-regs.

Methods: We included 60 patients with COPD stages II-IV, mean age was 57.8±10.9 years, m/f=50/10, mean duration of disease was 10.6±3.5 years. The observation period was 24 weeks after administration of appropriate basis therapy (GOLD recommendations). At visits were performed spirometry, index BODE, SGRQ. Peripheral blood mononuclear cells were isolated from heparinized blood by Ficoll density gradient (1.077 g/ml). The circulating percentage of CD4+FOXP3+ T-regs in peripheral blood was estimated by the flow cytometry analysis (FACSCalibur Becton Dickinson, USA) using appropriate monoclonal antibodies.

Results: Persons with the levels of CD4+FOXP3+ T-regs cells less than 7% in peripheral blood, were characterized by significant reductions in SGRQ-scores from 53,29±36.3 points at visit 1 to 48,24±4,13 points at visit 2 (p<0.05); stable increase in FEV1 from 37.7±3.08% (visit 1) to 46.63±3.39% (visit 2) (p<0.05); decreased BODE index from 410.1±37 points (visit 1) to 346.0±43 points (visit 2) (p<0.05). COPD patients with the level of CD4+FoxP3+ more then 7% didn’t have the positive dynamics of clinical and functional parameters as a result of a 24-week treatment of patients. The levels of T-regs could influence on the efficiency of the basis therapy of COPD.

P2305
Peripheral blood neutrophil activity during D. pteronyssinus induced late-phase airway inflammation in asthma and rhinitis patients
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Conclusions: High level of CD4+FoxP3+ Tregs (>7%) is associated with impaired response to basis therapy COPD.

Background: Recent investigations suggest that neutrophils may play an important role in the late-phase allergen-induced inflammation in allergic airway diseases.

Aim: To evaluate neutrophil chemotaxis, phagocytosis, and reactive oxygen species (ROS) production in patients with allergic asthma and rhinitis challenged with inhalated D. pteronyssinus.

Methods: Twenty eight patients with allergic asthma and 27 with rhinitis, all sensitized to D. pteronyssinus, as well as 10 healthy subjects underwent challenge with D. pteronyssinus. Neutrophils from peripheral blood were isolated 24 h before as well as 7 h and 24 h after challenge. For chemotaxis analysis neutrophils were stimulated with interleukin-8, and for ROS analysis as well as for phagocytosis were stained with S. aureus bacteria. Neutrophil functions were analyzed flow cytometrically.

415s
P2306
Upregulation of myeloid derived suppressor cells (MDSCs) in chronic obstructive pulmonary disease and its relationship with disease severity
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MDSCs have received growing interest as suppressors of immune responses in cancer, induced in the attempt to escape immune surveillance. MDSCs have been recently implicated in immune modulation in chronic inflammatory diseases, particularly autoimmune. Since we proposed an autoimmune component in COPD, we examined the induction of MDSCs in peripheral blood of smokers with COPD with or without lung cancer. In particular, we evaluated the α chain of the IL-4 receptor (IL-4Rα, which has been proposed as a marker for MDSCs) in patients with COPD (n=102, 8 with concomitant cancer) compared to subjects with a similar smoking history who did not develop COPD (n=8) and non-smokers (n=10). The expression of IL-4Rα was increased in monocytes from smokers with COPD (P<0.01) and was higher in patients with COPD and concomitant cancer (10±1.6%) compared to non-smokers (9.4±1%; P<0.05 for both). This increase was particularly evident in COPD patients with concomitant cancer (23±3%) but was also present in those without cancer (16±1%). A similar IL-4Rα pattern was observed in the granulocytic fraction of blood leukocytes (8±1 vs 3±2 vs 4±2.2%). Of note, IL-4Rα expression was not linked to smoking status or cumulative history, but was correlated with the degree of airflow limitation (P<0.01 and P<0.03, respectively). MMP2 and 9 mRNA were upregulated in BAL cells (P<0.001 and P<0.03, respectively). MMP9 protein was elevated in BALF (P<0.001). Serum concentrations of TIMP4 paralleled increased expression of MMP2 and 9 mRNA in BAL cells (P<0.005 and P<0.007, respectively). The number of TIMP1 transcripts correlated with the number of months free of exacerbation(s) during 2-years follow-up after the BAL sampling (p=0.03).

In conclusion, distinct expression profiles of MMPs/TIMPs were observed at systemic and local level in our COPD patients. These pilot data will be subject to further extension and verification, including subanalyses according to the GOLD stage.

Grant support: IGAUPU LF_2012_07, CZ.1.05/2.1.00/01.0030.
tively) and 20 man from control group. Lymphocytes were isolated by two-color labeled monoclonal antibodies flow cytometry to examine the quantities and percentage of CD4+CD25+ T cell, CD4+CD25++ (CD4(+)Treg), CD3+CD19- T cell, CD3+CD4+ T cell, CD3+CD8+ T cell, respectively. Enzyme immunoassay was used to detect the expression of interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), procollagen (PCT) and C-reactive protein (CRP). Mann-Whitney test was used for comparison between data before and after treatment and control group.

Results: In patients with mild and moderate AECOPD take place significant decreasing of Treg cells (CD4+CD25++) from 3.3+0.8% in control to 1.1+0.17% and 1.3+0.12%, respectively (p < 0.01). Interestingly that percentage of Treg didn’t change in dynamics of conventional therapy. Reliable increase of TNF-α and decrease of PCT take place in both groups (p < 0.01). Nevertheless CRP and IL-10 levels of patients with COPD don’t differ from the same values of control group.

Conclusion: The decrease of Treg response and the lost balance between inflammatory/antiinflammatory cytokines, suggest a lack of regulation of the systemic inflammatory response that may contribute to pathogenesis in AECOPD of mild and moderate stage.

P2311

The declined CD4+ CD25+ Treg cells in patients with moderate to severe asthma associated with over-expressed Th2 response

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Background: Recent studies have showed that Th2 cells can induce the apoptosis of CD4+CD25+ Treg cells or resist the immunosuppressive effect of Treg cells. We hypothesize that an imbalance of Th2/Treg is presented in patients with allergic asthma.

Methods: Twenty-two patients with mild asthma, 17 patients with moderate to severe asthma and 20 healthy donors were enrolled. All patients were allergic to house dust mites. The proportions of peripheral blood CD4+CD25+ Treg cells and Th2 cells were determined by flow cytometry. The concentration of IL-10, TGF-β and IL-4 in plasma was determined by ELISA. The expression of Foxp3 and GATA-3 mRNA in PBMCs from asthmatic patients and healthy donors was detected by RT-PCR.

Results: Compared with healthy donors and patients with mild asthma, the frequency of CD4+CD25+ Treg cells and plasma IL-10 levels were decreased in patients with moderate to severe asthma. There was no difference of Foxp3 mRNA expression among three groups. However, the frequency of Th2 cells, IL-4 levels and expression of GATA-3 mRNA in patients with moderate to severe asthma was significantly lower than in the control group. The ratio of Th2/Treg and their cytokines was increased in allergic asthma, especially for moderate to severe asthma. The ratio of GATA-3/Foxp3 mRNA was increased in allergic asthma. Patients with moderate to severe asthma, the frequency of peripheral blood Treg cells was negatively correlated to the percentage of Th2 cells and IL-4 levels.

Conclusions: The decline of Treg cells in patients with moderate to severe asthma may play an important role in progress of the disease.

P2312

Peripheral blood Th17 cells and serum IL-17 levels in patients with D. pteronyssinus-induced late-phase asthmatic response

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Background: Biphasic cellular immune reaction which follows inhalation of allergen is the specific feature of allergic inflammation. Therefore, Th17 cells and IL-17 may have a role in the development of the late-phase asthmatic response in patients with allergic asthma.

Objectives: To evaluate the percentage of Th17 cells in peripheral blood (PB) and serum IL-17 levels in patients with D. pteronyssinus-induced late-phase asthmatic response.

Methods: We studied 28 patients with allergic asthma who developed early-phase asthmatic response (EAR) (n=16) and late-phase asthmatic response (LAR) (n=12) after bronchial challenge with D. pteronyssinus. The control group included 10 healthy subjects (HS). PB collection was performed 24 h before as well as 7 and 24 h after challenge. The percentage of Th17 cells was analyzed by FACS. Serum IL-17 levels were determined by ELISA.

Results: See Table 1.

Conclusions: D. pteronyssinus-induced late-phase asthmatic response in patients with allergic asthma is associated with increased percentage of Th17 cells in PB and elevated serum IL-17 levels.

P2313

ActiVin-A expression is increased in severe asthma and is involved in tissue angiogenesis

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Background: Our recent studies showed that ActiVin-A (Act-A), a cytokine belonging to the TGF-β superfamily, suppresses mouse allergic responses; however its effects on human asthma remain unknown.

Objectives: To determine ActiVin-A expression in healthy controls (CTRL) and asthmatics, identify its cellular sources and signaling mediators, and examine correlations with disease severity and airway remodeling.

Methods: Serum samples were obtained from 46 mild-to-moderate asthmatics (MMA), 27 severe asthmatics (SA) and 41 CTRL subjects (18 CTRL, 18 MMA, 19 SA) underwent bronchial challenge with endobronchial biopsy and BALF collection. Act-A levels in the serum were examined. Expression of Act-A and its principal signaling mediator ALK4 in the bronchial tissue were assessed by conventional microscopy, basement membrane thickness, goblet cell hyperplasia and angiogenesis (vessels/mm2) were also determined.

Results: Act-A levels were significantly increased in MMA and in MMA and SA in BALF. Serum Act-A was further increased during asthma exacerbation. Bronchial tissue Act-A expression was significantly increased in asthmatics, especially in the subepithelium in SA, while ALK4 expression decreased with disease severity. Act-A was mainly expressed by mast cells, neutrophils, macrophages and smooth muscle cells. Act-A and ALK4 were also localized in endobronchial cells, particularly in SA. Subepithelial Act-A expression correlated with angiogenesis and disease severity.

Conclusions: Our data suggest that Act-A plays a crucial role in asthma inflammation and participates in the regulation of angiogenesis in SA. Ongoing in vitro studies will further elucidate its specific role.

P2314

Relevance of measurement of serum periostin for diagnosing bronchial asthma and estimating its lung function abnormalities

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Bronchial asthma is diagnosed by combination of presence of characteristic symptoms and measurement of reversibility of lung function abnormalities. Non-invasive markers such as levels of exhaled nitric oxide (FeNO) and sputum eosinophilia have potential usefulness for diagnosis of bronchial asthma and determination of optimal treatment; however, these biomarkers contain several problems in specificity in diseases. Periostin, an extracellular matrix protein downstream of IL-4/IL-13 signals, has emerged as a novel biomarker for bronchial asthma. Particularly, it has been recently shown that efficacy of anti-IL-13 antibody can be predicted using serum periostin levels in steroid-resistant asthma patients. However, it still remains undetermined how measurement of serum periostin level is relevant for diagnosing bronchial asthma. The study group comprised 37 patients with asthma and 30 healthy subjects. In both groups, serum concentrations of SCCA1, SCCA2, periostin (SS18A SS17B) were measured. In asthmatic patients, serum IgE concentrations, eosinophil counts, and exhaled NO levels were also measured. Serum concentrations of periostin (SS18A SS17B) was significantly higher in the asthmatic patients than in the control subjects. Serum concentrations of both types of periostin strongly correlated with eosinophil counts and exhaled NO levels. In contrast, serum SCCA concentrations did not differ between the control subjects and asthmatic patients or significantly correlate with any variable studied. Our results suggested that serum periostin concentrations may be a significant diagnostic marker of bronchial asthma that correlates with eosinophil counts.
Methods: BALB/c mice were randomly assigned to three groups (asthma group, 4-1BB group and control group). Mice in the asthma group were sensitized and challenged with OVA. Agonistic 4-1BB mAb was administered in the 4-1BB group. Mice in control group were treated with PBS.

Results: (1) The serum IgE concentration [23.350 (65.945-42.635) ng/mL, vs. 99.292 (182.185-293.931) ng/mL, P<0.01], total number of cells [17.35±3.23×10^6 vs. 6.44±1.90×10^6, P<0.05] and eosinophils [9.79±3.38×10^3 vs. 9.91±0.37×10^3, P<0.05] in bronchoalveolar lavage fluid (BALF) and airway inflammation in the 4-1BB group were decreased compared with the asthma group. (2) Agonistic 4-1BB mAb treatment decreased IL-17 [225.747±15.000] ng/mL vs. (6.44×10^3) ng/mL, P<0.05] in bronchial airway in mice. Agonistic 4-1BB mAb inhibited the expression of Th17 cells (3.18±0.23)% vs. (20.32±2.62)% (P<0.01) and RORγt mRNA [10.76±3.28×10^-5] vs. (30.83±5.68×10^-5), (P<0.01) in lung.

Conclusions: Agonistic 4-1BB mAb treatment partially alleviated airway inflammation by restoring the function of Treg cells and inhibiting the proliferation and function of Th17 cells.

P2316
IL-25 secreted from epithelial cells has the potential to promote airway remodeling in asthma

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Introduction: Interleukin (IL)-25 plays a pivotal role in the pathogenesis of asthma, not only in airway inflammation, but also in airway remodeling.

Objective: To explore the function and significance of IL-25 in the pathogenesis of eosinophilic asthma (EA) and non-eosinophilic asthma (NEA).

Methods: Patients were diagnosed as asthma patients: 26 with EA, 24 with NEA. Serum and induced sputum from all the participants were collected and the level of IL-25 in the samples was determined by enzyme-linked immunosorbent assay (ELISA). Expression of IL-25 in bronchial epithelium and basement membrane thickness were quantified by immunohistochemistry.

Results: Compared with healthy control subjects, the lung function was impaired in patients with EA and NEA. ELISA results showed that the levels of IL-25 in the serum and induced sputum of asthmatic patients were significantly higher than healthy subjects (p<0.05). But there were no statistic differences between EA and NEA patients (p>0.05). The immunohistochemistry results indicated that high expression of IL-25 and thickened basement membrane were observed in asthmatic bronchial epithelium. Correlation analysis showed that the level of IL-25 in serum and induced sputum was positively correlated with the average thickness of basement membrane in asthmatic patients.

Conclusion: IL-25 secreted from epithelial cells has the potential to promote airway remodeling in asthma.

P2317
Inhibition of collagen receptors: α1β1 and α1β2 integrins decreases eosinophil transmigration, but has no impact on peripheral blood mononuclear cell movement through human microvascular endothelial cell monolayer

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Introduction: Recruitment of the inflammatory cells to the airways is mediated by adhesive molecules. Among integrins, the most important in cell trafficking are those containing α1 and β1 subunits. We hypothesized that also collagen integrin receptors: α1β1 and α1β2, are involved in asthma pathogenesis. We recently described increased expression of both: α1 and β1 subunits on blood eosinophils and α2 on CD4 T lymphocytes in asthma.

Aim: The aim of the study was to analyse effect of α1β1 and α1β2 integrin inhibition on transmigration of eosinophils and peripheral blood mononuclear cells (PBMC) through human microvascular endothelial cell lung monolayer in 12 healthy controls. We analysed also CD4/CD8 ratio in PBMC population before and after transmigration assay.

Methods: PBMC were separated by gradient centrifugation; eosinophils by gradient centrifugation and negative magnetic separation. For inhibition purposes we used snake venom derived anti-adhesive proteins: vepistatin, VP12, VL05 and VL04 (potential and selective inhibitors of α1β1, α1β2, α1β3 and α5β1 integrins, respectively).

Results: In both groups of subjects all anti-adhesive proteins inhibited eosinophil transmigration, but only VL05 and VL04 PBMC transmigration; CD4 T cells migrated better than CD4 in control samples, but their transmigration was decreased after incubation with anti-adhesive proteins.

Conclusion: These findings suggest that expression of α1β1 and α1β2 integrins are involved in eosinophil transmigration. The role of α5β1 on lymphocyte is probably different.

P2318
The prognostic value of CD8+ and CD25+ lymphocytes blood content for asthma exacerbation

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Methods: 48 patients 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 CD8+ and CD25+ lymphocytes in blood was carried out by flow cytometry.

Results: Patients with asthma exacerbation had significantly lower values of CD8+ lymphocytes than patients with asthma remission (20.4±1.52 % vs. 23.2±5.08 % (P<0.01)) and controls (20.4±1.52 % vs. 23.2±3.37 % (P=0.005), they also had significantly higher values of CD25+ cells than patients with asthma remission (10.2±2.43±6.09 % vs. 5.49±3.59±6.01 %; P<0.001) and controls (10.2±2.43±6.09 % vs. 5.49±3.59±6.01 %; P<0.001). The regression equation for the prediction of asthma exacerbation was: Z =exp(2.059±0.498)×0.28831X-0.20392Y+(0.289094×0.20392)+0.289094×0.20392Y, where X – % of CD25+ cells and Y – % of CD8+ lymphocytes. If Z≥0.5, the patient has remission; if Z<0.5, the patient has exacerbation; the above Z, the above asthma exacerbation probability.

Conclusion: Decrease of CD8+ lymphocytes blood content and increase of CD25+ lymphocytes blood content can predict for asthma exacerbation and allows to predict asthma exacerbation with the probability of 81%.

P2319
Lentikoterin (LTC4), aggravate blooomycin-induced pulmonary fibrosis in mice

Yoshiki Murayama, Hirokumi Hirata, Takeshi Fukuda, Masakazu Arima.

Methods: PBMC were separated by gradient centrifugation; eosinophils by gradient centrifugation and negative magnetic separation. For inhibition purposes we used snake venom derived anti-adhesive proteins: vepistatin, VP12, VL05 and VL04 (potential and selective inhibitors of α1β1, α1β2, α1β3 and α5β1 integrins, respectively).

Results: In both groups of subjects all anti-adhesive proteins inhibited eosinophil transmigration, but only VL05 and VL04 PBMC transmigration; CD4 T cells migrated better than CD4 in control samples, but their transmigration was decreased after incubation with anti-adhesive proteins.

Conclusion: These findings suggest that overexpression of LTC4 using trans-

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P2320 Continuous airway inflammation is related to the development of airway remodeling

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In bronchial asthma, airway remodeling leads to refractoriness to treatment. Recent studies have demonstrated that mechanical stress induces inflammation. For this hypothesis, we examined the effects of continuous mechanical stress and airway inflammation in the mouse. Mice were divided into three groups: an airway inflammation group (group A), a methacholine-inhalation-induced mechanical stress group (group B), and a control group (group C). On days 14 to 29 after sensitization by intraperitoneal injection of ovalbumin, the mice in each group inhalined physiological saline, ovalbumin or methacholine. Counts of eosinophils and other inflammatory cells, smooth-muscle/basement-membrane thickening, and goblet-cell hyperplasia were compared among the groups. Eosinophil counts increased with time in group A, but not in group B or C. Smooth-muscle thickening was slightly greater in group A and group B than in the control group up to day 10 after sensitization. Group A showed a continuous trend toward increased smooth-muscle thickness up to day 15. In contrast, group B showed a slight decrease in smooth-muscle thickness. The difference was more marked in the peripheral than in the central airway. Basement-membrane thickening progressed with time in group A, but was not evident in group B or group C. Goblet-cell hyperplasia calculated on the basis of mucus scores significantly increased in group A, but was unchanged in group B and group C. Conclusion: Mechanical stress was transiently associated with thickening and proliferation of airway smooth muscle, but this effect decreased with time, suggesting that chronic, continuous airway inflammation plays an important role in remodeling.

P2321 Blocking costimulatory signal for treating steroid-resistant asthma model

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Background: We have constructed steroid sensitive (SS) and resistant (SR) murine asthma models by transferring SS and SR helper T (Th) clones into unprimed mice, respectively. Effect of CTLA4-Ig was analyzed both in vitro and in vivo. Method: For in vitro experiments, ovalbumin (OVA) reactive 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. CTLA4-Ig was administered through nasal inhalation or venous injection. The number of infiltrating cells in bronchoalveolar lavage fluid (BALF) was measured. Results: SS and SR clones were selected in terms of the proliferation of antigen-stimulated clones. Airway inflammation of eosinophils and lymphocytes of mice transferred with SS clones were effectively inhibited by the administration of DEX. In contrast, those of mice transferred with SR clones were not significantly inhibited by DEX. Administration of CTLA4-Ig significantly suppressed in vitro proliferation of DEX-treated SR clones, and in vivo eosinophil infiltration of SR asthma model transferred with SR clones. Conclusion: Steroid sensitivity of Th clones measured in vitro were consistent with that of adaptively transferred asthma model measured in vivo. Steroid resistant asthma models can be treated by blocking costimulatory signal mediated through CD28-CD80 and 86.

P2322 The effects of inspiratory muscle training on interleukin-6 concentration during cycling-exercise and volitional hyperpnea

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The plasma concentration of interleukin-6 (IL-6) increases during cycling exercise (EX) (Starke et al. J. Physiol 2001; 533:385-591) and inspiratory resistive breathing (IRB) (Vassilakopoulos et al. Am. J. Physiol 1999; 277:R1013-R1019). Whether inspiratory muscle training (IMT) can attenuate the magnitude of the IL-6 response to EX and volitional hyperpnea (VH) rather than IRB is unknown. Therefore, we tested the hypothesis that IMT would reduce the IL-6 response to EX and/or VH. Twelve male participants performed either 6 weeks of pressure-threshold IMT (n=6) or placebo (PLA) training (n=6). Before and after training, participants undertook three, 1 hour experimental trials: (i) passive rest; (ii) EX; and (iii) VH. EX was performed at maximum lactate steady state power. In VH, participants voluntarily mimicked at rest the breathing and respiratory muscle recruitment pattern attained during EX. IL-6 peaked immediately after EX for both the IMT and PLA groups (6.75±1.6 and 5.64±1.76 pg·ml⁻¹). Following training, this response was reduced (P<0.03) for the IMT but not the PLA group. Blood lactate concentration ([Lac⁻]₀) during EX was also reduced (P<0.05; P=0.09) for the IMT group only. IL-6 and [Lac⁻]₀ increased (P<0.05) during VH in both groups, but there was no effect of training on these responses. There were no increases in IL-6 or [Lac⁻]₀ over time in either group during passive rest. In conclusion, 6 weeks of IMT reduces IL-6 during EX but not VH. The reduction in IL-6 concentration following IMT may be related to a decreased carbohydrate utilisation as indicated by the post-IMT reduction in [Lac⁻]₀ during EX but not VH.

P2323 Assessment of the time course of chronic inflammation in the murine house dust mite model

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House dust mite (HDM) allergens are associated with allergic disorders and the use of this clinically relevant allergen is increasing in animal models. We assessed the chronic inflammatory time course and the anti-inflammatory efficacy of a phos- phodiesterase 4 inhibitor and a corticosteroid. BALB/c mice were challenged intransanally with HDM for 5 days/week for 5 weeks. Animals were sacrificed weekly 24 hours after final challenge and recruitment of inflammatory cells assessed in bronchoalveolar lavage fluid (BALF). Lung tissue was stained for the evaluation of a histopathological response. Roflumilast (10 mg/kg) and prednisolone (10 mg/kg) were administered orally twice daily from week 3. Chronic HDM extract exposure resulted in significant recruitment of eosinophils, neutrophils, lymphocytes and macrophages as early as week 1, peaking (1.13±0.32, 0.31±0.05, 0.66±0.10 and 0.33±0.4 x 10⁶ cells/animal respectively) between Weeks 3 and 5. Within the lymphocyte population the proportion of B cells increased from 4 to 46% over the 5 week exposure period. Mice developed perivascular, peribronchiolar and alveolar inflammation which increased in severity during the five week exposure period. The inflammation was accompanied by epithelial and mucus cell hypertrophy/hyperplasia in the bronchi and bronchioles which reached maximum severity during weeks 3 to 5. Perivascular/peribronchiolar fibrosis peaked in week 5. Therapeutic treatment with prednisolone and roflumilast significantly (P<0.001) inhibited BALF cell recruitment and reduced the severity of the airway remodelling suggesting this model, in our laboratory, has the potential to test novel compounds for the treatment of allergic disorders.

P2324 Effects of exercise on lung inflammation in ovalbumin-sensitized and single challenged mice

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Background: Studies suggest that physical exercise reduces lung function decline and risk of exacerbations in asthmatic patients. However, the inflammatory lung response involved in exercise during sensitization remains unclear. Aim: To evaluate the effects of aerobic exercise in an experimental model of sensitization and single ovalbumin (OVA) challenge. 419s
Methods: Male Swiss mice were divided into 4 groups: mice non-sensitized, non-exposed to OVA or exercise (Control, n=7); animals submitted to moderate treadmill exercise (Exercise, n=6), animals sensitized (OVA 10 μg) and single exposed to aerosolized OVA 1% (30 min) (OVA, n=6) and animals sensitized to exercise and single exposed to OVA (OVA+Ex, n=6). 24 hours after a single OVA/saline exposure, anesthetized mice were euthanized and we performed measures of inflammatory cells from bronchoalveolar fluid (BALF); IL-4, IL-5, IL-10, IL-1ra from lung tissue by enzyme-linked immunosorbent assay and qualitative assay and measures of IgG1 and IgE OVA-specific by IgE. The median of titles of IgE and IgG1 OVA-specific in OVA+Ex group was significantly lower than OVA group, and IL-4 and IL-5 were also decreased in OVA+Ex when compared with OVA group (p<0.05). Levels of IL-10 and IL-1ra did not reach significance difference.  

Conclusion: Our results showed that aerobic physical exercise attenuated the acute lung inflammation induced by a single OVA-challenge in sensitized mice, suggesting immunomodulatory properties of exercise on sensitization process in asthma.

P2325

Effects of swimming on lung inflammation in ovalbumin-sensitized and challenged mice

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Background: Epidemiologic studies have suggested that aerobic exercise decreases asthma prevalence and severity, improving aerobics capacity. However, the effects of high intensity exercise during sensitization on lung inflammation in asthma still unclear.

Objective: To evaluate the effects of high intensity exercise during sensitization process on lung inflammation in an experimental model of allergic pulmonary inflammation.

Methods: Male Swiss mice were divided into 4 groups: mice non-sensitized, non-exposed to ovalbumin (OVA) or submitted to exercise (Control, n=12); animals submitted to swimming 30 min/day for 21 days (Exercise, n=7); animals OVA sensitized (OVA 10 μg) and exposed to OVA (OVA+Ex, n=12); (30 min/day, 48 hours during four days) (OVA, n= 9) and animals sensitized, submitted to swimming and exposed to OVA (OVA+Ex, n=11). 48 hours after last exposure to OVA/saline, anesthetized mice were euthanized and we performed measures of total inflammatory cells from bronchoalveolar fluid (BALF), IL-4, IL-5, IL-10, IL-1ra and immunoglobulin IgE by enzyme-linked immunosorbent assay (ELISA).

Results: Swimming sessions decreased total number of cells from BALF as well as IgE, IL-4 and IL-5 levels in OVA sensitized and challenged mice (p<0.05). On the other hand, levels of IL-10 and IL-1ra showed a decrease in OVA+Ex group when compared with OVA group (p<0.05).  

Conclusion: In this experimental model exercise decreased pro-inflammatory cytokines, but also decreased regulatory/anti-inflammatory cytokines, maybe suggesting that during high intensity exercise, anti-inflammatory effects are not mediated by regulatory cytokines in sensitization process in allergic pulmonary inflammation.

P2326

Poly IC causes exacerbation in a murine allergic inflammation model driven by house dust mite in Freund's complete adjuvant

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Background: Recent epidemiological and experimental reports have suggested that helminth infection could also play a role limiting the availability of Fe, which would otherwise support bacterial growth. In the present study we hypothesized that these innate defenses would be impaired in asthma, associated with an increased bacterial burden in the airways.

Antimicrobial protein concentrations were determined in bronchial wash (BW) samples obtained from mild asthmatic and healthy volunteers. To examine the relationship between these proteins and bacterial load, measurements of lipopolysaccharide (LPS) and adjuvant associated factor (LTA) were made.

Results: BW samples were obtained from mild asthmatics (n=16, 26.76.2) and healthy controls (n=16, 25.06). Lactoperoxidase, lactoferrin, transferrin, and lysozyme concentrations were determined using ELISAs. LTP concentrations were established using the urea method. LPS measurements were made using the Limulus Amebocyte Lysate assay and LTA concentrations determined using ELISA.

Significantly lower BW transferrin (p<0.01 Mann Whitney U-Test) and lysozyme (p<0.03) concentrations were observed in asthmatics. A similar trend was apparent for lactoperoxidase (p=0.08), though for this and the remaining proteins considered intra-individual variation was apparent. Correspondingly BW LPS was significantly greater (p=0.04) in asthmatics, concentrations were not simply related to transferrin or lysozyme levels.

These results reveal impaired microbicide defense at the air-lung interface of mild asthmatics. Such a deficiency could render the asthmatic airway more susceptible to infection.

P2328

Helminth extract from opisthorchis felineus suppresses allergic inflammation through modulation of dendritic cells phenotype

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Background: The objective of this study was to use poly IC, a synthetic analogue dsRNA, to elicit exacerbation in a murine model of allergic pulmonary inflammation driven by house dust mite (HDM) in Freund's Complete Adjuvant (FCA). This model, developed in partnership with UCB as part of UIBOPRED WP6, is characterized by airway hyperresponsiveness (AHR) and a mixed T-helper phenotype [1].

Methods: Mature DCs were cultured from peripheral blood monocytes of healthy control (n=17) and asthmatic patients (mild BA, n=19; severe BA, n=24) using IL-4 and GM-CSF during 6 days. DCs were stimulated with O.f. extract and LPS on day 4 of incubation. After culturing DCs were harvested and labeled for CD86, CD11c, CD200 and analyzed using flow cytometry.

Results: O. f. inhibited the expression of co-stimulatory molecules as CD80 in mature DCs. Number of CD86+CD200+ DC was significantly decreased in different severity of BA compared to healthy donors. Patients with mild and severe BA had increased levels of CD200+ DCs compared to controls.

Conclusions: Our findings suggest that levels of co-stimulatory molecules expression on DC are important in immune response balancing and polarization. Increased levels of co-stimulatory molecules as CD86 on DC after helminth stimulation with O.f. might suppress airway inflammation in BA.

Conclusions: Poly IC exacerbates the inflammation and AHR in a murine model that mimics certain aspects of persistent asthma. This model could be used to investigate new mechanisms of action underlying viral exacerbation in persistent asthma and for the assessment and evaluation of novel therapies for such condition.

TSLP pathway blockade is a potential strategy for asthma treatment, as TSLP modulates cytokine production by mast cells and regulates the activation of dendritic cells (DCs), which prime the differentiation of naive T cells into inflammatory Th2 cells. We thus tested the effects of TSLP blockade on the development of allergenic inflammation and bronchocostriction in cynomolgus monkeys after Ascaris suum allergen challenge. Antibodies against human TSLP were generated and competitively neutralized. Animals were dosed once, either with nontreated MD-DCs, and siRNA against IL-27 and anti-IL-12 mAb suppressed the effect of GSH-OEt on IFN-α production by CD4(+) T cells compared to control subjects. Interleukin-27 α-p28 siRNAs and α-phosphorylated STAT3 and upregulation of α-SMA,collagen I expression were detected in intranasal OVA on days 14 and 21 (OVA/adjuvanted group). The animals received a-DEC-205-OVA treatment after OVA sensitization (OVA/DEC group). The treatment consisted of two injections of a-DEC-205 a week apart. We found that treatment with a-DEC-205 decreased significantly allergic inflammation as revealed by total cell numbers and eosinophils counts in bronchoalveolar lavage (BAL) fluid. We treated the group treated with a DEC-205 but not with the isotype control, we observed a reduction of total and OVA-specific IgE antibodies as well as IL-4 and IL-5 levels in BAL. Furthermore, treatment with a DEC-205 decreased the methacholine-induced respiratory trachea pattern associated with allergy. Our results indicate that treatment with anti-DEC-205 monoclonal antibody conjugated to OVA is effective in reducing allergic responses in animals previously sensitized to OVA. These results suggest a potential therapeutic use of a DEC-205 in allergic disorders.
P2334 Which children have the strongest longitudinal associations between early exposure to environmental tobacco smoke and age of asthma development? Elinor Simons 1,2, Teresa To 1, Rahim Moineddin 1, David Stieb 1, Sharon Dell 1,2, 1Child Health Evaluative Sciences, Hospital for Sick Children, Toronto, ON, Canada; 2Respiratory Medicine, Hospital for Sick Children, Toronto, ON, Canada; 3Family and Community Medicine, University of Toronto, ON, Canada; 4Air Quality Health Effects, Health Canada, Ottawa, ON, Canada

Objective: We sought to understand the effects of risk factors such as atopy on the longitudinal association between early-life exposure to environmental tobacco smoke (ETS) and age of physician-diagnosed asthma (PDA) development in childhood.

Methods: In the Toronto Child Health Evaluation Questionnaire, parents of 5619 grades 1-2 students reported age of PDA development, exposure to ETS during pregnancy and the first year of life and age of PDA development. We used Cox proportional hazard models, we conducted stratified analyses by potential effect modifiers.

Results: Household ETS exposure prevalence was 8.3% during pregnancy and 10.6% in the first year of life; 15.5% of children developed PDA, 31.2% had a history of atopy and 9.8% had a history of maternal asthma. Children exposed to ETS during pregnancy developed asthma sooner (adjusted hazard ratio (aHR) 1.27, 95% confidence interval (CI) 1.00-1.61). Stronger associations were seen among children without a history of atopy (aHR 1.92, 95% CI: 1.42-2.61) and without maternal asthma (aHR 1.74, 95% CI: 1.34-2.25); these relationships persisted for ETS exposure in the first year of life (aHR 1.52, 95% CI: 1.12-2.07 and 1.39, 95% CI: 1.08-1.79, respectively).

Conclusions: Longitudinal associations between ETS exposure during pregnancy or the first year of life and age of PDA development are stronger in children without a history of atopy and without maternal asthma. Greater understanding of these associations may guide hypotheses regarding possible mechanisms of association and suggest strategies for exposure reduction in higher-risk children.

P2336 Prognosis of allergic and non-allergic asthma

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Some studies indicate that atopy is less important as a predictor of severe asthma. Remission is more uncommon in allergic asthma than in non-allergic asthma. The purpose of this study was to investigate the prognosis of asthma and risk factors for asthma onset, especially sensitization of specific allergens. A cohort of three age groups responded to a respiratory questionnaire in 1990 and 2003. At baseline, 2060 subjects who reported respiratory symptoms and 482 controls responded to interviews, spirometry and skin prick test. A total of 721 asthmatics and 976 subjects without respiratory disease were clinically verified. At follow-up in 2003, 340 subjects with persistent asthma and 186 subjects with asthma remission were identified while 76 subjects reported new asthma onset. Sensitisation to pets and a high symptom score were significant determinants of persistent asthma (ORs 3.23 [95% CI 1.95-5.67], and 5.76 [2.35-13.34] respectively), and of asthma onset, (ORs 2.65 [1.13-4.86] and 1.7 [1.21-2.35].
respectively). A high self-reported responsiveness to airway irritants (OR 1.6 [1.12-2.2]), and more asthma medications (OR 2.0 [1.32-2.9]) were additional risk factors for persistent asthma at the follow-up. By the older age group decreased the risk of having persistent asthma or asthma onset. In conclusion, the findings of this study show that asthmatics sensitized to pets have a more severe prognosis than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Our study indicates that special care should be given to asthmatics who report having problems with a high number of airway irritants as such patients are more likely to suffer from persistent problems.

P2337
Standardization, sensitivity and specificity of an ash (Fraxinus excelsior) pollen allergen extract
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Background: Ash (Fraxinus excelsior), a wind-pollinated tree species causing spring time pollinosis, is the main representative of the Oleaceae family in temperate zones.

Aims and objectives: There is a need to standardize allergen extracts. Here we calibrated the biological activity of an ash pollen in-house reference preparation (BHRP) in allergic subjects and assessed the sensitivity and specificity of a prick test solution prepared from this BHRP.

Methods: 27 ash pollen allergic subjects, with ash pollen and nOe l 1-specific serum IgEs (sIgE) >0.2 kUA/L and >0.7 kUA/L, respectively and positive ash pollen nasal challenge tests (NCT) participated. Skin prick test (SPT) with BHRP was performed and the concentration inducing a mean wheal diameter of 7 mm was defined as 100 IR/mL. Subsequently, a 100 IR/mL solution of BHRP was assessed in 30 ash allergic subjects (history of ash allergy and ash-specific sIgE >0.7 kUA/L) and 30 non-allergic subjects (no history of allergy and ash-specific sIgE <0.35 kUA/L).

Results: The 100 IR/mL concentration corresponded to 1/148 weight/volume. All ash allergic subjects had a positive SPT (>3mm) and 29/30 non-allergic subjects had a negative SPT. Therefore, the sensitivity of the 100 IR/mL solution was 100% [88.6-100] and its specificity was 96.7% [83.3-99.4].

Conclusions: A 100 IR/mL prick test solution for in vivo diagnosis of ash pollen allergy was shown to be highly sensitive and specific.

P3239
Effectiveness of omalizumab in improving quality of life in patients with 'steroid-resistant' asthma and severe allergic rhinitis
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Asthma is a heterogeneous disease, not only in its clinical expression and course but also in its response to treatment with deleterious effects on Quality of life (QoL). Anti-IgE can spare these patients with unnecessary exacerbations and have a better QoL. The objective of this study was to evaluate the effectiveness of omalizumab treatment in improving QoL in patients with severe allergic rhinitis and asthma.

Methods: 41 patients aged ≥ 18 years with steroid-resistant asthma were enrolled in this open label study. Patients were examined at baseline and were treated with omalizumab administered subcutaneously every 2 or 4 weeks (at least 0.016 mg/kg/IgE/μL), in addition to existing treatment. At both visits, investigators assessed QoL on a 4-point scale in the following domains: nasal, ocular and asthmatic symptoms. Scores were calculated for individual symptoms, total scores for each domain. Patients were also assessed on impairment of sleep and daily activities.

Results: Omalizumab significantly reduced scores from baseline in both nasal and ocular symptoms. Reductions were also seen in the asthmatic symptom scores: significance was noted in wheezing (P=0.0002) and breathlessness scores (P<0.0002). At baseline, 62% of patients had some degree of daily activity impairment, increased to 81% in the final visit only 31% had daily activity impairment. Similarly, while 55% of patients had some sleep impairment at baseline, this was reduced to 28% at the final visit.

Conclusions: This open label study demonstrated that omalizumab was an effective treatment for the symptoms and sleep/day life impairments associated with severe allergic rhinitis and asthma.

P2340
Population pharmacokinetics of tralokinumab, an investigational anti-IL-13 monoclonal antibody, in asthmatic and healthy adults
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Interleukin-13 (IL-13) is considered a critical mediator in the development and maintenance of asthma. Tralokinumab (CAT-354), a human IgG4 monoclonal antibody that specifically neutralizes IL-13, is currently trials in subjects with uncontrolled, severe asthma.

The aim of this study was to develop and evaluate a population pharmacokinetic (PK) model of tralokinumab.

Four phase I studies and one phase 2a study constitute the data to be analysed comprising a population of 247 healthy and asthmatic adults. Nonlinear mixed-effects modeling of pooled data was conducted using the software NONMEM®. The influence of demographic features on tralokinumab PK was evaluated by covariate analysis. Predictive performance of the model was assessed through simulations. The PK parameters for a 2-compartment model after IV and SC dosing were all well established. We retrospectively reviewed medical records 12 months pre- and post-omalizumab initiation in patients (≥12 years) with severe persistent asthma who were (n=81) or were not (n=55) hospitalised for asthma in the year before omalizumab initiation. Baseline characteristics in hospitalised and non-hospitalised patients were similar: mean age 39.7 and 43.6 years; 27.2% vs 22.7% females, respectively. A high self-reported responsiveness to airway irritants (OR 1.6 [1.12-2.2]), and more asthma medications (OR 2.0 [1.32-2.9]) were additional risk factors for persistent asthma at the follow-up. By the older age group decreased the risk of having persistent asthma or asthma onset. In conclusion, the findings of this study show that asthmatics sensitized to pets have a more severe prognosis than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Our study indicates that special care should be given to asthmatics who report having problems with a high number of airway irritants as such patients are more likely to suffer from persistent problems.

P2338
The APEX study: A retrospective review of outcomes in patients with severe allergic asthma who were not or were hospitalised in the year prior to omalizumab initiation in UK clinical practice
Neil Barnes1, Adel Mansur2, Andrew Menzies-Gow3, Amr Radwan4, on behalf of the APEX Study Investigators. 1Respiratory Medicine, London Chest Hospital, London, United Kingdom; 2Respiratory Medicine, Birmingham Heartlands NHS Trust, Birmingham, United Kingdom; 3Asthma and Allergy, Royal Brompton Hospital, London, United Kingdom; 4Respiratory Medicine, Novartis Pharmaceuticals UK Limited, Frimley/Camberley, Surrey, United Kingdom.

The link between increasingly severe asthma and increased hospitalisation risk is well established. We retrospectively reviewed medical records 12 months pre- and post-omalizumab initiation in patients (≥12 years) with severe persistent asthma who were (n=81) or were not (n=55) hospitalised for asthma in the year before omalizumab initiation. Baseline characteristics in hospitalised and non-hospitalised patients were similar: mean age 39.7 and 43.6 years; 27.2% vs 22.7% females, respectively. A high self-reported responsiveness to airway irritants (OR 1.6 [1.12-2.2]), and more asthma medications (OR 2.0 [1.32-2.9]) were additional risk factors for persistent asthma at the follow-up. By the older age group decreased the risk of having persistent asthma or asthma onset. In conclusion, the findings of this study show that asthmatics sensitized to pets have a more severe prognosis than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Our study indicates that special care should be given to asthmatics who report having problems with a high number of airway irritants as such patients are more likely to suffer from persistent problems.

P3241
Cough variant asthma may be a incipience of bronchial asthma
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Cough variant asthma (CVA) is characterized by chronic cough that persists for more than two months and suggested to be a precursor of bronchial asthma (BA). To analyze if the position of cough variant asthma is early or mild stage of the classical bronchial asthma analyzed according to the airway inflammation,
bronchial hyperresponsiveness, airway obstructive damage, newly diagnosed 46 cough variant asthma patients and 57 bronchial asthma patients naive to oral or inhaled corticosteroids and free of asthma exacerbation were subjected to spirometry, impulse oscillometry (IOS), bronchial hyperresponsiveness test, induction of sputum, and measurement of fractional exhaled nitric oxide (FeNO).

P2342 Effects of budesonide/formoterol combination therapy versus budesonide on airway dimensions in asthma
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Background: The combination of inhaled corticosteroids and long-acting β2-agonists results in improved asthma symptom control compared with inhaled corticosteroids alone, but the effects of combination therapy on airway structural changes are still unknown.

Aims and objectives: The aim of the study was to compare the effects of budesonide/formoterol versus budesonide on airways dimensions and inflammation in asthma.

Methods: Fifty asthmatic patients were randomized to treatment with budesonide/formoterol (200/μg, two inhalations bd) or budesonide (200 μg, two inhalations bd) for 24 weeks. Airway dimensions were assessed by CT, and wall area correlated with body surface area (WA) and with body mass index (BMI) was assessed by IOS, wall thickness (Tc/BSA) and luminal area (As/BSA) at the right apical segmental bronchus were measured. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaire (AQLQ) were also evaluated.

Results: Significantly decreases in WA/BSA (p < 0.05), WA/BMI (p  < 0.001) and Tc/BSA (p < 0.05), and increases in As/BSA (p < 0.05), and improvements in the AQLQ and the frequency of exacerbations were observed in patients treated with budesonide/formoterol compared with budesonide. The reduction in sputum eosinophils and increase in FEV1 % were greater for budesonide/formoterol compared with budesonide. The changes in WA were significantly correlated with changes in sputum eosinophils and FEV1 % (r = 0.84 and r = 0.64).

Conclusions: Budesonide/formoterol combination is more effective than budesonide for reducing airway wall thickness and inflammation in asthma.

P2343 Effects of breast feeding on the prevalence rates of asthma, rhinitis and eczema in Chinese school children
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Background: Exclusive breastfeeding for at least 4 months is recommended by many governments and allergy organizations to prevent allergic disease. There is conflicting evidence concerning the relationship between breast feeding and asthma, wheezing illness and allergic disorders. The objective of this study was to investigate whether there is any association between breast feeding and asthma and allergic disorders in Chinese schoolchildren.

Methods: Study subjects comprised 10824 randomly selected 6 to 18 year old schoolchildren from Shijiazhuang in Hebei Province in China. Information on breast feeding, asthma, rhinitis and eczema was gathered by parental questionnaire using the Chinese version of ISAAC questionnaire.

Results: Children who have been breastfed had significantly lower prevalence rates of exercise-induced wheezing, asthma ever, and rhinitis ever than those who have not (3.1% vs 4.2%, p < 0.05; 1.6% vs 2.7%, p < 0.05; 2.7% vs 3.9%, P <0.05; 10.2% vs 12.4%, P <0.05; 12.5% vs 16.2%, P<0.001 and 11.4% vs 13.2%, P<0.05, respectively). There was a similar trend with chronic cough. Children who have been breastfed more than or equal to 12 months had lower prevalence rates of ever wheezed, wheeze in the past year, exercise-induced wheezing, persistent cough past year, ever had rhinitis, and ever had eczema than those who have been breastfed less than 12 months (3.1% vs 6.8%, P<0.05; 1.6% vs 2.7%, P<0.05; 2.7% vs 3.9%, P<0.05; 10.2% vs 12.4%, P<0.05; 12.5% vs 16.2%, P<0.001 and 11.4% vs 13.2%, P<0.05, respectively). The present study confirms the protective effect of breastfeeding on symptoms of asthma, rhinitis and eczema.

P2344 Effects of water aerosol on pediatric allergic asthma
Martin Gaisberger, 1 Renata Sanowicz, 1 Hedemarie Doblas, 1 Predrag Kolar, 1 Angelika Meder, 1 Josef Thulhammer, 1 Anna Selinom 1, Isidor Huttegger 1, Markus Ritter 1, Arnulf Hartl 1, 1 Institute of Physiology and Pathophysiology, Paracelsus Medical University, Salzburg, Austria; 2 Institute of Physics, University of Belgrade, Serbia; 3 Department of Molecular Biology, University of Salzburg, Austria; 4 Clinical Centre, University of Sarajevo, Bosnia and Herzegovina; 5 Department of Pediatrics, University Hospital Salzburg. Paracelsus Medical University, Salzburg, Austria

Objective: Ionized water aerosols have been suggested to exert beneficial health effects on pediatric allergic asthma. Their effects was evaluated in a controlled randomized clinical trial as part of a summer asthma camp.

Methods: Asthmatic allergic children (n=54) spent three weeks in an alpine asthma camp; half of the group was exposed to water aerosol for one hour per day, whereas the other half spent the same time at a “control site”. Immunological analysis, lung function and FeNO testing was performed during the stay, and sustaining effects were evaluated after 2 months. Symptom score testing was done over a period of 1 days.

Results: The water aerosol group showed a significant improvement in all lung function parameters whereas the control group only in peak expiratory flow. All patients showed significant improvement in symptom score and significant decrease of FeNO after the camp. Only the water aerosol group exhibited a long lasting effect on asthma symptoms, lung function and inflammation in the follow-up examination. Induction of IL-10 and regulatory (Treg) cells was measured in both groups, with a pronounced increase in the water aerosol group. IL-13 was significantly decreased in both groups, whereas IL-5 and eosinophil cationic protein were decreased only in the water aerosol group.

Conclusion: Our findings confirm the induction of Treg cells and reduction of inflammation by climate therapy. They indicate a synergistic effect of water aerosols resulting in a long lasting beneficial effect on asthma symptoms, lung function and airway inflammation.

P2345 Simultaneous analysis of clinical markers for predicting increased lung function fluctubility in stable asthma
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Background: Airway hyperresponsiveness (AHR) has been shown to be associated with the loss of asthma control. Predicting the increased fluctuation of lung function might be useful to regulate the future risk of poor asthma control because peak expiratory flow (PEF) variability well correlates with AHR.

Objective: We simultaneously analyzed the clinical markers for predicting increased PEF variability in stable asthma.

Methods: We studied non-smoking asthmatic patients who were receiving conventional therapy and clinically stable for 8 weeks. Patient medical records were obtained and asthma control questionnaire (ACQ), spirometry, and exhaled nitric oxide fraction (FENO) were measured. Associations between these variables and PEF variability over a week (Min/Max) were prospectively assessed.

Results: 52 of 287 asthmatics (17.5%) showed the increased PEF variability (Min/Max > 80%). These subjects were receiving more intensive therapy, but had more severe asthma symptoms, more airflow obstruction, and more evidence of airway inflammation. Especially, ACQ, forced expiratory volume in one second (FEV1) and BO were significantly correlated with changes in sputum eosinophils and FEV1 % (r = 0.84 and r = 0.64).

Conclusions: These results suggested that ACQ, %FEV1 and FENO can stratify risk for increased fluctuation of lung function among the clinically stable asthmatics.

P2346 Impact of allergy diagnosis on patients’ perceptions and experience of HDH allergy: A European survey
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Background: We assessed allergy awareness and diagnosis in a survey in four European countries. A post-hoc analysis determined the impact of diagnostic status on the perception of house dust mite (HDM) allergy and its management.

Methods: 4016 adults (France: n=1001; Germany: n=1002; Italy: n=1004; Spain: n=1009) answered an anonymous, online, questionnaire on their perception and personal experience of HDM allergy. The results were analyzed according to whether the subjects had been diagnosed with HDM allergy by a physician (n=611) or not. Survey procedures complied with the ESOMAR International Code of Marketing and Social Research Practice.

Results: 56% of the overall survey population stated that they experienced symp-
tom's (repetitive sneezing, nasal discharge, stuffy nose, eye irritation and breathing difficulties). 15% had been diagnosed with HDM allergy and another 23% thought that they were allergic to HDMs but had not been diagnosed. Of the diagnosed patients, 47% presented year-round symptoms, 35% had seasonal symptoms and 14% rarely had symptoms. A high proportion of diagnosed patients considered that their symptoms were due to dust (66%) or indoor air pollution (27%), versus 66% for HDMs. 87% of diagnosed patients felt well informed, whereas 37% of the latter had not identified HDMs as the cause of their symptoms. Diagnosed patients appeared to be more aware that untreated HDM allergy can progress to asthma when that allergy is difficult to treat.

**Conclusion:** Physician-diagnosed HDM allergy patients had greater levels of awareness of HDM allergy and its management than non-diagnosed patients. However, some topics need to be reinforced through health education measures.

**P2347**

Helminths for asthma: Findings of a Cochrane systematic review

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**Background:** Helminths modulate the natural immune response of their human hosts, and may prevent or cure immune-mediated or allergic diseases, such as asthma. Recent randomised clinical studies support this hypothesis.

**Objectives:** To assess the safety and effectiveness of helminth therapy in people with asthma.

**Methods:** We searched the Cochrane Airways Group Specialised Trials Register and additional sources for published and unpublished trials. We included all randomised controlled trials where the intervention was any helminth species administered to people with asthma. We combined dichotomous data using risk ratio (RR) and continuous data using mean difference (MD).

**Results:** We found 5 published reports, describing 2 studies (64 adult participants). Both studies used a single percutaneous application of 10 third stage Necator americanus larvae. Pooled efficacy data showed no difference in airway hyperresponsiveness between the helminth and placebo groups (MD 0.51, 95% CI –0.54 to 1.56) and no difference in study dropouts (OR 2.15, 95% CI 0.36 to 12.76). Other outcomes (asthma symptoms, use of reliever inhalers, quality of life) did not differ between the groups. Adverse events were few.

**Conclusions:** There was no clinical benefit from helminth therapy. The trials however were small and not powered to show effectiveness. Administered to humans in carefully measured doses, helminths appear to be safe. More preclinical studies should be performed, before larger and extended duration trials of helminths for asthma are carried out. "Trickle colonisation" with helminths may be more effective. A better understanding of the host-helminth bolus, but this therapeutic approach has not yet been tested for asthma.

**P2348**

Changes in total and specific IgE following treatment with mebendazole in patients with persistent asthma and HDM allergy to Ascaris lumbricoides

Rosanna, Non-randomised study.

**Background:** Recent studies have reported that patients with ascaridiasis and high levels of total and specific IgE were included in the study. Though they had been treated as chronic bronchitis patients with bronchial asthma, and these cases of bronchial asthma and sinus complications are reported to correlate with worsening of symptoms of asthma. Diagnosis of rhinitis and sinusitis are commonly diagnosed by clinical symptoms, X-ray, laryngoscope and sinus CT, but there are only a few reports of CT findings of sinus in patients with bronchial asthma.

**Patients and methods:** From April 2010 to December 2011, 115 patients with bronchial asthma were enrolled in this study. Duration of disease, treatment steps (i.e. hormonal treatment, smoking cessation, using bronchodilator, etc) and comparison of sinus CT finding were evaluated.

**Results:** Eighty-four patients (73%) showed sinusitis by sinus CT in these 115 patients. Nasal polyps were detected in 15 (13%) patients, and higher treatment steps were observed in patients with bronchial asthma complication sinusitis (p<0.05). Nasal symptoms were detected in 76 (66%), and nasal voice (61, 53%) is significantly highly detected in patients with bronchial asthma complication sinusitis. ACQ and parameters of pulmonary function were not significantly different in asthmatic patients with or without sinusitis.

**Conclusion:** Incidence of sinusitis in our study was relatively higher than the incidence of 66.3% previously reported by Matsuo et al. (2008). Patients with sinusitis detected by sinus CT tend to receive higher treatment steps, and it is speculated that sinus CT is useful for detecting and evaluating sinusitis as a complication of bronchial asthma.

**P2350**

Chronic parasanal sinusitis exacerbates allergic inflammation in patients with asthma and contributes to refractoriness to treatment

Necator americanus (i.e. hookworm) larvae. Pooling of data showed no difference in airway hyperresponsiveness between the helminth and placebo groups (MD 0.51, 95% CI –0.54 to 1.56) and no difference in study dropouts (OR 2.15, 95% CI 0.36 to 12.76). Other outcomes (asthma symptoms, use of reliever inhalers, quality of life) did not differ between the groups. Adverse events were few.

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Efficacy and safety of 300IR 5-grass pollen sublingual tablet in allergic patients with and without asthma

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**Background:** Efficacy and safety of 300IR tablet has been demonstrated. Here we report the impact of asthma status on efficacy and safety.

**Methods:** Grass pollen allergic adults were randomised to placebo or 300IR pre-and co-seasonally for 3 seasons, starting 4 months (4M) or 2 months (2M) prior to each season and continuing for its duration. Asthmatic patients requiring no more than GINA Step 1 therapy could be included. The primary efficacy endpoint, Average Adjusted Symptom Score (AAdSS), adjusting rhinoconjunctivitis symptoms for rescue medication use, scale 0-18) during the pollen period in Year 3, was analysed by ANCOVA. Asthma presence at baseline was a pre-specified covariate. Treatment by asthma status interaction was tested.

**Results:** Among 581 patients included in the Year 1 full analysis set, 14.1% were asthmatic, with a balance between groups. vs. each of the other two groups). Asthmatic subjects sensitized to both aero- and food allergens had higher levels of FeNO and sECP than non-sensitised or non-atopic (p<0.001). Food allergy is common among children with allergic asthma and has been linked with respiratory allergies (RAs; allergic rhinitis and asthma) in order to identify national gaps and patients’ needs. The survey was part of the 4-year Allergy Awareness Project of the European Federation of Allergy and Airways Disease Patients Associations, Brussels, Belgium

**Aim:** To evaluate, from the patients’ perspective, how European cares for patients with respiratory allergies (RAs; allergic rhinitis and asthma) in order to identify national gaps and patients’ needs. The survey was part of the 4-year Allergy Awareness Project of the European Federation of Allergy and Airways Disease Patients Associations (EFA).

**Methods:** Data were collected via an online 3-part questionnaire: 1) Basic facts: epidemiology, disease definitions, prevalence and costs; 2) Access to care: diagnosis, management, role of healthcare professionals in patient management and follow-up; 3) Quality of care: national policies and best practices. EFA member associations (n. 38) received the questionnaire. The survey was a part of the 4-year Allergy Awareness Project of the European Federation of Allergy and Airways Disease Patients Associations (EFA).

**Results:** Associations from 18 countries returned the questionnaire. RA affect 20%-30% of the European population. But RAs, and particularly allergic rhinitis, are not considered serious diseases, and thus often remain underdiagnosed and undertreated despite the heavy burden they place on patients and society. In all 18 countries, direct RA costs reach millions of euros. In most countries, patients have difficulty in seeing specialists, and coordination among physicians is lacking.

**Conclusions:** We have seen reduced costs and better quality of care.

**References:**

1. European countries


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4. Department of Social Sciences and Communication, University of Salerno, Fisciano (Sa), Italy.

5. Communication and Research, Scientific Communication Srl, Naples, Italy.

6. Patients Support, Asthma Fonds, Amsterdam, Netherlands.

7. Project and Fundraising Office, European Federation of Allergy and Airways Disease Patients Associations, Brussels, Belgium.
Conclusions: Awareness of RAs and their social burden is low. There is a need for better prevention and coordination among healthcare professionals. Patients’ associations can help increase public awareness, and must be actively involved in devising and implementing RA management and education programs.

258. Asthma: mechanisms of airway inflammation

P2357
The effects of inspiratory muscle training on the interleukin-6 response to intense volitional hyperpnoea
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Vassilakopoulos et al. (Am. J. Physiol. 1999; 277:R1013–R1019) demonstrated a breathing-induced interleukin-6 (IL-6) response. Whether inspiratory muscle training (IMT) can attenuate this response is unknown. Therefore, we tested the hypothesis that IMT can reduce IL-6 response to volitional hyperpnoea (VH) in young healthy men. Twelve male participants performed either 6 weeks of pressure-threshold IMT (n=6) or placebo (PLA) training (n=6). Prior to training, a maximal incremental cycling test (max) was performed. Before and after training, participants undertook two 1 h experimental trials on separate days: passive rest and VH. In VH, they voluntarily mimicked at rest the breathing and respiratory muscle recruitment pattern equal to 70-80% of the maximum minute ventilation achieved during max. IL-6 increased (P<0.01) following the pre-training VH and was (mean±SD) 5.02±0.63 and 4.87±0.86 pg·mL-1 at 2 h post for IMT and PLA groups, respectively. [Lac-]B remained (P>0.01) elevated above baseline values for the duration of VH at 1.36±0.24 and 1.29±0.18 mmol·L-1. The IL-6 (-29%) and [Lac-]B (-11%) responses were reduced (P<0.05) for the IMT, but not for the PLA group. There were no increases in IL-6 or [Lac-]B over time for either group during passive rest and no evidence of diaphragm fatigue during any trial. In conclusion, 6 weeks of IMT reduces the magnitude of the IL-6 response to VH with no evidence of diaphragm fatigue. The reduction in IL-6 may be related to the post-IMT reduction in [Lac-]B.

258. Asthma: mechanisms of airway inflammation

P2358
Estrogen protects against airway inflammation via upregulation of SLPI and downregulation of IL-33
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Airway epithelium (AE) can modify airway responses through production of anti-inflammatory mediators like secretory leukoprotease inhibitor (SLPI) and pro-inflammatory mediators like interleukin-33 (IL-33). Estrogen can modulate AE responses and we therefore investigated how estrogen affects severity of airway inflammation and SLPI and IL-33 production in mice. Female balb/c mice were ovariectomized (OVX) or sham-treated and received a 0.1 mg estrogen (E2) pellet at OVX or not (all groups n=8). Four weeks after OVX, mice were sensitized i.p. with OVA and alum on days 1 and 7 and challenged with 1% OVA on days 14-20. On day 21, allergic inflammation (OVA-specific IgE, eosinophils) and production of IL-33 and SLPI were assessed.

Ablating estrogen significantly increased airway inflammation as compared to sham-treated mice. Treating OVX mice with E2 significantly reduced the higher airway inflammation induced by OVA as judged from lower eosinophil numbers in lung and lower OVA-specific IgE levels in serum. In the parenchyma of E2-treated OVX mice we found more type II alveolar epithelial cells (AECII) expressing IL-33. IL-33 production in mice. This study shows that estrogen protects female mice against the development of airway inflammation and this is associated with higher SLPI and lower IL-33 production by AECII. We therefore postulate that estrogen has a protective effect on asthma development through induction of anti-inflammatory SLPI production and inhibition of pro-inflammatory IL-33 production by AECII.
P2359

IL-4 induces Th2 cells to resist the IL-27 counterregulation by downregulating STAT1 and STAT2 phosphorylation
Zhongchi Chen, Shanze Wang, Chunchui Bai, Rafeul Alam, Hua Huang. Division of Respiratory, Zhongshan Hospital, Shanghai, China

Rationale: Asthma is a chronic airway inflammation caused by overproduction of Th2 cytokines. IL-27 has been shown to inhibit differentiation of naive CD4+ cells into Th2 cells in mice. However, it is not clear whether IL-27 can inhibit Th2 cell differentiation in asthmatic patients.

Methods: Purify CD4+ T cells from human PBMC and mice spleen were cultured under Th2 or Th2 + IL-27 conditions. IL-4 and IFN-gamma were detected by ELISA. IL-27r and p-STAT1 were determined by qRT-PCR and Western blot respectively.

Results: Human IL-27 suppressed Th2 differentiation in healthy subjects (p=0.006), but failed to do so in asthmatics (p=0.064). The suppressive effect of IL-27 on Th2 development was independent of IFN-g, IL-10 and T-bet. However, studies with STAT1-knockout mice showed that this inhibitory effect of IL-27 was STAT1-dependent. IL-27 resistance to Th2 differentiation in asthmatics was not dependent on impaired IL-27r. In further found that Th2-inducing conditions could induce resistance to IL-27 in a dose-dependent manner and IL-4 is the most critical factor. Although IL-2 is imperative in Th2 cell priming, it does not contribute to induction of the IL-27 resistance. We demonstrated that high dose of IL-4 treatment resulted in impairment of STAT1 phosphorylation, but not STAT3 or STAT4 phosphorylation.

Conclusions: IL-27 suppresses the development of Th2 immune response in both mice and human, which is STAT1-dependent, but independent of IFN-g, IL-10 and T-bet. CD4+ T cells from asthmatics developed resistance to IL-27-mediated inhibition. IL-4 induced resistance to IL-27-mediated inhibition by impairing STAT1 signaling.

P2360

Regulatory role of antigen-induced IL-10, produced by Tr1 cells, in airway neutrophilia in a murine model for asthma
Takeshi Nabe1,2, Kashiya Yada1,2, Anke Siechert1,2

Asthma is a chronic airway inflammation caused by overproduction of Th2 cytokines. IL-27 has been shown to inhibit differentiation of naive CD4+ cells into Th2 cells in mice. However, it is not clear whether IL-27 can inhibit Th2 cell differentiation in asthmatic patients.

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P2363

Exposure to ozone shifts natural killer cells co-cultured with epithelial cells towards a type II phenotype
Laurent Nicol2,1, Benjamine Mariand1,2, An Lausanne, Switzerland; 2Faculty of Biology and Medicine, UNIL, Lausanne, Switzerland

Asthma is a chronic airway inflammation caused by overproduction of Th2 cytokines. IL-27 has been shown to inhibit differentiation of naive CD4+ cells into Th2 cells in mice. However, it is not clear whether IL-27 can inhibit Th2 cell differentiation in asthmatic patients.

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Conclusions: IL-27 suppresses the development of Th2 immune response in both mice and human, which is STAT1-dependent, but independent of IFN-g, IL-10 and T-bet. CD4+ T cells from asthmatics developed resistance to IL-27-mediated inhibition. IL-4 induced resistance to IL-27-mediated inhibition by impairing STAT1 signaling.

P2364

Probiotics and symbiotics: Effects on chronic asthma in mice
Seri Sagar1,2, Aletta D. Kranefeld1, Niki A. Georgiou1,2, Johan Garssen1,2, Gert Folkerts1,2, Aletta D. Kranefeld1, Niki A. Georgiou1,2, Johan Garssen1,2

Asthma is a chronic inflammatory disorder of the airways characterized by structural changes of the airways which may contribute to airway obstruction and airway hyperresponsiveness. Modulation of the intestinal microbiota by probiotics and related products as a potential therapy for allergic diseases has been subject to investigation. Several murine models of asthma and clinical studies demonstrated beneficial effects of probiotics and symbiotics in asthma management. However, the effects on chronic symptoms of asthma have never been investigated in murine models.

Methods: Mice were sensitized twice (day 1 and 12) with ovalbumin (OVA)-injected alum and challenged from day 17 till 23 daily with OVA. From day 24 till day 56, animals were challenged with OVA 3 times a week and on the same days the animals were treated with either control solution or glucocorticoids (GCS)

Results: Treatment with probiotics or GCS significantly inhibited the OVA-induced increase in basal airway resistance and hyperresponsiveness. Probiotics, but also symbiotics and GCS significantly reduced pulmonary leukocyte infiltration by 50% especially eosinophilia. Neutrophilia in the airways was reduced by GCS and probiotics. Effects on airway remodelling are in process.

Conclusion: The probiotics and symbiotic used in this study seem to be as potent as GCS in reducing cell infiltration in mice with chronic asthma.
In summary, our data provided the first evidence of YKL-40-induced IL-8 expression and increased proliferation and migration of BSMCs. By comparison, IL-8-depleted conditioned culture media (YKL-40-BEAS-2B-CM) to BSMCs, which led to YKL-40 treatment. In addition, we treated BEAS-2B with YKL-40 and added YKL-40 showed YKL-40 induced IL-8 at the transcriptional level. Furthermore, BEAS-2B hypoxia significantly elevated and were associated with asthma severity. Although these studies raise the possibility that YKL-40 may influence asthma, the mechanisms remain unknown. In this study, we investigated the mechanisms involved in YKL-40-mediated IL-8 production from human bronchial epithelial cells (BEAS-2B) and analyzed the soluble factors (including IL-8) secreted by BEAS-2B-exposed to YKL-40 that were responsible for increasing proliferation and migration of primary normal human bronchial smooth muscle cells (BSCMs). We found BEAS-2B treated with YKL-40 resulted in a significant increase of IL-8 expression and release. Moreover, YKL-40 mediates phosphorylation of JNK, ERK, but not p38 in BEAS-2B. Transfection using a NF-κB-luciferase reporter also showed YKL-40 induced IL-8 at the transcriptional level. Furthermore, BEAS-2B pretreated with inhibitors of JNK, ERK or NF-κB decreased IL-8 release upon YKL-40 treatment. In addition, we treated BEAS-2B with YKL-40 and added the conditioned culture media (YKL-40-BEAS-2B-CM) to BSCMs, which led to increased proliferation and migration of BSCMs. By comparison, IL-8-depleted YKL-40-BEAS-2B-CM failed to induce the proliferation and migration of BSCMs. In summary, our data provided the first evidence of YKL-40-induced IL-8 expression in BEAS-2B via MAPK (JNK, ERK) and NF-κB pathways, and the induced IL-8 was found to further stimulate the proliferation and migration of BSCMs. Our results raise the possibility that YKL-40 may play a role in asthma by inducing IL-8 production.
did not change in both ROG-pDNA3.1- and ROG-sRNA-transfected Th1 and Th2 cells (P = 0.05).

**Conclusions:** ROG can inhibit the expression of Th1 and Th2 cytokines by down-regulating the expression of ICOS, which could be a potential regulating target for asthma treatment.

**P2370**

Long-term bortezomib treatment decreases allergen-specific IgE but fails to amend chronic asthma in mice

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Since allergen-specific immuno-global E (IgE) enables mast cells and eosinophils to react on allergen-contact it plays a critical role in the formation of allergic inflammation and has been identified as a target for asthma therapy. By inhibiting the proteasome, bortezomib efficiently depletes Ig-secreting plasma cells and, thus, reduces Ig-serum titers. The present study evaluates the therapeutic potential of Bortezomib in a mouse model of chronic experimental asthma. Therefore, BALB/c mice were sensitized to ovalbumin (OVA) and challenged with OVA-aerosol for twelve weeks. Bortezomib treatment was started after six weeks of challenge, and continued for one week (short-term) or six weeks (long-term), respectively, with a dosage of 0.75 mg/kg body weight with two intra-venous injections weekly. Airway responsiveness to metacholine, lung histology, Ig serum titers, and plasma cell numbers were assessed. In mice with chronic experimental asthma short-term treatment resulted in decreased eosinophil numbers in BAL fluids, while long-term treatment significantly lowered serum titers of anti-OVA IgE. Nevertheless, neither short-term nor long-term treatment significantly diminished ed plasma cell numbers, anti-OVA IgG1 serum titers, allergic airway inflammation or improved lung function. These results demonstrate that Bortezomib has no therapeutic effect on chronic experimental asthma in mice. Therefore, Bortezomib treatment could have only limited value as plasma cell depleting therapy against allergic bronchial asthma.

**P2371**

A low total sputum cell count is a marker for asthma remission during adolescence

Khalid Basak1, Zamir Al-Shammari1, Laurie Lau2, Wilfred Karmous3, Susan Ewart4, Ramesh Kurukulaaratchy1, 1Clinical and Experimental Academic Unit, Respiratory Biomedical Research Unit, and David Hide Asthma and Allergy Research Unit, University JSC, Astana, Kazakhstan; 2Respiratory Medicine, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; 3Asthma, Childrens Disease No. 1, Astana Medical University JSC, Astana, Kazakhstan; 4Veterinary University JSC, Astana, Kazakhstan

One of less studied is the test of histamine serial dilutions sensitivity and exactly this test may be very important for antihistamine preparations effectiveness study.

**Materials and methods:** We studied 96 patients; from them 48 were patients of ENT department, who suffered from drug hypersensitivity reactions of various severity, from mild urticaria to anaphylaxis (study group). The control group consisted of 48 ENT patients with same diseases, but without drug hypersensitiv- ity. Patients were determined into “study” and “control” group according to “case-control” principle. Seven day before histamine sensitivity tests cell anhi-sensitization preparation were stopped. Histamine serial dilutions test was performed with standardized prick-needle. We used test 1:0.1 histamine preparation. The end point was histamine dilution that caused papule ≥ 2mm in diameter.

**Results and discussion:** In the control group in 54.2% the end point was ≥ 0.1 histamine dilution, in 29.2% - ≥ 1.0, in 7.3% - ≥ 1.0, in 5.1% - > 1.0. There were few cases, when our patients debit react by papule formation to 0.1% histamine dilution and reacted only to 0.1% of histamine. In patients with drug allergy we found an elevated skin sensitivity. Thus, the end-point 1:2 was found in 39.5% of patients, 10-3 - in 21.6%, 10-4 - in 9.9%. The difference in 10-2 dilutions and 10-3 dilutions between the control and studied group was statistically significant. We concluded that in patients with drug allergy the increased skin sensitivity to histamine was found, and the level of this hypersensitivity should be considered in individual antihistamine preparations prescription.

**P2372**

New enzyme linked immunosorbent assay using recombinant antigens from Saccharopolyspora rectivirgula for Farmer’s lung disease serodiagnosis

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Since allergen-specific immuno-globulin E (IgE) enables mast cells and eosinophils to react on allergen-contact it plays a critical role in the formation of allergic inflammation and has been identified as a target for asthma therapy. By inhibiting the proteasome, bortezomib efficiently depletes Ig-secreting plasma cells and, thus, reduces Ig-serum titers. The present study evaluates the therapeutic potential of Bortezomib in a mouse model of chronic experimental asthma. Therefore, BALB/c mice were sensitized to ovalbumin (OVA) and challenged with OVA-aerosol for twelve weeks. Bortezomib treatment was started after six weeks of challenge, and continued for one week (short-term) or six weeks (long-term), respectively, with a dosage of 0.75 mg/kg body weight with two intra-venous injections weekly. Airway responsiveness to metacholine, lung histology, Ig serum titers, and plasma cell numbers were assessed. In mice with chronic experimental asthma short-term treatment resulted in decreased eosinophil numbers in BAL fluids, while long-term treatment significantly lowered serum titers of anti-OVA IgE. Nevertheless, neither short-term nor long-term treatment significantly diminished ed plasma cell numbers, anti-OVA IgG1 serum titers, allergic airway inflammation or improved lung function. These results demonstrate that Bortezomib has no therapeutic effect on chronic experimental asthma in mice. Therefore, Bortezomib treatment could have only limited value as plasma cell depleting therapy against allergic bronchial asthma.
antigens in pigeon serum regardless of possessing PFL, and there was no difference in magnitude of response between the groups. No pigeon-specific IL-4, IL-5 or IL-17 ELISPOT response could be detected in any individual.

**Conclusion:** These findings show that an unconventional T cell response is generated in conjunction with pulmonary exposure to pigeon antigens that may be necessary but not sufficient to cause PFL disease, and so further analysis of these cells is warranted.

P2375

**Roles of periostin in vascular remodeling of allergic granulomatous angiitis in murine model**

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**Background:** We reported an allergic granulomatous angiitis (AGA) model of C57BL/6 mice (Exp Lung Res 2010). We also reported the suppressive effects of imatinib mesylate (IM) on vascular remodeling (ERS 2010). Periostin is a matricellular protein involved in airway remodeling in asthma and pulmonary fibrosis.

**Objectives:** To elucidate the role of periostin (PO) in vascular remodeling in AGA, we measured the concentrations of PO in bronchoalveolar lavage fluids (BALF) and serum in an AGA model of C57BL/6, in BALB/c as control and in C57BL/6 treated with IM.

**Methods:** C57BL/6 and BALB/c were sensitized with ovalbumin (OVA). They were exposed to aerosolized OVA daily for 7 days. C57BL/6 mice (im treated) were also administered with IM (4.5 mg/kg, p.o.) in parallel with daily exposure to aerosolized OVA for 7 days (n=12). On the 7th day, BALF was performed and the lungs were excised for pathological analysis. The concentrations of PO in BALF and serum were measured and the values were expressed as mean ± SE.

**Results:** The PO concentration in BALF of sensitized C57BL/6 mice exposed to OVA was significantly higher than that of BALB/c (C57BL/6 vs BALB/c; 39.3±6.58 vs 13.56±2.42%, p<0.003). PO in BALF of the IM treated C57BL/6 was significantly reduced compared to positive control mice (control vs IM treated; 40.3±1.85 vs 39.3±1.95%, p=0.019). The pathological scores were reduced significantly in the IM treated group compared to the control group (control vs IM treated; 3.67±0.2 vs 2.20±0.2, p=0.004).

**Conclusion:** The PO concentration in BALF was associated with vascular remodeling in a murine AGA model, suggesting its pivotal role in myofibroblast proliferation in pulmonary arteries.

P2376

**Challenges in the management of patients with ANCA-associated vasculitides**

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**Background:** Granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis are antineutrophil cytoplasm antibodies (ANCA)–associated vasculitides with significant morbidity and mortality.

**Objective:** We evaluated the evolution of 12 patients diagnosed in our clinic between 2000 and 2011, treated with conventional treatment (prednisolone and pulse cyclophosphamide initially, and in remission with prednisolone and azathioprine).

**Results:** We evaluated 12 patients (10 females), median age of 46 years (range 20-74), with a median duration of follow up of 5.2 years (range 1-12 years).

**Conclusions:** Six patients had relapses (50%), 1 developed subglottic stenosis, 1 retro-orbital pseudo tumor and 2 patients developed lung abscesses inside a cavity which imposed lobectomy after unsuccessful antibiotic treatment. Two patients developed lung tuberculosis (one multi-drug-resistant) and 1 pulmonary nocardiosis linked to resected lobectomy after unsuccessful antibiotic treatment. Two patients developed careful dialysis for renal failure. Two patients died of stroke (1) and severe active vasculitis (1). Older age and renal failure were predictors of death.

P2377

**Omalizumab decreases IgE production in patients with severe allergic asthma**

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**A pharmacokinetic-pharmacodynamic model predicts that omalizumab reduces production of IgE.** 2. To test this hypothesis serum total-IgE concentrations were quantified in 64 patients with severe allergic asthma (mean±SEM; 46.2±13 yrs, 41 female, 81±6±15 kg, total IgE; 397±189 IU/ml, FEV1±1 L±1.1 L or 67±2±2.4%, pred, CNO0 51.2±7.4 phb treated with omalizumab (median 450 mg/month). Total serum IgE, asthma control (ACQ), lung function (FEV1) and exhaled nitric oxide (eNO) were evaluated at baseline (w0, n=64), after 16 weeks (w16, n=64) and after 52 weeks (w52, n= 24) of treatment.

50 patients responded to omalizumab treatment. Overall (n=64), after 16 weeks ACQ (w16 vs w0, 0.34±0.18, p<0.001), FEV1 (w16 2.3±0.12; p=0.01) and eNO (w16 40.1±5.4; p=0.027) improved significantly. Total IgE increased by 536±141 IU/ml (w16 984±215 IU/ml; p<0.01). Changes in total-IgE did not differ between responders and non-responders. After 52 weeks total IgE was 634±197 IU/ml, a decrease by 99±53 IU/ml vs. week 16 IgE levels, whereas ACQ, FEV1, and eNO remained stable. In this period total IgE serum concentrations decreased in 19 of 24 patients.

These results support the conclusion that long-term omalizumab treatment reduces IgE production. Further, total serum IgE should provide a means to monitor IgE production and guide individual treatment decisions.

**Low PJ, Renou D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma. PKPD analysis of a biomarker, total IgE. Br J Clin Pharmacol 2011; 72(2):306-320.**

P2378

**Impact of omalizumab treatment persistence on asthma control**

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Omalizumab is indicated for moderate to severe allergic asthma patients with inadequately controlled symptoms. The purpose of the current study was to evaluate the impact of omalizumab treatment persistence on asthma control. Health insurance claims from the MarketScan database (2002Q1-2011Q2) were analyzed. Asthma patients with >12 months of continuous omalizumab use after the first omalizumab claim (index date) following 6 months of continuous omalizumab use were included. A 12-month landmark period following the index date was used to assess treatment persistence, defined as uninterrupted treatment without a gap of ≥ 28 days in omalizumab use. The impact of persistence with omalizumab treatment on asthma-related emergency-department (ED) visits and hospitalizations occurring between months 13 and 24 was evaluated. Multivariate time-varying Cox regressions were also conducted to assess the adjusted impact of treatment interruption (lack of persistence) on asthma control from month 1 to month 24.

In total, 3044 patients (mean age: 48.5; female: 62.4%) formed the study population. Persistence with omalizumab treatment at 12 months (39% of patients) was associated with a 51% reduction in the mean (SD) number of ED visits per patient (persistence vs. non-persistence: 0.064 [0.3] vs. 0.129 [0.5], P<0.001) and a 28% reduction in hospitalizations (0.131 [0.4] vs. 0.182 [0.6], respectively, P=0.034). Multivariate analyses corroborated these findings (HR [95% CI] for persistence vs. non-persistence: 0.064 [0.3] vs. 0.129 [0.5], P<0.001). Changes in total-IgE did not differ between responders and non-responders. After 52 weeks total IgE was significantly reduced compared to positive control mice (control vs. IM treated: 2.42%, p=0.003). PO in BALF of the IM treated C57BL/6 was significantly reduced compared to positive control mice (control vs. IM treated: 40.1±5.4; p=0.027). The pathological scores were reduced significantly in the IM treated group compared to the control group (control vs. IM treated: 3.67±0.2 vs. 2.20±0.2, p=0.004).

**Conclusion:** The management of patients with ANCA-associated vasculitides is difficult, and marked by significant adverse effects of the therapy.

**259. Aspects of clinical asthma**

**P2379**

**Gender medicine and different prevalence in asthma by reports on anti-IgE (omalizumab) treatments**

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**Background:** Generally, pathogenesis and prevalence of bronchial asthma indi-
cates that age and sex are the major risk factors. Detailed physiological mechanisms of the changing sex ratio are not fully known. We investigated the influence of gender on anti-IgE treated asthmatics.

**Methods:** We pooled data from ten published studies from 1999 with more of our data of severe persistent asthma treated with omalizumab (anti-IgE) monoclonal antibody. Static analysis was used to find gender risk factors as the ratio of treatment effect difference on standardized exacerbation rate and frequency of asthma exacerbations.

**Results:** The studies included 3270 omalizumab treated patients, whose had severe persistent asthma according to Global Initiative for Asthma (GINA) classification. Analysis of two groups male vs female showed that the efficacy of omalizumab on asthma exacerbations was unaffected by patient age, gender, baseline serum IgE (split by median) or by 2- or 4-weekly dosing schedule, although a more large number of women were treated (92115349, 59% women vs 41% men; p < 0.001) and benefit in absolute terms appeared to be greatest in women patients which had a more severe asthma, defined by a lower value of percentage predicted forced expiratory volume in 1 s (FEV1) at baseline, this subgroup showed odds of being a responder (composite definition) 1.25 times higher (95% confidence interval, 1.18 to 3.01) than men.

**Conclusions:** These results suggest that in population of asthmatics treated with anti-IgE the number of women is higher than men, it confirms that asthma should be considered with different approach by the gender for being adequately controlled on current therapy.

**P2380**

Factory predicting airflow obstruction in severe asthmatics

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Singapore, Singapore

Severe asthma was defined as “treatment-resistant severe asthma” and includes asthmatics on highest level of recommended treatment (high-dose Inhaled Corticosteroids (ICS) or high-dose ICS plus Long-Acting Beta2 Agonists combination) 1.

Airway remodeling was defined as FEV1 ≤60% FVC. Factors predicting remodeling were studied which include demographic profile, duration of asthma, allergen sensitization, presence of bronchial hyper-reactiveness, asthma-related comorbidities and frequency of acute exacerbations. 270 fulfilled severe asthma definition. Amongst these patients, 59 had airway remodeling. Airway remodeling was associated with increasing number of allergic sensitization (p=0.032). Amongst those with 5-8 allergic sensitization, 37.5% (n=12) had FEV1 ≤60%. In comparison, 15.9% (n=7) had FEV1 ≤60% amongst those with 1-4 allergic sensitization. The presence of bronchial hyper-reactiveness on methacholine challenge test, significant bronchodilator response and smoking were also significantly associated with FEV1 ≤60% (p < 0.001, p=0.011 respectively).

Frequency of asthma exacerbations (steroid burst, admissions and unscheduled emergency department visits), duration of asthma and presence of bronchial hyper-reactiveness on methacholine challenge test, significant bronchodilator response and smoking were also significantly associated with FEV1 ≤60% (p < 0.001, p=0.011 respectively).

We have found that patients with broader spectrum of allergic sensitization were more likely to have airway remodeling. Early detection of allergic sensitization may be important and aggressive treatment of allergies may be able to arrest or reverse the remodeling process. Our findings concur with previous reports of presence of bronchial hyper-reactiveness, bronchodilator response and smoking being risk factors for remodeling.

**P2381**

Severe asthma in old patients is characterized by signs of immunosuppression and by lymphocyte resistance to glucocorticoids

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The aim of this study was to investigate the adaptation system in asthmatic patients. Twenty one patients were enrolled into the study. In 15 patients the clinical course was evaluated as severe and 6 patients demonstrated the middle asthma (mean age, 60.3±2.5 and 30.8±3.0 years, respectively). Individual susceptibility of peripheral blood lymphocytes (PBL) to glucocorticoids (GCs) was evaluated by Δh value calculation: an integrative parameter, including the level of mitogen-induced lymphocyte proliferation and inhibition degree of the cell proliferation by dexamethasone. In healthy subjects the mean h value calculation: an integrative parameter, including the level of mitogen-induced lymphocyte proliferation and inhibition degree of the cell proliferation by dexamethasone. In healthy subjects the mean Δh value was −0.24±0.30 (negative values of Δh correspond to high cell sensitivity to GCs). Results of the study are presented in the Table 1.

Aim: To correlate asthma phenotypes with hospitalisation, in acute exacerbations of asthma.

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe asthma</th>
<th>Middle asthma</th>
<th>P value</th>
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<tr>
<td>Length of disease (years)</td>
<td>19.6±3.6</td>
<td>12.4±3.3</td>
<td>0.17</td>
</tr>
<tr>
<td>FVC</td>
<td>89.3%</td>
<td>89.4%</td>
<td>0.6</td>
</tr>
<tr>
<td>FEV1</td>
<td>67.7%</td>
<td>71.8%</td>
<td>0.43</td>
</tr>
<tr>
<td>ACTH (µg/ml)</td>
<td>12.0±1.7</td>
<td>23.1±4.8</td>
<td>0.05</td>
</tr>
<tr>
<td>TGFβ1 (ng/ml)</td>
<td>1796.6±1026</td>
<td>1246±1810</td>
<td>0.024</td>
</tr>
<tr>
<td>Δh</td>
<td>2.0±0.18</td>
<td>1.0±0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PBL proliferation (cpm*)</td>
<td>14542±2339</td>
<td>34567±7690</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*pCpm, counts per minute.

**P2382**

Compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy

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Background: Subcutaneous(SCIT) and sublingual (SLIT) allergen immunotherapy is a safe and effective treatment of allergic rhinitis, but high levels of compliance and persistence are crucial to achieving the desired clinical effects. The objective was therefore to assess levels and predictors of compliance and persistence among grass & tree pollen, and house dust mite immunotherapy users in real-life, and estimate costs of premature discontinuation.

**Methods:** A retrospective analysis of a community-pharmacy database from The Netherlands containing data from 6486 patients starting immunotherapy for one or more of the allergens of interest between 1994 and 2009. 2796 patients received SCIT and 3690 received SLIT. Time-to-treatment discontinuation was analyzed and included Cox proportional Hazard models with time-dependent covariates, where appropriate.

**Results:** 82% of patients did not reach the minimally required duration of treatment of three years (SCIT: 77%, SLIT: 93%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively. Of the persistent patients, 58 per cent were never late in picking up their medication from the pharmacy. Other independent predictors of premature discontinuation were prescription, with general practitioners prescribing longer persistence than those of allergologists and other medical specialists, multiple-allergen therapy, higher socioeconomic status, and younger age. Direct medication costs per nonpersistent patient were €3,800.

**Conclusion:** Persistence is better in SCIT users than in SLIT users. Further studies are needed to determine whether persistence can be improved by administering the therapy close to the patient’s home.

**P2383**

Changes in the prevalence of asthma, rhinitis and eczema in different age groups in Chinese schoolchildren

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Introduction: Little is known about the prevalence of allergic diseases in children of different ages. This study aimed to investigate the prevalence of allergic diseases in children over a wide age range in Chinese schoolchildren in Shijiazhuang city in Hebei Province in China. In a cross-sectional study, we studied 10824 Chinese schoolchildren, aged 6-18 years, using ISAAC questionnaire. We classified children into three age groups: 6-8 years, 9-12 years, and 13-18 years. Asthma symptoms had significantly decreased with age from 6-8 year age group to 13-18 year age group (ever wheeze from 7.9% to 2.8%, P < 0.001, current wheeze from 2.2% to 1.4%, cough from 11.6% to 10.6%, and ever asthma from 1.3% to 0.5%, P<0.001, respectively). Rhinitis symptoms had significantly increased with age from 6-8 year age group to 13-18 year age group (ever rhinitis from 11.2% to 16.4%, P<0.001, current rhinitis from 8.2% to 11.6%, rhinconjunctivitis from 3% to 3.5%, P<0.05, and hay fever from 3.3% to 4.8%, P<0.05, respectively). Rash and eczema symptoms had significantly decreased with age from 6-8 year age group to 13-18 year age group (rash ever from 2.7% to 2.0%, current rash from 1.8% to 1.0%, P<0.001 and eczema from 15.4% to 7.2%, P<0.001, respectively). The study shows that symptoms of asthma and eczema had significantly decreased with age in these children while rhinitis symptoms had significantly increased indicating that rhinitis symptoms are major public health problem in Chinese children. The study will help to implement intervention strategies to control symptoms of rhinitis in this population.

**P2384**

Phenotypic predictors for hospital admission in adults with asthma: A case-controlled study

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Background: RTIs are a known risk factor for admission with asthma exacerbation. Few studies give further insight to other possible risk factors.

**Aim:** To correlate asthma phenotypes with hospitalisation, in acute exacerbations of asthma.
Conclusions: Pulmonary function test changes after cessation of inhaled corticosteroid
asthma control. Cost and easily applicable questionnaires that are validated in the assessment of
CARATa and ACT test scores. This study highlights the importance of using low
significant association between subjective control of the disease and CARATt, score (CARATa) and ACT test (r=0.8, p
It may be possible that patient s with a FEV1 above 95% predicted
asthma Control of allergic rhinitis and asthma test, asthma control test and FeNO in
Asthma exacerbation is more likely in those who are atopic and
atopy and FeNO (p
Se Ig E levels and eosinophils were found to be positively correlated (p=0.027), however, no correlation was established between acute or convalescent Se IgE and duration of asthma, personal or family history of atopy (p<0.05). There is no significant difference between Se IgE levels in different BMI classes or in different age
groups (p<0.05). This study demonstrated a statistically significant association between subjective control of the disease and CARATt, CARATa and ACT test (p<0.05). It was demonstrated a statistically significant association between atopy/positive bronchodilatation test and FeNO values were higher (p<0.05).This study demonstrated a statistically significant correlation between the total CARAT (CARATa) and ACT test (r=0.7, p<0.05), as well as between asthma CARAT sub-score (CARATa) and ACT test (r=0.6, p<0.05). It was demonstrated a statistically significant association between subjective control of the disease and CARATt, CARATa and ACT test (p<0.05).

Methods: Control of allergic rhinitis and asthma test, asthma control test and FeNO in

Objective: Assessment of asthma and/or rhinitis control through the application of two questionnaires and the measurement of Fractional Nitric Oxide concentration in exhaled breath (FeNO).

Results: Ninety patients, 65.7% women, mean age 32.6±17.9 years. Of these, 63.3% had asthma and rhinitis, 24.8% had asthma and 11.9% had rhinitis. The mean FeNO was 36.4±24.4 ppb (min/max=4/115). 58.7% patients were atopic and a statistically significant association was established between atopy and FeNO (p<0.05). In patients with acute bronchodilatation test, FeNO values were higher (p<0.05). A positive correlation between age of asthma onset and a

P2388

Control of allergic rhinitis and asthma test, asthma control test and FeNO in

rhinitis that, in a two months period, visited a respiratory function laboratory to

to perform lung functional tests with measurement of FeNO and to whom were applied 2 questionnaires: Control of Allergic Rhinitis and Asthma Test (CARAT) and Asthma Control Test (ACT).

Results: 109 patients, 65.7% women, mean age 32.6±17.9 years. Of these, 63.3% had asthma and rhinitis, 24.8% had asthma and 11.9% had rhinitis. The mean FeNO was 36.4±24.4 ppb (min/max=4/115). 58.7% patients were atopic and a statistically significant association was established between atopy and FeNO (p<0.05). In patients with acute bronchodilatation test, FeNO values were higher (p<0.05).

Conclusions: Asthma exacerbation is more likely in those who are atopic and have a longer duration of asthma. This was not evident for smoking asthmatics and BMI. Convalescent Se IgE levels are higher in males post exacerbation.

Methods: We included 109 asthmatics admitted with an acute exacerbation over 14 months; matched for age and sex with a 100 well-controlled asthmatics from asthma clinic. Information on sociodemographic variables, clinical and laboratory data was collected. Acute and convalescent (at 6 weeks) titter of serum immunoglobulin E (Se IgE) and serum eosinophil count were taken. SPSS was used for statistical analysis.

Results: We detected a positive correlation between age of asthma onset and a

family history of atopy (p<0.0001) and a family history of atopy (p<0.023); but no correlation with Se IgE levels was found (p<0.05). There was no significant difference in the number of hospitalisations over the previous year between smokers and non-smokers (p=0.308). The difference between convalescent Se IgE levels in males (mean 324) and females (mean 159) was statistically significant (p<0.029). Acute Se IgE levels and eosinophils were found to be positively correlated (p<0.027), however, no correlation was established between acute or convalescent Se IgE and duration of asthma, personal or family history of atopy (p<0.05). There is no significant difference between Se IgE levels in different BMI classes or in different age groups (p>0.05). This study demonstrated a statistically significant association between subjective control of the disease and CARATt, CARATa and ACT test (r<0.05). It was demonstrated a statistically significant association between atopy/positive bronchodilatation test and FeNO values were higher (p<0.05).

Conclusions: Asthma exacerbation is more likely in those who are atopic and have a longer duration of asthma. This was not evident for smoking asthmatics and BMI. Convalescent Se IgE levels are higher in males post exacerbation.

Introduction: Parental passive smoking has been associated with adverse respira-
tory outcomes in children. Evidence remains inconclusive as to whether smoking is a risk factor for allergic disorders in children. The aim of the study was to evaluate the association between paternal smoking and symptoms of asthma and allergies in Chinese schoolchildren.

Body: We studied 10824 Chinese schoolchildren from Shijiazhuang city in Hebei province in China. We used an ISAAC questionnaire and we added questions related to paternal smoking. The prevalence of paternal and maternal smoking in China is 56.52% and 1.34%, respectively. The prevalence rates of all symptoms of asthma, rhinitis and eczema were significantly higher in children exposed to paternal passive smoking compared with children not exposed to paternal smoking (wheeze ever 6.5% vs 4.6%, P<0.001; current wheeze 2.3% vs 1.5%; exercise-induced wheezing 3.9% vs 2.4%, P<0.001; cough 13.2% vs 8.7%, P<0.001; ever rhinitis 15.3% vs 11.6%, P<0.001; current rhinitis, 10.8% vs 8.1%; hay fever 4.7% vs 3.7%, P<0.05; ever chronic rash 2.9% vs 1.8%, P<0.01; current rash 1.8% vs 0.9%; and eczema 12.9% vs 9.7%, P<0.001, respectively). The study which is part of a major longitudinal study on Chinese children shows an association between parental smoking and symptoms of asthma, rhinitis and eczema and that Paternal passive smoking is an important risk for asthma and allergic children in China.

P2389

Contribution of lung function tests in asthma screening: About a

respiratory panel

Introduction: The major difficulty in epidemiological studies of asthma is due to
the methods used to formulate the diagnosis. Studies conducted through ques-

Conclusions: In the absence of gold standard, it is difficult to define asthma in
epidemiological studies. If the measure of bronchial hyperresponsiveness has a specificity similar to questionnaires on asthma symptoms, it is also less sensitive.

P2389

Does allergens influence resistin levels in children with allergic rhinitis?

Conclusion: The purpose of this study was to confirm the relationship between resistin levels and atopy and to assess whether these levels were influenced by Skin Prick Test (SPT) patterns in children with nasal obstruction.

Methods: 35 children (15 males; mean age 9 yr) were selected for nasal obstruc-
tion: 12 monosensitized to house dust mites (HDM), 10 to grass pollens (GP) and
35 children (15 males; mean age 9 yr) were selected for nasal obstruction in 11 individuals, 7 of which were reversible. Fifty subjects gain more than 12% in forced expiratory volume (FEV1). Of these, 20 did not report symptoms of asthma but had symptoms of atopy. We deduce that 19.6% of asthmatics had a reversibility and 6.8% were asymptomatic.

Conclusions: In the absence of gold standard, it is difficult to define asthma in
epidemiological studies. If the measure of bronchial hyperresponsiveness has a specificity similar to questionnaires on asthma symptoms, it is also less sensitive.
were 5.5 ng/ml in children sensitized to HDM and 3.6 ng/ml in those sensitized to GP. This difference was statistically significant (0.001 < p < 0.01).

**Conclusions:** Our results confirm that serum resistin levels are associated with the allergic inflammatory process in children. Among patients with AR, higher resistin serum levels also showed a stronger association with HDM monosensitization. Thus, resistin, as a proinflammatory protein, may be influenced also by persistent allergen exposure.

**Results:** Resistin serum levels associated with HDM monosensitization. Our results confirm that serum resistin levels are associated with the allergic inflammatory process in children. Among patients with AR, higher resistin serum levels also showed a stronger association with HDM monosensitization. Thus, resistin, as a proinflammatory protein, may be influenced also by persistent allergen exposure.

**Methods:** Serum resistin levels were measured by ELISA in 100 children (50 with AR and 50 healthy children) with a mean age of 12 years.

**Results:** Resistin serum levels associated with HDM monosensitization. Our results confirm that serum resistin levels are associated with the allergic inflammatory process in children. Among patients with AR, higher resistin serum levels also showed a stronger association with HDM monosensitization. Thus, resistin, as a proinflammatory protein, may be influenced also by persistent allergen exposure.

**Background:** Asthma is a problem worldwide, with an estimated 300 million affected individuals. Obese and asthma are both chronic conditions affecting millions worldwide.

**Aim:** To assess serum leptin levels in obese and non-obese patients with bronchial asthma.

**Methods:** This study was performed on 120 asthmatic patients, 60 patients (50%) were obese and 60 patients (50%) were non-obese according to BMI. According to the GINA guidelines, they were classified into mild, moderate, severe and very severe asthma. Serum leptin level measurement for all patients was done after 8 hours fasting, by ELISA technique.

**Results:** Serum leptin level showed a significant increase in serum of obese asthmatics (23.2 ± 3.8) than non-obese asthmatics (7.9 ± 3.1). There was a highly significant increase in serum leptin level in obese asthmatic females than in non-obese asthmatic females with the same degree of asthma (p < 0.001). In obese asthmatic males, there was a significantly higher increase in serum leptin level in obese asthmatic females than in non-obese asthmatic males with the same degree of asthma (p < 0.001). Also, there was a highly significant increase in serum leptin level in obese asthmatic females than obese asthmatic males with the same degree of asthma (p < 0.001). In non-obese asthmatic females and non-obese asthmatic males with the same degree of asthma (p < 0.001). The results of this study showed a significant positive correlation between serum leptin level and grades of asthma as well as a significant negative correlation between serum leptin level and FEV1, FVC and FEV1/FVC (p < 0.001).

**Conclusions:** The high serum leptin level in asthmatic patients is related to and affected by; the high BMI, female gender and degree of asthma severity.

**Effectiveness of therapy:** The peak effectiveness of therapy was achieved after 6 months of treatment. In the group of patients who continued treatment, a significant improvement in pulmonary function was observed. The decrease in FEV1 and FVC was less pronounced in the group of patients who continued treatment for 6 months compared to those who discontinued treatment after the first 3 months.

**Conclusion:** The peak effectiveness of therapy was achieved after 6 months of treatment. In the group of patients who continued treatment, a significant improvement in pulmonary function was observed.

**References:**

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**P2395**

Epidemiological study of bronchial asthma among preparatory school pupils in Assuit district
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**Background:** The prevalence of asthma and allergies is increasing in both western and developing countries. Few studies evaluated asthma prevalence in Egypt.

**Aims:** Determination of the prevalence and risk factors of asthma among preparatory school children in Assuit district, in upper Egypt.

**Subjects and methods:** A cross sectional study was conducted among preparatory school students in Assuit city and two rural areas in Assuit governorate in upper Egypt. Twelve schools were selected randomly from different regions in Assuit city and two rural areas. The total coverage of the students included was 1048 (482 boys and 566 girls).

**Data were collected by self administered questionnaire (in Arabic Language) which was fulfilled by the participants.**

**Results:** Of the 1048 positively responding subjects, 65 fitted the diagnosis of asthma with over all prevalence of 6.2%. No significant difference was found between urban and rural areas (P: 0.075). A positive family history of allergy and the presence of other allergic disease were significantly associated risk factors for asthma.

**Conclusion:** Bronchial asthma is a significant health problem among children and adolescents in Assuit governorate and needs special care services. Wider scale multi-center studies in upper Egypt and other localities of Egypt are needed to outline the profile of bronchial asthma among children and adolescents in the whole country.

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**P2396**

The in vitro effect of vitamin D on peripheral blood mononuclear cell cytokine expression in COPD
Niall Steward, Richard Wood-Baker. Centre for Clinical Research Excellence (Respiratory), University of Tasmania, Hobart, TAS, Australia

**Background:** Vitamin D is recognised as a powerful modulator of immune responses. It promotes T helper 2 (Th2) immunity and the anti-inflammatory cytokine Interleukin-10 (IL-10). However, little is known about the effects of vitamin D on the immune response in COPD, a Th1 mediated disease.

**Aims and objectives:** We hypothesised that in COPD vitamin D would push a Th2 response, with increased levels of the Th2 cytokine Interleukin-4 (IL-4) and the suppressive cytokine IL-10. Such a shift could be beneficial in COPD.

**Methods:** We recruited 10 COPD subjects from whom we isolated peripheral blood mononuclear cells (PBMC) and measured serum 25(OH)D. PBMC were stimulated with antibodies to the T cell receptor either with or without added blood mononuclear cells (PBMC) and measured serum 25(OH)D. PBMC were stimulated with antibodies to the T cell receptor either with or without added

**Results:** For both IL-4 and IL-10, we observed a biphasic effect of vitamin D supplementation. For those with low (<30nmol/L) and high (>80nmol/L) serum 25(OH)D, added vitamin D suppressed IL-4 and IL-10 (Figure 1,2). Between these two levels, vitamin D increased expression.

**Conclusions:** Serum 25(OH)D levels may be an important determinant of the usefulness of vitamin D in beneficially modifying the immune response in COPD.

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**P2397**

Experience of surgical treatment of massive purulent-destructive processes of the lungs and pleura
Stanislav Skryabin. Murmansk Regional Hospital by P.A. Bayandin, Murmansk, Russian Federation

Given the conditions of the Far North and the specificity of the social status of some patients, we have extensive experience in the surgical treatment of massive, widespread purulent-destructive processes. Despite the possibility of treating this disease patients conservatively, performing minimally invasive procedures, we concluded that it remains relevant surgical radical intervention - lung resection, removal of empyema cavity, to prevent chronicity and recurrence of the process. We have experience treatment 679 patients: 340 conservatively, 369 surgically.

The main indications for radical surgery have been ineffective conservative therapy and the progression of the process, the recurrence of a chronic process, initially massive processes, life-saving operation: bleeding, a large pulmonary pleural fistula, the threat of sepsis (big abscess, gangrene and empyema).

We are get almost patiens fit for the operation (conservative therapy). We performed 380 operations: 151 lobectomy, 15 lobectomy, 64 atrial resections, 18 - segm-

mentectomy, 67 - pneumonectomy, 40 - decortications and elimination of empyema cavity without resections, 16 - VATS decortications, 9 - reimplantations stump of bronchus. We have good results after operations: only 5 patiens died (1.3%), 48 - complications (13%) (13 of them - inconsistence of stump of bronchus),360 patiens (97.6%) - after radical interventions recovered.

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**P2398**

Effectiveness of partial lung resection at multi-drug resistance of tuberculosis mycobacteria
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Partial resection of lung at multiple drug resistance of mycobacteria was performed in 59 patients (males 36, females 23) in ages 17 – 54 years. All the patients had fibrous-cavernous tuberculosis with long clinical course (over 3 years) and resistance of mycobacteria to isoniazid + rifampicin in 4 patients, to isoniazid + rifampicin + streptomycin – in 24, to isoniazid + rifampicin + streptomycin + ethambutol – in 31. The characteristic peculiarities of illness were dissemination (61.0%) and progress (45.8%) of the tubercular process, pulmonary hemorrhage (27.1%), various somonitant pathology (32.2%), and ineffective ofpreced-

ing long treatment. After pre-operative chemotherapy (pirazinamid + amicacin + ofloxacin + prothionamide + paraaminosalicylic acid + cycloceryl) with pneu-

moperitoneum, UV irradiation of blood, transfusion of protein, saline and synthetic solutions, a segmental lung resection was performed in 9 patients, lobectomy – in 38, combined resection – in 12. After operations, bronchial fistula and pleural empyema developed in 4 patients, early re-activation of tuberculosis – in 3. These complications were eliminated in 6 patients.

Good effectiveness of partial lung resection was reached in 58 patients (98.3%).

One patient (1.7%) died from the progress of post-operative pleural empyema and cardio-pulmonary insufficiency.
P2399
Lung resection in hematologic patients with pulmonary invasive fungal disease: Changing pattern in recent years
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Division of Hematology, University Hospital, Basel, Switzerland; 2 Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital, Basel Switzerland; 3 Division of Hematology, University Hospital, Basel, Switzerland; 4 Division of Infectious Diseases & Hospital Epidemiology, University Hospital, Basel, Switzerland; 5 Department of Pathology, University Hospital, Basel Switzerland.

Pulmonary invasive fungal disease (IFD) is a frequent complication in patients with hematologic malignancies. We analysed the outcome of 71 hematologic patients undergoing lung resection for suspected pulmonary IFD at a single centre and we compared patients operated before 2002 (group A n=41) with those undergoing surgery after 2002 (group B n=30). Forty-four patients were neutropenic and 41 had a platelet count below 50 x 10^9/L. 45 non-anatomical resections and 26 lobectomies were performed. Fungal infection was histologically proven in 53 patients. Reseption was needed in 4 cases: bronchial stump dehiscence, persistent air leak, chylolithorax and seoma. Minor complications at the site of surgery occurred in 14 cases. In only two cases there was an uncontrolled disseminated fungal infection. Overall mortality at 30 days was 7% (5/71). The age was significantly higher (group B 40y versus group A 49y, p=0.0239) in the recently operated patients and also the number of reoperations was significantly higher (group B versus group A 17% in group A vs 90% in group B, p<0.0001) was found between the two groups. Recently operated patients underwent VATS in 47% of cases as compared to 5% in group A. In contrast to group A there were 6 cases of rare fungal infections in group B (Case of histoplasmosis, 2 Rhizopus, Micor, Zygomycetes).

Conclusion: Lung resection is a therapeutic option for hematological patients suffering from pulmonary fungal infection with an acceptable morbidity and mortality. In recent years patients were older, sicker, VATS was performed more often and in a considerable number of cases rare fungi could be detected.

P2400
Argonplasma coagulation in surgery of pulmonary tuberculosis

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Background: Argonplasma coagulation (APC) proved itself to be a hæmostatic tool in various fields of surgery (Farin G., Grund K.E. 1994). Coagulation occurs without contact the active electrode with the tissue, while the flow argon displaces the zone of coagulation of oxygen, which reduces burning of tissue. The problem of bleeding in surgery of severe forms of pulmonary tuberculosis (PTB) is difficult and unsolved.

Aim: To study APC in this field and assess initial (first) results.

Method: APC was applied in 66 cavitary PTB patients with the help of High-frequency electrosurgical APC generator. Namely, in 13 pneumonectomies, in 20 lobectomies, and in 24 cases for debridement of empyema cavity including 12 videothoracoscopic procedures. In cases of firm adhesions pnumonectomy was performed using regimen BLEND cutting with coagulation. For haemostasis during lobectomies, and in 24 cases for debridement of empyema cavity including 12 videothoracoscopic surgeries BLEND cutting with coagulation was used.

Results: None of the patients were approached with thoracotomy and decortication is recommend. This may identify underlying causes.

Conclusion: Simultaneously transdiaphragmatic approach to liver and lung cysts
Yener Aydin1, Mine Celik 2, Ali Bilal Ulus 3, Atilla Ergul 4, and Nurlay Karacagol 5.

Department of Thoracic Surgery, Afyon Kocatepe University Medicine Faculty Hospital, Afyon, Turkey.

Results: None of the patients were approached with thoracotomy and decortication is recommend. This may identify underlying causes.

Conclusion: Simultaneously transdiaphragmatic approach to liver and lung dome cysts is a safe and effective treatment method

P2403
The management of postoperative complications in childhood pulmonary hydatid cysts
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Background: Hydatid disease in children has previously been discussed many times in the literature. However, management of postoperative complications has been rarely discussed. In this study, the complications of our cases are evaluated and discussed.

Material and methods: Ninety-seven patients under 16 years of age with hydatid cysts who were operated on between January 2001 and January 2007 were analyzed retrospectively. All the patients were followed up with examination and chest X-ray after surgery. The complications occurred in the first 48 hours after surgery are considered as early complications, and the complications between 48 hours and 30 days are considered as late complications.

Results: 61 male and 36 female pediatric hydatid disease patients with a mean age of 10.31 were operated on. Postoperative first 48 hours, atelectasis was observed in 17 cases (17.5%) and bronchoscopy was performed for these patients. After 48 hours, pneumonia occurred in one patient and he was treated with antibiotics. Prolonged air leak was observed in 4 patients (4.1%) and they were treated with continued tube thoracostomy. 2 patients with prolonged air leak were hyperventilated with positive pressure under general anesthesia. Wound infection was seen in 2 patients. Regular wound dressing and antibiotic treatment were performed for these cases. Empyema was occurred in 2 patients. In these cases antibiotics were given and tube thoracostomy was continued.

Conclusion: Atelectasis, which is most common postoperative complication, should immediately be treated. It should be kept in mind that early treatment of atelectasis prevents the development of greater complications in children.

P2402
Simultaneously transdiaphragmatic approach to liver and lung cysts
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Department of Thoracic Surgery, Ataturk University, Erzurum, Turkey; 2 Department of Anesthesia and Reanimation, Ataturk University, Erzurum, Turkey.

Background: Hydatid cysts are clinical problem at developing and non developed countries. Liver and lung are the two organs which they often settle. In this study we aimed to present lung and liver hydatid cysts which we underwent transdiaphragmatic surgery.

Methods: Consecutive 50 patients with lung and liver hydatid cyst whom underwent surgical treatment by transdiaphragmatical way at our clinic between January 1998 and December 2011 were evaluated retrospectively.

Results: Twenty-four (48%) patients were male and 26 (52%) patients were female. The average age of the patients was 34±21 (3-72 years old). All cases have liver cyst and 37 of them also have lung cyst. In 9 of the 37 patients with lung cyst, bile cysts were bilateral (17 patients). In patients whom have multiple cysts the largest cyst diameter has been 9±3.5 cm (4-18.40). Forty-eight cases of the patients were approached with thoracotomy, one of them is approached with laparotomy and one of them is approached with median sternotomy. In 49 cases it was interwoven to lung and in 1 case it was interwoven to lung by phrenotomy. Excessive biliary drainage was observed in postoperative 2 case. In one case fistulate was observed from drain path which is placed in liver cyst. Plevral effusion was observed in one patient. None of the patients was no hospital mortality. Average hospital stay was 9±4.38 (3-21 days).

Conclusion: Simultaneously transdiaphragmatic approach at lung and liver dome cysts is a safe and effective treatment method

P2401
TB empyema
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Background: Parapneumonic effusion mostly is resolved with medical management but sometimes became complicated. We studied the etiology and possible underlying causes of it.

Materials and method: Study on 81 patients with postneumonic empyema which required decortication carried out in Kashan, Shahid Beheshti General Hospital, from Oct 2006 to Dec 2011, Management of patients such as appropriate antibiotic, and thoracotomy and tube drainage was done in internal medicine ward. Complicated cases were referred to us for thoracotomy and decortication.

Conclusion: Partial resections at fibrous-cavernous tuberculosis with multiple drug resistance of mycobacteria is a highly effective method of treatment and it heals 98.3% of patients with chronic pulmonary pathology.
How severe pulmonary hemorrhage influence on surgical tactics at patients with lung abscess and gangrene

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Objective: How severe pulmonary hemorrhage influence on surgical tactics at patients with lung abscesses and gangrene. We retrospectively investigated 42 consecutive pre-school patients who underwent surgical treatment.

Methods: We retrospectively investigated 42 consecutive pre-school patients who were diagnosed and surgical treated for hydatid cysts in our clinic between January 1998 and December 2011. The authors present a group of 12 patients with destroyed lung secondary to tuberculosis and gangrene. The study assessed the efficiency of surgical intervention in the form of intrapleural cut of cavity (cut of abscess) with excision of externally walls of bronchial arterios.

Results: At 1797 patients with lung abscess without severe pulmonary hemorrhage operation of various chronic destructive lung disease. Of these, the tuberculosis was observed in 23 people, a chronic abscess - with 16 people, bullous disease - in 23 people, aspergilloma - with 3 people.

Conclusions: At 28 cases' cyst was in only one lung, in 5 cases' cyst was in single lung, in 35 cases cyst was in bilateral lungs. Average cyst diameter was 6.2 cm. It was interventioned to right lung and liver cysts by transdiaphragmatic approach. Conlusion:

Intrapleural cut of cavity (cut of abscess) with excision of externally walls of bronchial arterios. We have performed 8 pneumonectomies, 69 lobectomies, 16 wedge resections. Mortality = 6 patients (3.9%). From 68 patients with severe pulmonary hemorrhage 10 dead before operation. To another 58 patients at first we perform rengionenovascular embolization of bronchial arterios, then 16 pneumonectomies, 42 lobectomies. General mortality = 26 patients (38.2%).

Background: Hydatid cyst is a major health problem in developing countries and it usually settled in lungs in children. In this study we aimed to present our pre-school children cases with lung hydatid cysts that we underwent surgical treatment.

Methods: We retrospectively investigated 42 consecutive pre-school patients who were diagnosed and surgical treated for hydatid cysts in our clinic between January 1998 and December 2011.

Results: Seventeen (40.5%) patients were female and 25 (59.5%) patients were male. The average age of the patients was 5.2±1.3 (between 2-7 ages). The most common symptoms were cough (%74), chest pain (%26.2) and fever (%26.2). Twenty eight cases' cyst was in only one lung, in five cases cyst was in single lung and in six cases cyst was in bilateral lungs and liver, in three cases cyst was in bilateral lungs. Average cyst diameter was 6.2±2.4 (2.1-12 cm). It was interventioned to right lung and liver cysts by transdisphragmatic approach together in five cases. In different stance operation was performed to nine patients with bilateral cyst hydatid.

Conclusion: Surgery is the definite treatment of lung hydatid cyst. The most important way to protect against adverse effects of thoracotomy is to eliminate routes of transmission. The postoperative complications were very good, the mortality and morbidity rates being comparable with other pathologies.
evaluated until delivery at tertiary care centres. This approach guaranteed an easy admission and immediate surgical treatment in our Institute. CT and angi/CT were performed in all pts prior to operation to confirm diagnosis.

Results: All pts underwent open lateral thoracotomy (18 pts/lobectomy, 4pts/segmentectomy respectively). Age at intervention ranged 1-51 days (mean 10.6±7.2). CCAM localisation was: right lung lower lobe (7), left lung upper (6) and lower (1). Of those children. Following shows that early surgical intervention does not disturb development very well tolerated.

Conclusions: 1 Most CCAMs are diagnosed prenatally by means of routine USG analysis. 2 Early surgical treatment of CCAMs is safe and elective lobectomy appears to be very well tolerated. 3 Follow-up shows that early surgical intervention does not disturb development of those children.

P2411
Computed tomography-detected apical bullae in young men with Marfanoid phenotype
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Subpleural bullae in young men are often the cause of primary spontaneous pneumothorax (SP), which is one of the common thoracic surgical conditions requiring hospital admission. Screening and prevention SP have not been developed so far, because the lung bullae pathogenesis in young people is not known.

One hypothesis suggests a hereditary weakness of the connective tissue, the most developed so far, because the lung bullae pathogenesis in young people is not known.

Computed tomography (CT) performed 50 clinically healthy men with no episodes of primary SP in history. Marfanoid phenotype was diagnosed in identifying specific major and minor criterion (skeletal, skin, eye, vascular, and others), which together made it impossible to diagnose the full Marfan syndrome. Deficiency of alpha 1-antitripsin was rejected after a genetic test. The average age of the surveyed was 24 years. The men were smokers with a mean age of 24 years. The frequent maximal size of bullae was 0.5-1cm and the average number of bullae was 1-6. In almost all of the cases bullae were located in the apex. In 5 cases bullae were spread more extensively and were found up to the level of the carina and in 2 patients also bellow the carina. Correlation analysis confirmed the association between bullae and smoking history, as well as the severity of skeletal changes. These data confirm the importance of hereditary diseases of connective tissue in the genesis of bullous emphysema. CT scan may be useful for determining the risk and prevention of primary SP.

P2412
An extraordinary triplet and a single surgery: Lung cancer, retained bronchial foreign body and actinomycosis
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This unique and previously undocumented report illustrates an extremely rare co-occurrence of early staged-primary bronchial carcinoma, retained organic bronchial foreign body and actinomycosis on the right lower lobe of a patient in whom resection surgery was curative. A 67-year-old man was hospitalized to evaluate the etiology of recurrent pneumonia. Thoracic computed tomography revealed an ill-defined mass with heterogeneous density, invading nearly total of the right lower lobe. Fibroptic bronchoscopy showed a rigid, mobile, gray endobronchial lesion on the orific of right lower subsegments associated with dense granulation tissue. Histopathological examination of the biopsy from the upper segment was reported as bronchogenic carcinoma. Right lower lobectomy was performed. During the removal of the lower lobe, a hard, brownish foreign body was detected on the orifice of lower lobe subsegments. The foreign body was retained seed of "Cherry laure". Also in the parenchyma, focal fields of actinomycosis was detected. In cases with retained bronchial foreign body in whom chronic respiratory problems (actinomycosis as well) lead investigative approaches, a simple bronchoscopy may offer the chance of the diagnosis of an early-stage bronchogenic carcinoma. It is a debate to conclude that chronic retained foreign body is the cause of the neoplastic course.

P2413
Diaphragmatic plication for diaphragmatic eventration: An evaluation of mid-term results
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Diaphragmatic eventration is a rare congenital anomaly in the musculary portion of the diaphragm. Eventration of the diaphragm is occur due to congenital or acquired etiology, is thought to be caused by an acquired complete or in complete paralysis of the diaphragmatic leaf. Operative repair is indicated for adult patient who has symptoms. Classically thoracostomy approach and diaphragmatic plication have been the approaches of choice forsymptomatic diaphragmatic eventration. The aim of our study was to objectively assess our mid-term results of diaphragmatic plication for hemidiaphragmatic eventration with the use of PFT.

We performed 28 diaphragma plication and analysed pre and postoperative pulmonary function tests (PFT) at our instution between 2006-2012. All operation performed under lateral decubitus position and one lung ventilation. The classical approach was a posterolateral thoracotomy through 7th intercostal space. The thinned diaphragmatic leaf was repaired with plication. We compared pre and postoperative PFT, we found significant improvements in PFT results at 3 months after operation. We had no postoperative mortality or any other major complication. Diaphragmatic plication for hemidiaphragmatic eventration demonstrated significant midterm improvements in symptom and pulmonary function test results.

P2414
Complex surgical solution for thoracic wall necrotizing fasciitis
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Necrotizing fasciitis of thoracic wall is a severe disease which is associated with a high rate of mortality, especially for immunosuppressed patients. Multiple drainage incisions, excision of necrotic tissues and appropriate antibiotics represent the best therapeutic solution.

The authors present the case of a 43 years old male, diagnosed with left empyema secondary to pulmonary tuberculosis. A left tube thoracotomy was performed for drainage, followed by surgical empysema (secondary to increase air leaks) and necrotizing fasciitis surrounding the tube thoracotomy, which has extended to left hypochondrium. First, multiple drainage incisions were performed, with excision of necrotic tissues and antibiotics. Azonin's procedure was performed after, closing the left bronchus and the air leaks were stopped.

After 18 days, the thoracic wall wounds were healed, allowing left pneumonectomy to be performed. Sputum exam became negative soon after closing the left main bronchus.

Closing the left main bronchus using the Azonin's procedure stopped the air leaks, which led to decreased of microbial contamination of the thoracic wall wounds and good out-come.
P2415
Thoracoscopic video-assisted partial resection of rib for pain control in patient with atypical pulmonary and bone Langerhans histiocytosis
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Introduction: Langerhans histiocytosis (LH) is a rare disease that occurs in 1-2.2 millions of people, which affects mainly children and adults between twenty and forty years old. Bones affection is an rarely occurs.

Clinical case: A 19 year old female with severe pain and discomfort of left subskapular area. After CT procedure, it was found that there are bilaterally a great number of small diffusely scattered nodular lesions in the lung parenchyma and formations, destructed cortex on the 5-th rib with the suspected for histiocytosis X.

Treatment: A video-assisted thoracoscopic (VATS) partial resection of the fifth rib has been made, under three port. Lung biopsy has been made over several suspected lesions. The postoperative period has been uneventful. The pain and the discomfort were reduced.

Conclusion: VATS resection of the rib could be a good modern approach to eradicate or interference of pain in the rib LH. VATS remains the ultimate cross-cutting unique therapeutic approach for the treatment of the bone Langerhans-cellular histiocytosis and change the quality of life in these patients.

P2417
The role of video-assisted thoracic surgery on the diagnostic evaluation and the therapeutic management of thoracic injuries
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Aim: The aim of this study was to evaluate the experience of our institution with the use of video-assisted thoracic surgery (VATS) in chest trauma. 

Materials and methods: Between January 1999 and December 2011, 75,126 patients presented with chest trauma to the emergency room, and 6865 were admitted to our service. Fifty five (55) hemodynamically stable patients (0.8%) underwent VATS. They were 44 men and 11 women with an average age of 42 years (range, 19–67 years).

Results: Indications included post-traumatic hemothorax in 26 patients, and post-traumatic empyema in 7, treated after 24 h of trauma. Indications for exploratory VATS in the acute phase included suspected diaphragmatic injury in 6 patients, persistent pneumothorax in 5, continued hemorrhage in 8 and removal of intrathoracic foreign body in 3. There was no mortality and complications occurred in 8 patients (14.5%).

Conclusions: Management of hemodynamically stable thoracic injuries by using VATS provides diagnostic accuracy and therapeutic efficacy. It can be successfully applied in the trauma setting and surgeons should gain experience with its use.

P2418
Over 2000 cases of thoracic trauma – 10 years experience of a single clinical centre
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Objectives: We present the experience of our clinic in the diagnosis and treatment of thoracic trauma, there being some controversial issues in this field in medical literature.

Material and methods: This study encompasses 2156 cases admitted over a period of 10 years (2002 – 2011). Patients were analyzed in terms of sex, age, causative mechanism, as well as thoracic and extrathoracic lesions. Methods of diagnosis and surgical treatment, complications that occur, duration of hospital stay, and evolution under treatment are presented.

Results: Hospitalization due to thoracic trauma represents on average 21% of all admissions. Cases of polytrauma (35%) were managed by a multidisciplinary team. Regarding diagnostic tools, computerized tomography was used in 35% of the cases and bronchoscopy in 6%. Fine needle aspiration biopsy was used for the differential diagnosis of pulmonary contusions in 1.4% of the cases. The most frequent thoracic lesions were rib fractures, pleural effusions, and pulmonary contusions. Pleurotomy was most frequently used (47%) while thoracotomy was used in 8% of the cases operated upon. Complications affected 18% of the cases. 76% of patients that required over 3 weeks of hospitalization presented with extensive pulmonary contusion. Unfavorable results were seen in 4% of the patients while 2.6% of the patients died.

Conclusions: Thoracic trauma represents a difficult challenge, often with a surprising evolution. The diagnosis and application of the best surgical management, often with the help of a multidisciplinary team, is paramount. Associated pulmonary contusion prolongs hospital stay.

P2419
Spontaneous rib fractures
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Introduction: Other than trauma, rib fracture can occur in patients spontaneously due to a severe cough or sneeze. In this study, patients with spontaneous rib fracture were analyzed according to age, sex, underlying pathology, treatment and complications.

Materials and methods: 12 patients who presented between February 2009 and February 2011 with spontaneous rib fracture were analyzed retrospectively. The patients were evaluated according to anamnesis, physical examination and chest X-rays.

Results: 7 patients (58.4%) were male. The age of the patients ranged from 34 to 77 years (mean ± SD. 55.9±12.20). All patients had severe cough and chest
pain. Multiple rib fractures were detected in five patients (41.7%). The fracture were detected most frequently between 4th and 9th ribs. 8 (66.66%) patients had COPD; 2 (16.66%) patients had bronchial asthma and 2 (16.66%) patients had osteoporosis as well. The patients with COPD and bronchial asthma were treated with high dose steroids for over a year. Bone densitometry revealed high risk of bone fracture in all patients.

Conclusion: Spontaneous rib fracture due to severe cough may occur in patients with osteoporosis or with COPD and bronchial asthma receiving long-term steroid therapy. If these patients have severe chest pain, chest radiography should be evaluated for bone lesions particularly.

P2420
Analysis of 430 chest trauma patients in Kashan trauma center: 2003-2011
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Background: Chest trauma as a potentially life threatening injury is increasing with increased number of high-speed accidents in Iran.

Methods: 430 patients were treated for chest trauma (Mar 2003 and Dec 2011) patients’ age and gender, blood pressure, respiratory rate on admission, Glasgow Coma Scale (GCS) scores, types of trauma, the extent of intra thoracic injury, types of associated injuries, length of hospital and ICU stay, morbid conditions, and deaths were analyzed.

Results: 343 pt were male (80%).Mean age was 37.67±19.14. 305 patients (70.9%) had blunt and the rest (29.1%) penetrating chest trauma. (83patients (19%) had hemorhorax 53 patients (12%) pneumothorax and the rest were cardiac, (10%), great vessel (12%) and tracheal injuries (8%). Rib fracture was the most common thoracic injury with 270pt (63%), were treated with closed thoracotomy drainage 65 patients (15%) had hemorhorax and lung contusion, whoever 42patients (11%) of penetrating injury and lung contusion leads to empyema, who need thoracotomy with decortications and diaphragmatic repair Motorcycles and car accidents were the most common etiologic causes in 331 (76%).

The most frequent extra-thoracic injury with (33%) was pelvic and limb injuries, while (25%) needed surgical intervention during the first 24 hours. The most common operation was laparotomy. Mean duration of hospital stay was 7.49±4.75 days (range: 1-70) and ICU stay 19.71 days. Overall mortality was (1.7%) Conclusion: Chest trauma is a major preventable cause of mortality and morbidity in our country. Systolic blood pressure ≤90, pulse rate ≥120, respiratory rate ≥29, GCS ≤8 at the time of admission, and blunt type of trauma were found as the predictors of mortality and morbidity.

P2421
Our first steps in osteosynthesis of fractured ribs using Matrix Rib technologies
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Objective: Surgical management of multiple fractured ribs is the one of the undecided questions of thoracic trauma.

Aim: Illustration of our experience of osteosynthesis of fractured ribs using Matrix Rib technologies.

Materials and methods: Since December 2011 we have operated 5 patients. All they had blunt thoracic trauma with multiple fractured ribs and other injuries. Number of fractured ribs was from 4 to 9. Three patients had bilateral rib fractures. Also, 2 patients had hemorhorax, 1 patient had fracture of sternum, and 1 patient had rupture of left cupula of diaphragm. The middle terms from moment of trauma to operation were 1.5 days. To all of patients we have applied Matrix Rib technologies for rib osteosynthesis. The number of synthesized ribs was from 2 to 5.

Also we have performed 3 thoracoscopy (1 including suturing of diaphragm) and 1 osteosynthesis of sternum. Results: We have observed all 5 patients during postoperative period. The average of ventilation days was 2.4. There were no respiratory or wound complications. All patients had early activation. The respiratory function improved rapidly, increase of FVC before discharge was 25%. Long-term results didn’t show any significant respiratory function.

Conclusion: The osteosynthesis is the indicated operation at multiple and bilateral rib fractures. It helps to early activation, prevents complications and improves respiratory function.

P2422
Predictive factors for succeeded thoracoscopic treatment in patients with retained hemothorax-experience from two centers
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Introduction: In 5–55% of retained hemothorax cases the chest tube doesn’t allow adequate evacuation of hemothorax. Video-assisted thoracis Surgery (VATS) decreases the need of thoracotomy in these cases.

Aim of study: A retrospective analysis of patients, operated on for retained hemothorax, was performed in two thoracic surgery centers in order to investigate the predictive factors for succeeded VATS treatment.

Materials and methods: For five years period a total of 50 patients were operated on for retained hemothorax (35 by VATS and 15 by thoracotomy). The demographics and clinical parameters (age, sex, type of trauma, side of hemothorax, days after chest tube insertion, diameter of chest tube, antibiotic use, quantity of hemothorax, additional diaphragmatic injury, ribs trauma, days after trauma, injury severity score and abbreviated injury severity score) of all cases were investigated with univariate analysis by logistic regression analysis (statistical significance when p<0.05).

Results: The perioperative antibiotic prophylaxis (OR, 2.4[1.9-4.9]; p=0.03), the volume of hemothorax >900 cc. (OR, 4.2[1.6-8.9]; p=0.01), the diaphragmatic injury (OR, 3.4[2.0-8.6]; p=0.04) and the period between the trauma and surgery (OR, 4.8[3.4-12.1]; p<0.001) were found to be the leading factors predicting conversion to thoracotomy.

Conclusion: VATS is effective in patients with performed perioperative antibiotic prophylactic, with no diaphragmatic injury, early performed chest tube drainage and hemothorax with volume less then 900 cc.

P2423
Bronchoscopic approach in the treatment of postoperative bronchopleural fistula
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Aim: Bronchopleural fistula (BPF) is one of the worst complications of thoracic surgery. Its incidence is between 0.8-15%. Its mortality can reach up to 70%. Most important reason of death is accompanying aspiration pneumonia or ARDS.

Method: Consecutive 13 cases that were treated bronchoscopically due to postoperative bronchopleural fistula were evaluated.

Results: Twelve of the patients were male. Mean age was 55.6 (35-71). Fistula was located at the right in 9 cases while located on the left in 4 of them. Reoperation was applied to seven of the cases for squamous cell carcinoma, one of the cases for adenoacarcinoma, one of the cases for aspergilloma and one of the cases for tuberculosis sequel. Silicon Y stent was placed in two and straight silicon stent was placed in one of the cases. In one of the cases in which empyema surgery was applied, lingula segments were closed by suture. Small size fistula was closed by coagulation. Three of the cases were died 6, 35 and 94 days after the stent insertion. Procedures were successful in eight, partly successful in one and not successful in four of the cases.

Conclusion: If surgical reconstructive repair could not be done in postoperative bronchopleural fistula, mortality is high. In these cases, bronchoscopic treatment is the only treatment option. Cure can be obtained in some of the cases in which infection control is maintained. Survival is significantly increased in cases with wide fistulas after stent insertion.

P2424
Stratification of risk factors of developing of bronchopleural fistula after pneumonectomy
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Background: It is known that bronchial stump fistula (BSF) is general causes of efficacy decrease of surgical treatment of pulmonary cancer. Stratification of patients with local distributed and disseminated cancer forms of any localization is scientifically proved and it allows to determine heterogeneity of patients’ group
in relation to the nearest and remote prognosis as well as to work out volumes of surgical treatment into practice.

Methods: Stratification data of risk factors of bronchial stump failure (BSF) development in 575 patients, who underwent primary pneumonectomy in this article were presented. Control group (CG) consisted of 477 patients, 390 patients of them had different tumors of the lungs and 87 patients had parulent diseases of the lungs. The main group (MG) consisted from 98 patients. Formation of risk groups depending on localization of disease showed that in the planning of left sided PE minimum risk was determined in 258 (67.9%) patients, mean risk - in 83 (21.8%) patients and maximum risk - in 39 (10.3%) patients.

Results: An incidence of BSF after PE in patients of CG accounted for minimal risk 1.3%, at an average – 16.0%, and maximal – 32.3%, in its turn, an implementation of factor estimation of risk degree of development of BSF after PE in MG allowed to reduce an incidence of this complication until 0.0%, 2.6% and 9.1% respectively.

Conclusion: Peculiarities of a tactics of surgical intervention in PE must be determined strong in accordance with risk degree of development of BSF and, depending on the latter, include various in their efficacy of hermetization as well as work volume of accomplishment methods of suturing bronchus stump and consolidation of suture line.

P2425
Extremely rare complication of pulmonary resection: Systemic tumor embolization (A case report)
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Introduction: Determining of systemic tumor embolization during pulmonary resection is a rarely seen situation. Tumor emboli of metastatic tumors of the lungs are extremely rare unlike to primary lung cancers. Herein, we presented a case of systemic tumor embolism during metastasectomy of Ewing’s sarcoma.

Case report: A 41-year-old man underwent right lower lobectomy for Ewing’s sarcoma of the anterior chest wall. Then he was followed-up for three months period. The patient underwent metastasectomy for nodular lesion of right lower lobe after four years from initial resection. He was hospitalized again for the symptoms of dyspnea and pleuritic chest pain six months after the first metastasectomy. Computed thorax tomography was revealed metastatic recurrence involving the entire right lobe. Then the patient underwent a right lower lobectomy. In the operation, when we divided the right lower pulmonary vena after dissection, we did not see any bleeding. In second postoperative day, he had a severe left leg pain. There was no pulsation of dorsalis pedis artery and the lower extremity ulcer was seen. In fourth postoperative day, the patient had left leg pain, dyspnea with intercostal retractions. Breathing sounds were diminished at the right hemithorax. Distal part of the NGFT was seen at the pleural space via thoracostomy system in chest X-ray. Pleural effusion and pneumothorax were also determined. NGFT was removed immediately and chest tube thoracostomy was applied. Medical therapy was rearranged due to the patients clinical situation. NGFT must be applied with care also chest X-ray controls may be helpful for prevention morbidity and mortality of malposition.

P2427
Delayed traumatic diaphragmatic hernia: Case series
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background: Traumatic diaphragmatic rupture after blunt trauma is an uncommon condition, and often is initially missed diagnosis. We report 5 cases of traumatic diaphragmatic rupture after blunt injury 20±6 years prior to admission.

Case 1: 37-year-old man with chronic vomiting abdominopelvic pain and recently thoracic empyema, he had car accident 2 years ago. Left thoracotomy revealed small perforation of stomach which repaired and reduced in abdominal cavity, then diaphragm repaired (fig. 1).

Case 2: 25-year-old man with multipli injury 2 years ago admitted for acute abdomen. Thoracotomy revealed oniomoc and transverse colon left hemi thorax (fig. 2).

Case 3: 43-year-old female with chest trauma in car accident at right posterolateral thoracotomy revealed herniation of right liver lobe (fig. 3).

Case 4: 29-year-old female with chest trauma and rib fractures in 3 year ago left thoracotomy revealed herniation of omontome left liver lobe some part of left coloc and stomach after reduction of this organs diaphragm repaired (fig. 1).

Case 5: 47-year-old man with history of vomiting abdominopelvic pain abd dyspnea in barium study stomach. Spleen transverse, colon small bowel lie in left hemi thorax with left l thoracotomy this organs reduced diaphragm also repaired (figs. 4-7).

Case 6: 67-year-old man with history of vomiting abdominopelvic pain, respiratory insufficiency, sepsis he had car accident 16 years ago left posterolateral thoracotomy was done due to stomach torsion gangrene was happened. after operation the patient die.

Conclusion: In patients with gastro intestinal complaints and history of chest and abdominal trauma, must have high index suspicion to diaphragmatic injury.

P2428
The pleura and rheumatoid arthritis: A case series
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Background: Pleurisy is observed in almost 30% and effusions can be recurrent, occasionally leading to fibrothorax in chronic seropositive rheumatoid arthritis [Chest 1991; 100:235-238]. Pulmonary nodules occur in up to 5%, 50% cavitating to cause pneumothorax, haemoptysis or bronchopleural fistula.

Recurrent pneumothoraces and effusions are difficult to manage by surgical decortication [1 Thor Cardiovasc Surg 1975; 6:347-354].

Case series: We report four cases of chronic seropositive rheumatoid arthritis on longterm immunomodulator therapy, presenting with pleural effusions which were prone to recurrence & complicated by development of pneumothorax. The common theme was all had chest drains inserted initially, then surgical pleurodesis, re-presented with recurrent pleural effusions draining purulent material after failed pleurodesis and had indwelling pleural catheters inserted. One isolated Aspergillus species and died of multiorgan failure; the rest were left with indwelling chest drains.

Discussion: Our case series highlights the paucity of evidence in management of complicated rheumatoid pleural disease and calls for registries of interventions for
such patients. It is important to initiate early conservative approach in management of rheumatoide pleural effusions as surgical management is problematic due to trapped lung and pleural rind. Opportunistic infections in the context of an ever of rheumatoid pleural effusions as surgical management is problematic due to such patients. It is important to initiate early conservative approach in management of pleural effusion pH, Karnofsky score and the degree of pleural involvement were investigated. The last one was defined from 0 (minimum) to 3 (maximum) for each parietal, visceral and diaphragmatic pleuras at the time of thoracoscopic.

Background: Postoperative pulmonary complications (PPCs) following cardiothoracic surgery remained to be alarmingly high. This study was done to determine the risk factors associated with PPCs following cardiothoracic surgery in children 6 years old and below who underwent cardiothoracic surgery from November 1, 2010-October 31, 2011 at the Philippine Heart Center.

Methods: A prospective cohort study was done among 120 patients. Thirty five risk factors were included. Outcome measures included postoperative pulmonary complications. Comparisons of categories between with and without postoperative complications were done using Chi-square and independent T-test for all continuous variables. All independent variables were entered into a binary logistic regression model.

Results: The incidence of PPCs in this study is 73%. The history of respiratory tract infection (RTI), preoperative mechanical ventilation, high pulmonary artery pressure (PAP), hypertension, hypercoagulability, lymphocytopenia, prolonged protime, hypoalbuminemia, high ASA and RACHS-1 scores, prolonged postoperative mechanical ventilation, recovery room (RR) stay, pediatric intensive care unit (PICU) stay and length of postoperative hospital stay were associated with PPCs. Tidal breathing analysis was not found to be significantly associated with PPCs.

Conclusion: Fourteen out of the 35 risk factors were associated with PPCs in children 6 years old and below. With the incidence of PPCs remaining to be high especially in the lower pediatric age group, knowing the risk factors of its occurrence is of paramount importance.

P2430 The retrospective analysis of reasons of prolonged air leakage after pulmonary resection
Armen Benyan1, Evgeny Korymasov1, Sergey Pushkin1
Chair of Surgery, Samara State Medical University, Samara, Russian Federation; Department of Thoracic Surgery, Samara Regional Clinical Hospital, Samara, Russian Federation

Objective: Prolonged air leak is one of the most frequent complications after pulmonary resections. The aim of our study is to identify the reasons of prolonged air leak by carrying out a retrospective analysis of cases with such complication.

Materials and methods: We have studied 878 case reports of patients, who underwent pulmonary resection, for last 10-year period (2002-2011). The patients had chronic non-specific lung diseases – 266 (30,3%), interstitial lung diseases – 192 (21,9%), tumors – 182 (20,7%), purulent diseases of lung – 112 (12,7%), parasitic diseases – 71 (8,1%), tuberculosis – 55 (6,3%). We have performed: 218 lobectomies, 25 segmentectomies, 271 open and 364 VATS wedge resections.

Results: Prolonged air leak we have observed at 85 patients (9,7%). The reasons of prolonged air leak were integrated into 3 groups: a) reasons due to inadequate drainage functioning – 21 patient (2,4%); b) reasons due to thoracic wall – 2 patients (0,2%); c) reasons due to operated lung – 62 patients (7,1%). At 68 patients the problem was eliminated by use of different therapeutic and auxiliary methods. Re-operation was needed at 18 patients (2,0%). During re-operation we have also revealed: migration of drainage – at 3 patients, pulmonary fistula on resection line – at 9, unnoticed bulla on previous operation – at 1, lung destruction with bronchopleural fistula – at 2, lung laceration because of pleural adhesions – at 2, perforation of lung tissue with drainage – at 1 patient. The pathologic reason of prolonged air leak was eliminated in every case.

Conclusion: Identification of reasons of prolonged air leak assists to timely application of different curative methods for its elimination.

P2431 Karnofsky score, pH and degree of pleural involvement as prognostic factors for survival in patients with malignant pleural effusions
Alekseandr Yanuklin1,2, Anastas Chapkanov1, Krassimir Mourdjev3, Angel Chekanov1, Dainis Pētrovs4

Objective: The patients with malignant pleural effusions (MPE) have a short survival which is influenced by different factors. We investigate the prognostic value of pleural effusion pH, Karnofsky score and pleural involvement in these patients.

Methods: A prospective study was carried out for the period of 2.5 years. A total of 100 MPE patients were treated by video-assisted thoracoscopic surgery with or without pleurectomy in case of trapped lung. Their preoperative fluid pH, Karnofsky score and the degree of pleural involvement were investigated. The last one was defined from 0 (minimum) to 3 (maximum) for each parietal, visceral and diaphragmatic pleuras at the time of thoracoscopic.

Results: The overall survival of 21 months in patients with pH>7,40 was statistically longer compared to the 15 months in patients with pH<7,40 (p<0,001). Patients with Karnofsky score 10-30 had overall survival up to 6 months, instead of these with Karnofsky score 70-80, who were alive for 21 months. The patients with scores 40-50 and 60 have a survival between 10 to 17 months. A coherence were also found between fluid pH and Karnofsky score and index of correlation equal to 0,5636, also between Karnofsky score and degree of pleural involvement with index correlation 0,766 and pH and pleural involvement with index equal to 0,6749.

Conclusion: We can conclude that some preoperative factors (pH and Karnofsky score) and intraoperative one (degree of pleural involvement) can be useful as prognostic factors for survival in MPE patients.

P2432 Late radiation injury in preoperative chemoradiotherapy
Yunika Takahashi, Ei Miyamoto, Takeya Terashii, Hiroshi Hamakawa
Thoracic Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

Background: Preoperative chemoradiotherapy (CRT) seems to increase survival rates in advanced non-small cell lung cancer. In the evaluation of this study, overall survival (OS) and early complications are generally referred. However, the influence of induction CRT remains controversial. Therefore, the aim of this study is to identify the reasons of prolonged air leak after thoracic surgery. The incidence of this complication is 16.3% in all patients.

Methods: From 1996 to 2010, 167 patients treated with major lung resections after CRT (139 lobectomy, 24 pneumonectomy, 3 wedge resection, and 1 segmentectomy) were enrolled. They were treated with platinum-based regiments and had 40 Gy delivered to the primary tumors, hilum and mediastinum. The postoperative condition of residual lungs was assessed in 142 cases.

Results: 72 patients died. Of 72, 49 died of lung cancer, 17 died of other disease, and 6 died of postoperative complications (operative mortality was 3.0%). Of other disease death, 3 aspergilllosis and 2 idiopathic pulmonary fibrosis were related to induction therapies. The 5-year OS rates of p-stage 0, 1a, 1b, 2a, 3a and 3b were 72%, 62%, 52%, and 42% respectively. The 5-year OS rates of p-N0, N1, and N2 were 69.5%, 50.7% and 22.0% respectively. In 142 cases assessed postoperative condition of residual lungs, 27(19.0%) mild fibrosis, 36(3.5%) severe fibrosis, 37(26.1%) shrinkage, and 96(3.5%) cavitated dead score formation occurred. Radiation injury appeared when residual normal lung was irradiated.

Conclusions: Preoperative CRT increased survival rate in patients who achieved p-N0, but was associated with higher rates of pneumonectomy and operative mortality. Radiation might affect postoperative devastation in residual lungs. This therapy should be performed cautiously.

P2433 Enlarging the lung donor pool by using extended criteria donors: a single-center study
Jana Somers1, Caroline Meers1, Shana Wouters1, Stijn Verleden2, Annemie Vaneylen2, Bart Vanaudenaerde2, Geert Verleden3, Dirk Van Raemdonck4,4
Laboratory for Experimental Thoracic Surgery, KULeuven, Vlaams-Brabant, Belgium; Laboratory for Pulmonary, KULeuven, Vlaams-Brabant, Belgium; Division of Pneumology, UZ Leuven, Vlaams-Brabant, Belgium; Divison of Thoracic Surgery, UZ Leuven, Vlaams-Brabant, Belgium

Previous studies have reported comparable medium-term outcome after lung transplantation (LTx) from extended-criteria donors (ECD) when compared to standard-criteria donors (SCD). However, long-term outcome after LTx from ECDs is not well studied. All effective heart-beating lung donors within our hospital network between 2006 and 2007 (n=50) were classified (SCD, n=23; ECD, n=27) according to the criteria listed in Table 1. Lung recipients were followed up to 5 years. Survival, rates of acute and chronic rejection, pulmonary function (VC, FEV1), total and differential cell count and IL5 levels in BAL were compared between groups. IL8 concentration was measured in BAL using standard ELISA. Differences in donor groups were assessed using Fisher’s exact test, unpaired t-test, Mann-Whitney test or repeated measurements ANOVA. Survival curves were calculated with the Kaplan-Meier method and compared using the log-rank test.

No significant differences were seen in 5-year survival (87% vs. 70%; p=0.14).
freedom from BOS (70% vs. 63%; p=0.44), rate of acute rejection, pulmonary function, total and differential cell count of lymphocytes and neutrophils between lung recipients from both donor groups. A significant difference in the course of IL8 concentration over time after LTx was observed (p=0.002) between SCDS and ECDs. The acceptance of ECDs doubled the number of transplants performed annually.

This policy did not negatively influence long-term results after LTx.

P2434
Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation
Thomas Fuehner1, Christian Kuehn2, Tobias Welte3, Gregor Warnecke2, Jens Gottlieb1, Christian Kuehn2, Karen Olsson1, Igor Tudorache2, Tobias Welte3, Gregor Warnecke2, Jens Gottlieb1.

Endotracheal intubation in patients with end-stage lung disease before lung transplantation (LuTx) is associated with a poor outcome. New bridging strategies of critical patients are of major interest.

We performed a retrospective, single-center, intention-to-treat analysis of consecutive LuTx candidates with terminal respiratory or cardiopulmonary failure receiving "awake ECMO" support. The outcomes were compared with a historical control group with conventional mechanical ventilation (MV group).

Twenty-six patients (58% female, median age 44 years, range 23-62) were included in the awake ECMO group and thirty-four patients (59% female, median age 36 years, range 18-59) in the MV group. The duration of ECMO support or mechanical ventilation, respectively, was comparable in both groups (awake ECMO: median 9 days; MV: median 15 days; p=0.02). Six of 26 (23%) patients in the awake ECMO group and 10/34 (29%) patients in the MV group died before a donor organ was available (p=0.20). Survival at 6 months after Tx was 80% in the awake ECMO group versus 50% in the MV group (p=0.02).

P2435
Rehabilitation after lung transplantation with extracorporeal membrane oxygenation
Martin Daesch1, Thomas Fuehner1, Tobias Welte1, Gregor Warnecke2, Jens Gottlieb1, Christian Kuehn2, Karen Olsson1, Igor Tudorache2.

Extracorporeal membrane oxygenation (ECMO) is applied in respiratory failure before lung transplantation (LTX). The success of pulmonary rehabilitation (PR) following LTx with ECMO is unknown. Hypothesis: a 3-week inpatient PR in ECMO-treated patients is as efficient as in conventional transplanted.

Following LTx, 26 patients (12 female, median age 58 years, range 30-69) were included in the awake ECMO group and thirty-four patients (59% female, median age 51 years, range 27-74) in the MV group. ECMO: median 9 days; MV: median 15 days; p=0.02. Six of 26 (23%) patients in the awake ECMO group and 10/34 (29%) patients in the MV group died before a donor organ was available (p=0.20). Survival at 6 months after Tx was 80% in the awake ECMO group versus 50% in the MV group (p=0.02).

Figure 1. Kaplan-Meier curve.

Patients in the awake ECMO group required shorter postoperative mechanical ventilation (p=0.04) and showed a trend towards a shorter postoperative hospital stay (p=0.06). Extracorporeal membrane oxygenation (ECMO) support in awake and non-ventilated patients is a new and promising strategy for bridging patients to LTx.

P2436
Prevalence of sleep apnea – Hypopnea syndrome among lung transplantation candidates
Ana Hernández Vieh1, Pedro Benavides Matas2, Maria Dolores Hisado Diaz3, Soreya Jorda Sanchez1, Alicia De Pablo Gafas4, Jesus Muñoz Méndez5, María Josefa Diaz De Atauri Rodríguez6.

Sleep and Lung Transplantation Units.

Aim: To analyze the prevalence and possible associated factors with the Sleep Apnea – Hypopnea Syndrome (SAHS) among patients evaluated for Lung Transplantation (LT).

Methods: Transversal descriptive study of a cohort of patients evaluated for LT, with a standard polysomnography (PSG), from September 2008 to February 2012. SAHS was defined as the presence of Apnea Hypopnea Index (AHI) ≥ 10 and excessive daytime sleepiness symptoms. Severity of these symptoms was evaluated by Epworth sleepiness scale. Anthropometric, clinical and blood test measurements were also analyzed in all patients.

Results: During this period a number of 52 patients were studied. 50% of them were male, average age was 54.8 years (SD ± 9.96). Principal LT indication pathologies were due to COPD (46.2%), Pulmonary Idiopathic Fibrosis (15.4%) and Usual Interstitial Pneumonitis (11.5%). PSG were performed with supplementary oxygen in 96.2% of the cases. AHI average was 8.26 (SD ± 9.96). SAHS was diagnosed in 13 patients (25%). Among these, 8 (61.5%) had COPD. Next table shows relationships between groups and principal analyzed variables.

Conclusions: In this series of LT candidate patients, prevalence of SAHS is high. We have not found anthropometric, clinical nor blood test data significantly associated with the diagnoses of SAHS which can contribute to make a clinical pretest suspect. Performance of a standard polysomnography in LT candidates is probably recommendable.

P2437
Coping strategies in patients awaiting lung transplantation
Torunn Stavnes Soyseth1, May Britt Lund1, Oystein Bjortuft1, Vidar Soyseth1, Aasta Heldal1, Geo Kulli1, Hauagst. Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, Oslo, Norway Medical Decision, Akershus University Hospital, Lørenskog, Norway Faculty of Health Science, Oslo and Akershus University College, Oslo, Norway

Introduction: Living with severe lung disease is a stressful situation. Constraint coping strategies may constitute an additional burden. We aimed to describe coping strategies in patients awaiting lung transplantation

Material and method: A national cohort of 121 consecutive patients was screened by psychometric questionnaires as part of the work-up for lung transplantation during the period 2006-2010. 86 of the patients scored the Ways of Coping Questionnaire (WCQ) (Lazarus and Folkman 1988). WCQ measures 8 different coping strategies (N=86).

Conclusions: In this series of LT candidate patients, prevalence of SAHS is high. We have not found anthropometric, clinical nor blood test data significantly associated with the diagnoses of SAHS which can contribute to make a clinical pretest suspect. Performance of a standard polysomnography in LT candidates is probably recommendable.

P2438
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Conclusions: In this series of LT candidate patients, prevalence of SAHS is high. We have not found anthropometric, clinical nor blood test data significantly associated with the diagnoses of SAHS which can contribute to make a clinical pretest suspect. Performance of a standard polysomnography in LT candidates is probably recommendable.
The patients had higher scores in emotionally-focused coping strategies than healthy references. This may be of clinical importance when it comes to understanding how patients deal with postoperative challenges.

**P2438**

The impact of smoking relapse on the outcome after lung transplantation

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Lung transplantation (LTx) is a treatment for end-stage lung diseases. Smoking free period of 6 months is required to be listed for LTx. We however reported that 17% of former smokers resume smoking after LTx. The current aim is to re-evaluate the prevalence of post transplant smoking resumption and the impact on outcome after LTx with as main parameters chronic rejection, solid tissue cancer.

All 335 LTx recipients currently in follow-up in our center were included and evaluated for past and current smoking habits by a questionnaire and an eCO measurement with an electrochemical (Bedfont ECSO, pieCO-V Smokekeyer) sensor (eCO > 10 ppm was considered positive). The association between smoking and solid tissue cancer was tested using a contingency table (GraphPad prism 4.0). 213 patients (65%) smoked before LTx of which 144 had COPD (43%). 35 patients (11%) reported smoking post-LTx of which 32 were transplanted for COPD (91%), 14 (4.2%) were current smokers. eCO was elevated in 23 patients of whom only 10 patients admit that they smoke.

Second-hand smoking was reported in 33% of the total population and 86% of the active smokers (78% had a smoking family member).

In the 35 patients admitting smoking post-LTx, 10 patients suffered from chronic rejection (28% compared with 25% of the total population) and solid tissue cancer was reported in 6 patients (17% compared with 7% of the total population) (p=0.03), median follow–up time in both groups is comparable. 11% of patients smoked after LTx, especially the COPD patients. There increased risk for de development of a solid tissue cancer. There is a discrepancy between the eCO and there questionnaire therefore combining with urinary cotinine seems to be necessary.

**P2441**

Use of immune cell function assay in immune surveillance of lung transplant recipients: Correlations with clinical outcome and other immune assays

Francesco Bini, Annmari Mäkinen, Riina Di Donato, Monica Mostromi, Tiberio Oggionni, Manuela Cova, Luisetti Maurizio, Federica Meloni. Haematological Pneumological & Cardiovascular Science - Section of Pneumology, University of Pavia & Foundation IRCSS Polliclinico San Matteo Pavia, University of Pavia, Italy

Introduction: Infection still remains a significant cause of morbidity after lung transplantation. The Cylex ImmunoKnow assay (IKA), provides a global assessment of CD4 T cell immune function to help monitor the immune reactive capacity of graft recipients. We use IKA in the immunological follow-up of lung recipients. We assess clinical utility of IKA and correlate its results with other immunological parameters.

Methods: IKA was always performed on clinical demand. From October 2008 to February 2012 we performed IKA on 110 samples. The values of CD4+ T cell activation were classified as strong (> 520 kc/s cell) and low (< 225). Than we correlated a subgroup of 74 IKA samples with CD4+ cells, CD8+ cells, ratio CD4+/CD8+, NK cells, CD4+CD25hiCD127low cells in blood and BAL.

Results: High correlation between lower values and the occurrence of infectious episodes was observed (p<0.05).

Number of infections and IKA levels

<table>
<thead>
<tr>
<th>Infections</th>
<th>No low IKA</th>
<th>No moderate IKA</th>
<th>No strong IKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infecions</td>
<td>80</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Non infections</td>
<td>30</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>54</td>
<td>42</td>
</tr>
</tbody>
</table>

Instead, no correlation was found with the biopsy confirmed diagnosis of acute rejection.

Values of IKA did not correlate with levels of tacrolimus (P=0.8).

Similarly, only a trend toward an inverse relationship was present with CD4+ cell counts.

As for Treg cells counts, again no significant correlation was present.

Of note in 81% of low IKA results, the test was the basis of a change in the immunosuppressive regimen.

Conclusion: IKA values are helpful in identifying patients at high infectious risk and can be used to adapt IS regimen to patient need.

**P2442**

Effect of the type of end-stage lung disease on postoperative evolution of lung transplantation patients

Marc Brosseau, Thomas Vandemoorte, Charles Poirier. Department of Medicine (Respirology Division), Centre Hospitalier de l’Université de Montréal (CHUM), Montreal, QC, Canada

Introduction: The postoperative period is a critical time in lung transplantation. It has already been established that the type of end-stage lung disease has an impact on the survival benefit after lung transplantation. However, the specific aspects of postoperative evolution such as mechanical ventilation duration (MVD), intensive care unit length of stay (ICU LOS), and hospital LOS have not been extensively studied.

Methods: We reviewed the experience in our center through a retrospective chart analysis of 201 patients who underwent lung transplantation from 2004 to 2010. We investigated if the MVD, ICU LOS, hospital LOS and the need for a tracheotomy LTx has been shown to be associated with bronchial anastomosis healing complications. We hypothesized that, in select LTx recipients, sirolimus due to its antiproliferative properties and minimal side effect profile when begun within the first post-operative month is safe and associated with a favourable short and long term outcome.

Materials and methods: Between December 2004 and October 2011, 62 LTx were performed in a single institution. Ten patients (16.1%) mean age 46.9±11.9 years old were selected to received early sirolimus based immunosuppression regime along with cyclosporine and prednisone with all receiving induction immunosuppression. Patients were selected to receive early sirolimus based on an uncomplicated post-operative course and decisively after bronchoscopic assessment.

Results: Sirolimus was begun on mean POD 20.5±5.4 (14-32). In hospital/30-day mortality was 0%. On-long term follow up 3 patients died, 2 due to bacterial infection and in one patient PCT infection. Mean survival was 3.6±1.9 years (1.1 – 6.9), 1-year survival was 90% and 5-year survival was 75%. In 4 patients (40%) sirolimus was stepped, in 3 due to infection and in one because of re-transplant. None of the patients displayed BOS based on FEVI. In the patients still taking sirolimus renal function was within normal range. The study patients did not suffer increased rate of bacterial, PCT or CMV infection when compared to standard immunosuppression patients.

Conclusion: Contradictive to previously published studies, our results show that early sirolimus based immunosuppression is safe and is associated with a beneficial side-effect profile.
are related to the underlying end-stage lung disease. We analyzed the data with
descriptive statistics to identify differences between subgroups. Access to medical
cards was granted by the Research Ethics Committee.

**Results:** Our results show that Idiopathic Pulmonary Fibrosis (IPF) patients have
much longer MVD, ICU LOS and hospital LOS; require more tracheotomies and
have higher mortality in the postoperative period when compared to other
end-stage lung diseases (Table 1).

**Conclusion:** Patients with IPF have longer ICU LOS and this seems to be related
to longer MVD. Further research could address methods of improving weaning
from mechanical ventilation in these patients.

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### P2443

**Outcomes of lung transplantation for bronchiectasis**

**Jodie Birch**, Katy Hester,®, Gareth Parry,®, Kate Gould,®. John Dark,®

**Stephen Clark,** Gerard Meachery,® James Lordan,®. Andrew Fisher,®

**Paul Corris,**®. António De Soyza.®

**4Transplantation and Immunobiology Group, Newcastle University, Newcastle upon Tyne, United Kingdom; 2Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne, United Kingdom; 3Department of Medical Microbiology, Freeman Hospital, Newcastle upon Tyne, United Kingdom; 4Transplantation and Immunobiology Group Institute of Transplantation, Freeman Hospital, Newcastle upon Tyne, United Kingdom**

**Background:** Non-cystic fibrosis bronchiectasis (nCFBr) is an infrequent indication for lung transplantation and poorly described compared to CF and COPD. We describe our experience in the largest series to date.

**Methods:** Retrospective review of case-notes and transplant databases from 1990 to 1999 (22 years). Two time cohorts were set (1990-2000 and 2001-present date).

**Results:** 43 patients with nCFBr underwent lung transplantation at our centre. 42 patients had bilateral lung and one had heart-lung transplantation. Median age at transplant was 48 years. Mean pre-transplant FEV1 was 22% predicted (range, 10%-49%; n= 38). At assessment 84% (32 of 38 complete datasets; p=0.02) were surviving 1 year post-transplant. More patients were transplanted in the first cohort (n=26 vs. n=17). Mean pre-transplant FEV1 (% of predicted) was similar in both time cohorts (21% vs. 23%; p=NS) though patients transplanted in 1990-2000 were younger (mean: 45 vs. 51 years, p=0.026). Our survival rates were 74% at 1 year, 64% at 3 years, 61% at 5 years and 48% at 10 years. Infection and multi-organ failure were common causes of death within 1 year pre-transplant.

**Conclusions:** P aeruginosa infection is not universally seen in our cohort. Our sur-

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### P2444

**Use of noninvasive ventilation in the early postoperative period of lung transplantation**

**Ana Hernández Yoth,® Regulo Avila Martinez,® Javier Sayas Catalán,® Alicia De Pablo Fajón,® Elvira López Lopez,® Virginia Pérez González,® Olga González,® Pablo Gámez García,® Pneumology Service, 12 de Octubre University Hospital, Madrid, Spain; 2Thoracic Surgery Service, 12 de Octubre University Hospital, Madrid, Spain; 3Anesthesiology Service, 12 de Octubre University Hospital, Madrid, Spain**

**Aims:** To describe the results of noninvasive ventilation [NIV] in the early postop-

**Methods:** Retrospective study of NIV in the early postoperative period of LT patients from October 2008 to December 2011. Patients were selected for post-

**Results:** During this period 41 patients had LT. Principal indications were due to

**Conclusions:** NIV can be a useful tool in the early postextubation period of lung transplantation. We observed a diminution of ICU length stay in the NIV group, although the difference was not statistical significant.

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### P2445

**Neurocognition in airway pathogens during the first year after lung transplantation: A single center experience**

**Zuzanna Kowalska,** Zoltan Suto, Gabriella Murakozy, Aniko Bohacs, Csaba Vajai, Kornzina Creebe, Gyorgy Losonczy, Veronika Muller. Department of Pulmonology, Semmelweis University, Budapest, Hungary

After lung transplantation (LuTx) high level of immunosuppression is needed to prevent rejection, which makes recipients more susceptible to infections. Pul-

**Results:** 13 patients (6 LuTx, 7 new LTx) were included in the univariate and multivariate analysis. Pneumonia infections are a major clinical problem during the first postoperative year and regular surveillance examinations and immediate adequate treatment is mandatory. As seasonality of respiratory tract infections is well known in chronic pulmonary diseases, we assessed pathogen spectrum and number of infections in the first postoperative year in LuTx recipients.

**Airway pathogens registered during the first posttransplant year in 16 Hungarian LuTx patients (underlying disease: cystic fibrosis: 8, interstitial lung disease: 4, obstructive lung disease: 3, primary pulmonary hypertension: 1) were analyzed. Microbiological samples were taken from upper and/or lower respiratory tract and serum as part of the routine care. Number of positive samples was analyzed according summer (S=March to August) and winter (W=September to February) period.

A total of 107 infections were registered during the first posttransplant year. The

**Conclusions:** More frequent pathogens were Gram negative bacteria (n=43) and fungi (n=39). Total number of respiratory infections in S were significantly less frequent as compared to W (S=49, W=61), including Gram positive: S=25, W=41; Gram neg-

**Table 1**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NICU mean (SD)</th>
<th>NIV mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.25 (13.86)</td>
<td>53.14 (13.32)</td>
<td>0.3071</td>
</tr>
<tr>
<td>Acute-Hypoxemia Index (number per hour)</td>
<td>11.57 (13.4)</td>
<td>7.55 (5.9)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.82 (5.0)</td>
<td>22.16 (3.3)</td>
<td>0.0624</td>
</tr>
<tr>
<td>Arterial pressure of CO2 (mmHg)</td>
<td>46.7 (12.1)</td>
<td>43.5 (9.8)</td>
<td>0.2405</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NICU group (mean, SD)</th>
<th>NIV group (mean, SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ventilation time in the ICU (hours)</td>
<td>4.15 (3.14)</td>
<td>3.88 (3.62)</td>
<td>0.6560</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>6.3 (2.5)</td>
<td>6.9 (2.6)</td>
<td>0.2048</td>
</tr>
</tbody>
</table>

**Conclusions:** NIV can be a useful tool in the early postextubation period of lung transplantation. We observed a diminution of ICU length stay in the NIV group, although the difference was not statistical significant.

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### P2446

**Microbiological impact of regular colistin use in a population of lung transplant recipients**

**Mohamed Al-Aloul,** Bashar Al-Shelhky,® Jamal Salal,® Barbara Isalska.®

**1Transplant Unit, Wythenshawe Hospital, Manchester, United Kingdom; 2Department of Microbiology, Wythenshawe Hospital, Manchester, United Kingdom**

**Aim:** To describe the results of regular colistin use in our LT recipients and we now present its impact on microbiological surveillance.

**Population:** 3 groups between June 2005 and December 2011. Gp1: IV colistin for new and past LTxs with confirmed or suspected gram negative infection not responding to treatment with tazorin (n=171). Gp 2: Prophylaxis in CF recipients with previous Pa to prevent/delay graft colonisation (n=32): colistin/TobI nebs alternate months for 1 year then withdraw.

Long term outcomes of lung transplantation (LTxs) are partly limited by infection. Due to increasing prevalence of multiresistant Pseudomonas aeruginosa (Pa) iso-

**Methods:** Use of noninvasive ventilation in the early postoperative period of lung transplantation (LT) for new and past LTxs with confirmed or suspected gram negative infection not responding to treatment with tazorin (n=171). Gp 2: Prophylaxis in CF recipients with previous Pa to prevent/delay graft colonisation (n=32): colistin/TobI nebs alternate months for 1 year then withdraw. Gp 3: Eradication of new Pa isolates in Pa naive recipients (n=29): 2 weeks of IV B-lactam+colistin followed by 3 months of nebulised colistin. Gp 2 and 3 had sputum/bronchial lavage tested 3 monthly for 1 year after treatment.

**Results:** Gp1 – 443 courses of IV colistin, median dose 3 mg/day for a median 16 days; pathogens were confirmed in 69%. Gp2 – continued growth, no growth and
Prevalence and outcome of donor transmitted Acinetobacter baumannii in acute rejection or initiation of acute rejection therapy within 3 months.

Eid Almutairy, Naseer Alshekaily, Basha Khan

Lung transplant recipients (LTR) are at risk of respiratory viral infection (VI). Our goal was to characterize clinical factors associated with upper or lower respiratory tract VI, as well as the relation between VI and acute graft rejection (AR) in a cohort of LTR patients.

Methods: LTR patients (n=112) from Lausanne & Geneva University hospitals had systematic nasopharyngeal swabs (NPS) and when indicated bronchoalveolar lavage (BAL) with transbronchial biopsy (N visits=903). We screened 18 distinct respiratory viruses with rt-PCR during: a) seven 6-week investigator-driven screening period (n=570), b) regular (n=124) and c) emergency visits (n=209).

Results: During follow-up, 172/903 VI (19%) were identified in 68/112 (61%) LTRs with 34/276 infected BAL and VI rate was highest during emergency visits (p<0.01).

P2447 Incidence of viral infections in patients with lung transplantation Pierre-Olivier Bridevaux1, John-David Aubert1, Paola Soccal1, Thierry Rochat1, Laurent Kaiser1, 2Pulmonary Division, University Hospitals, Geneva, Switzerland; 2Pulmonary Division, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Background: LTRs are at risk of respiratory VI. Our preliminary study shows basiliximab induction reduces incidence of acute rejection without significantly increasing the risk of CMV and invasive fungal infections.

Methods and patients: In an ongoing prospective study 28 clinically stable lung transplant recipients (16 male, age 54±8.4 years, BMI 25.5±4.1 kg/m², range 6 months to 9 years after transplantation) were screened for SDB by the Berlin Questionnaire and the Stop Bang Questionnaire. These results were compared to in-lab polysomnography (PSG). Diagnostic accuracy of both questionnaires was compared to gold standard PSG using a cut-off AHI of 10/h as definition for SDB.

Results: The prevalence of SDB was 57%. Sensitivity and specificity for the Berlin Questionnaire and the Stop Bang Questionnaire were 85% and 30%, respectively. The corresponding values for the Stop Bang Questionnaire were 8% and 80%, respectively. The corresponding values for the Berlin Questionnaire were 85% and 30%.

Conclusion: The diagnostic accuracy of the Berlin Questionnaire and the Stop Bang Questionnaire is high in order to identify patients with SDB in a lung transplantation population.

P2451 Kf determination after ischemia-reperfusion in lungs treated with sildenafil and tadalafil

Raúl Guerra, Carlos Bravo, Nadezdha Aguilar, Diana Aguilar, Patricio Santillán

Background: Donor transmission of organism to the lung transplant recipient is a known entity. The shortage of ideal donors and the increasing pool of lung transplant candidates is increasing the pressure to utilize extended donors. Large number of our donors have been on ventilator for extended period of time, hence bringing the risk of nosocomial infections. We describe our experience with acinetobacter baumannii pneumonia in the lung transplant patients.

Methods: Retrospective chart review of all the patients transplanted between March 2010 and August 2011. The patients with acinetobacter baumannii pneumonia transmitted from donors were compared to those not affected by such infections. The primary graft dysfunction, duration of mechanical ventilation, ICU length of stay, acute kidney injury and mortality were measured.

Results: A total of 18 patients underwent lung transplant during this period. There were 8 male and 10 female recipients. A total of 6 patients developed acinetobacter baumannii multdrug resistant pneumonia. The primary graft dysfunction was severe in all patients. median duration of mechanical ventilation was 14 vs. 2; median ICU length of stay was 19.5 vs. 6.5; acute kidney injury was 33% vs. 41% and mortality was 33% vs. 8% in the acinetobacter vs. non-acinetobacter group.

Conclusion: Infection of acinetobacter baumannii in respiratory culture from donor lungs was associated with worse outcomes in transplanted patients as compared to donor lungs without acinetobacter. Antibiotic coverage should be tailored to include this organism when suspected as soon as possible. Also a method for rapid identification of acinetobacter baumannii is needed.
263. Management of severe respiratory infections

P2453
Comparison of treatment outcomes in community-acquired pneumonia patients treated with beta lactam-macroide combination versus fluoroquinolone monotherapy

Oguz Kilinc1, Ozan Soyay2, Aykut Cilir2, Ayisn Sakar3, Sezai Tasbakan4, Hulya Ellidokuz5, Burcu Celek6, Cemil Cemikaya7, Canan Gunduz4, Abdullah Seyin1.

Chest Diseases, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey; 2Chest Diseases, Akdeniz University Faculty of Medicine, Antalya, Turkey; 3Chest Diseases, Celal Bayar University Faculty of Medicine, Manisa, Turkey; 4Bone Diseases, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey; 5Biostatistics, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

The clinical outcomes of patients with community-acquired pneumonia treated in accordance with the recommendations of Turkish Thoracic Society (TTS) guidelines and who had received beta-lactam-macrolide combination or fluoroquinolone (FQ) monotherapy were evaluated using the data from four contributing sites to the TURCAP database of TTS Assembly of Respiratory Infections. A total of 343 patients was included. Of these patients, 63.6% had received combination treatment and 36.4% had received FQ monotherapy. There was no difference between the two groups regarding age, gender and comorbidities. However, the mean Pneumonia Severity Index (PSI) scores were 101.8±35.8 and 91.0±28.9 (p=0.006) and CURB-65 scores were 2.3±1.0 and 2.0±0.8 (p=0.002), respectively. The length of hospital stay was 9.5±6.1 days in the combination and 8.3±4.4 days in the FQ group (p=0.24). The rates for cure, partial improvement and mortality were 59.1%, 28.2% and 12.8% for the combination group versus 72.6%, 24.2%, 3.2% for the FQ group, respectively. There was no significant difference between the two groups in terms of improvement rates; on the other hand, the mortality was higher in the combination group (p=0.03).

Conclusion: Regression analysis showed that mortality was associated with PSI score and not with the choice of antibiotic treatment. In this retrospective analysis of TURCAP database, the clinical success rates were similar in patients who received a combination of beta lactam and macrolide and fluoroquinolone monotherapy. The lower mortality observed in the latter group was found to be associated with less severe disease at presentation.

P2454
Pharmacokinetics and pharmacodynamics of newer fluoroquinolones in patients with lower respiratory tract infections

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Introduction: Levofloxacin (LVF) and moxifloxacin (MXF), have been recommended as first line therapy for patients with acute exacerbations of chronic bronchitis and community-acquired pneumonia. Aim: The aim of this study is to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of LVF and MXF for lower respiratory tract infections (LRTI).

Methods: Eighteen patients (2 groups of 9, aged 69.6±8.7 and 74.8±8.8) with LRTI received 500 mg LVF IV q12h or 400 mg MXF IV q24h. Serial blood samples were obtained at steady state condition (3rd day of therapy). Plasma concentrations were determined by a validated HPLC method. The PD target was evaluated for both antibiotics based on our hospital’s MIC90 of the most common respiratory pathogens.

Results: The PK data are presented in Table 1.

Table 1: PK data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cmax (μg/mL)</th>
<th>AUC24 (hr μg/mL)</th>
<th>CL (L/hr)</th>
<th>T1/2 (h)</th>
<th>Vss (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVF</td>
<td>6.26±1.02</td>
<td>53.9±18.97</td>
<td>20.5±7.8</td>
<td>9.49±1.14</td>
<td>208.6±8.77</td>
</tr>
<tr>
<td>MXF</td>
<td>4.86±1.11</td>
<td>38.02±5.57</td>
<td>70.7±3.1</td>
<td>14.5±6.95</td>
<td>171.9±6.88</td>
</tr>
</tbody>
</table>

Both antibiotics exhibited large volumes of distribution (Vss). They achieved the PD target in all patients against the majority of the strains of the common respiratory pathogens in our hospital, as shown in table 2.

Table 2: PD data

<table>
<thead>
<tr>
<th>Compound</th>
<th>AU/CMIC (S. pneumoniae)</th>
<th>AU/CMIC (H. influenzae)</th>
<th>AU/CMIC (M. catarrhalis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVF</td>
<td>AU/C0.05</td>
<td>AU/C0.03</td>
<td>AU/C0.06</td>
</tr>
<tr>
<td>MXF</td>
<td>AU/C0.25</td>
<td>AU/C0.06</td>
<td>AU/C0.06</td>
</tr>
<tr>
<td>152.0±22.27</td>
<td>633.6±92.78</td>
<td>633.6±92.78</td>
<td></td>
</tr>
<tr>
<td>p=0.005</td>
<td>p=0.001</td>
<td>p=0.102</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: LVF and MXF exhibit a favorable PK profile in patients with LRTI. There is adequate PD exposure against most strains of S. pneumoniae, H. influenzae and M. catarrhalis with low MICs.

P2455
Combination therapy (beta-lactam-macroide) vs fluoroquinolone monotherapy for the treatment of CAP

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Background: According to the 2007 IDSA/ATS guidelines for the treatment of CAP monotherapy with fluoroquinolones is the first choice and combination therapy remains an alternative treatment option. Combination therapy was the first recommended treatment option by the 2003 IDSA update of practice guidelines for the treatment of CAP.

Aim of study: The aim of this study was to assess whether any of the two proposed alternative treatment options for CAP is statistically superior and related with advanced clinical course.

Material and methods: A prospective observational study which incorporated 300 immunocompetent adults, who referred to the ER of “Sotiria” General Hospital for Thoracic Diseases and after diagnosed with CAP, were all hospitalized.

Results: 250 patients (83.3%) received combination therapy and 50 patients...
(16.67%) received monotherapy with fluoroquinolone. 235 (94%) out of the 250 patients who received combination therapy had a favourable clinical course (survived) and 15 (6%) had an unfavourable clinical course (died). 42 (85%) of the 50 pts who received monotherapy with fluoroquinolone survived and 8 (15%) of them died. The mortality rate of the second group was significantly higher than the mortality rate of the first group (15% vs 6% respectively, p=0.033).

**Conclusion:** The mortality rate of hospitalized patients with CAP receiving monotherapy with fluoroquinolones was significantly higher compared to patients receiving combination therapy. There are a few other studies supporting these results and one possible explanation could be the immunomodulating activity of macrolides, which is verified but still a field of detailed, extended and persistent investigation.

**P2456**

Tolerance of nebulised gentamicin in adult bronchiectasis – A single centre study

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**Background:** British Thoracic Society non CF bronchiectasis (nCFBr) guidelines suggest that long-term nebulised antibiotics should be considered in patients with more than 3 exacerbations per year. Nebulised gentamicin reduces bacterial load and exacerbations in nCFBr. Adverse effects can occur with aerosolised delivery of antimicrobials and so limit their use. We studied the tolerability of nebulised gentamicin in a real world population

**Methods:** We measured spirometry in nCFBr patients challenged with 80mg of nebulised gentamicin, at baseline, 1min, 5min, and 10min post nebulised gentamicin, assessing short term tolerability and benefits were assessed

**Results:** Forty-two patients (19male:23female) were enrolled Feb 10-Dec 2011. Mean age was 60yrs (range 17-77). Colonisation with *Pseudomonas aeruginosa* and *Staphylococcus aureus* was seen in 17(40%), 11(26%) and 4(9%) patients respectively. Mean baseline FEV1 was 1.48L(min 0.56 pred), range 0.3-3.7L/min (16-108% pred). Mean FEV1 was preserved at 1min (1.45L/min), 5min (1.52L/min) and 10min (1.53L/min) post nebulised gentamicin. There was no difference between pre-dose and 10min post-dose FEV1 (p>0.05). One patient was unable to tolerate the nebulised challenge due to fall in FEV1 and symptoms. Long-term, 8 patients (19%) were unable to tolerate nebulised gentamicin due to side effects. It was stopped in 5 patients (12%) as they did not report benefits

**Conclusions:** These data show nebulised gentamicin is well tolerated in acute challenges even in patients with severe airflow obstruction but long-term adherence declines. We aim to present microbiological data. The utility of acute challenge studies remain unclear in predicting longer term tolerability.

**P2457**

An audit of microbiological investigations performed on patients admitted with community acquired pneumonia

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**Introduction:** The British Thoracic Society (BTS) guidelines suggest that blood and sputum culture be performed in patients with moderately severe community-acquired pneumonia (CAP). Atypical testing and viral PCR are recommended in severe CAP. The aim was to identify whether the appropriate microbiological investigations are being performed on patients with CAP.

**Method:** This was a retrospective audit. CAP was defined as a clinical diagnosis of pneumonia in a patient with a new radiographic infiltrate. Microbiology investigations performed in CAP patients were compared against the same data collected in 94 CAP patients in 2008. The 2009 BTS guidelines served as the audit standard.

**Results:** 210 patients were included. 55% had blood cultures taken, with bacteremia confirmed in 15 patients. This compared with 70% having blood cultures in 2008, p=0.02. 16% (34) had sputum culture compared with 25% (24) in 2008, p=0.06.

11% had legionella antigen analysis compared with 16% in 2008. 10% had atypical serology carried out in 2011 and 22% in 2008. 12% had viral PCR compared to 5% in 2008.

In total, only 2.4% of patients had all of the recommended microbiology investigations (2.1% in 2008). 35.2% had no microbiology testing (21% in 2008, p=0.02).

**Conclusions:** Recommended microbiology investigations are underutilised in CAP patients at our centre. There has been a reduction in microbiological testing in comparison with 2008 figures.

**P2458**

Management of community acquired pneumonia (CAP) in a UK district general hospital (DGH)

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**Background:** Although there are published BTS guidelines [Thorax 2009;64(Suppl III)] for the management of CAP, its practice across UK hospitals is variable and at times lacking; in achieving satisfactory outcomes.

**Objectives:** To audit the management of patients admitted with CAP in a UK DGH.

**Method:** A retrospective audit was undertaken between the periods covering 01/10/2010-31/08/2011. We included all patients admitted through the emergency or community referral system with a radiological diagnosis of pneumonia. We excluded patients who were immunocompromised or under 16 years of age.

**Results:** A total of 56 patients (59% female; n=33) were included. CURB-65 score was documented in 20% (n=11). With regards to anti-microbial treatment, 12.7% (n=7) patients were given B-lactam alone, 76.3% (n=42) were given B-lactam + Macrolide, 10.9% (n=6) were given Levofloxacin and one patient each received either Meropenidazole or gentamycin. Time between diagnosis and first dose of antibiotic was greater than 4 hours in 57.3% (n=32) patients. 27% (n=15) patients received antibiotics against the published local guidelines (local guidelines followed BTS guidelines). Total length of stay varied from 0-101 days with a median of 7.5 days. There were 6 deaths within 30 days of discharge, of which 2 died on admission.

**Conclusions:** Despite guidelines, there was poor documentation and recognition of the severity of CAP. There was deviation from recommended prescribing, hence risking emergence of resistant strains. Many patients received antibiotics beyond the recommended time window. Therefore, hospitals need to make sure that guidelines are being followed, in order to achieve further reduction in morbidity and mortality.

**P2459**

Resistance of problematic Gram(-) respiratory pathogens selected from in-patients (Yaroslavl, Russia, 2011)

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**Pulmonology, Clinical Hospital #2, Yaroslavl, Russian Federation
Clinical Microbiological Laboratory, Infectious Clinical Hospital #1, Yaroslavl, Russian Federation

**Background:** The problem of the spread of resistant Gram(-) agents becomes more urgent. These changes in the respiratory pathogens in hospitals create difficulties in antibiotic therapy and lead to increase of patients’ lethality and the burden for general healthcare.

The aim of our study was to assess the prevalence of resistance of the problematic Gram(-) pathogens in hospitalized patients.

**Methods:** Pathogens were isolated from hospitalized patients in Yaroslavl. The selection of pathogens and the determination of resistance was performed centrally in the microbiological laboratory (NCCLS standards, disc-diffusion method).

**Results:** In 2011 in the city’s hospitals 98 strains of *Pseudomonas aeruginosa*, 71 - *Acinetobacter* spp were allocated from respiratory tract in hospitalized patients. Resistance of *P. aeruginosa* was extremely high practically to all drugs, including carbapenems. The only exception was polymyxin (all strains were sensitive). The average rate of resistance was 39.2%. Resistance *P. aeruginosa* to piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, meropenem, ciprofloxacin, gentamycin, amikacin was 51, 48, 48, 49, 54, 47 and 48% respectively. At a time, 99% of strains were sensitive, meropenem - 94%.

**Conclusions:** Most of the strains of *P. aeruginosa* and *Acinetobacter* spp show high resistance to antimicrobial agents. The greatest concern is the resistance to carbapenems in *Pseudomonas aeruginosa*. 448s
Evaluating flutter device and the active cycle of breathing technique in non-cystic bronchiectasis: The prospective randomised study

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Background: Chest physiotherapy is an important part of the routine treatment of patients with bronchiectasis. The aim of present study was investigate the efficacy of two frequently used physiotherapies in bronchiectasis: active cycle of breathing (ACBT) techniques and the Flutter device.

Methods: A prospective randomized study was performed in 36 stable patients with non-cystic bronchiectasis at home, in which 4 weeks of daily ACTB (n=17) were compared with the Flutter device (n=19). We compared symptoms, pulmonary function tests, dyspnea scores and Health-Related Quality of Life with two different physiotherapy techniques.

Results: Expiratory cough and Weakness was reduced (respectively p=0.000, p=0.004), sputum expectoration was increased (p=0.002), dyspnea score was reduced (for Medical Research Council p=0.001, for Borg Dyspnea Scale p=0.002) and Short Form-36 ‘Physical Health’ component summaries score was produced (for Medical Research Council p=0.001, for Borg Dyspnea Scale p=0.002)

Conclusions: Chest physiotherapy is a effective method increasing sputum expectoration, reducing symptoms and dyspnea score and party improvement Health-Related Quality of Life. ACTB and Flutter techniques are suitable usage a home-based treatment.

P2461

RCT of chest physiotherapy versus chest physiotherapy and pulmonary rehabilitation in non cystic fibrosis bronchiectasis

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Aim: To assess the efficacy of pulmonary rehabilitation(PR) in addition to regular chest physiotherapy in non-cystic fibrosis bronchiectasis.

Methods: Patients with bronchiectasis were invited to participate if their exercise tolerance was limited, due to bronchiectasis, from Edinburgh Bronchiectasis clinic, in a prospective study 15 received chest physiotherapy and 15 received PR-chest physiotherapy. Review was at baseline/4 weeks/8weeks/end of intervention and 20 weeks(completion of study). Outcome measures were improvement in incremental shuttle walking test(ISWT), endurance walk test(EWT), health related quality of life(HRQoL),St-Georges Questionnaire(SGRQ) and Leicester Cough Questionnaire(LCQ).

Results: Results are presented as mean(standard error). The minimum clinically important difference(MCID) for SGRQ and LCQ was 4 and 1.3 units respectively. Comparison of changes between the 2 groups was calculated using unpaired t-tests.

Conclusions: PR in addition to regular chest physiotherapy, improves exercise tolerance and HRQoL in bronchiectasis and the benefit was sustained at 3months post end of PR.

P2462

Unexpectedly high incidence of pneumothorax in patients with pulmonary Mycobacterium avium complex infection

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Aims: To assess the effectiveness of inhaled colistin in elderly patients with non cystic fibrosis bronchiectasis (CF) bronchiectasis in chronic bronchial infection with pseudomonas aeruginosa, where there is limited evidence for elderly patients

Methods: Prospective, controlled, randomized and open. We included patients with HRCT diagnosed bronchiectasis, after an acute exacerbation admission and appropriate antimicrobial therapy. We collected data on demographics, clinical and functional characteristics, admissions and sputum microbiology. We followed the patients for one year, evaluating microbiological results, functional tests, readmissions and exuhs.

Abstract P2464 – Table 1

<table>
<thead>
<tr>
<th></th>
<th>Acapella only</th>
<th>Acapella+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>8 weeks</strong></td>
<td><strong>20 weeks</strong></td>
</tr>
<tr>
<td>ISWT (m)</td>
<td>343.3 (44.3)</td>
<td>338.66 (42.24)</td>
</tr>
<tr>
<td>EWT (m)</td>
<td>70.67 (43.69)</td>
<td>94.67 (161.55)</td>
</tr>
<tr>
<td>SGRQ (Score)</td>
<td>40.56 (3.92)</td>
<td>39.15 (4.47)</td>
</tr>
<tr>
<td>LCQ (Units)</td>
<td>40.56 (3.92)</td>
<td>14.64 (1.38)</td>
</tr>
</tbody>
</table>

p values represent differences between 2 groups (using unpaired t tests), at time points indicated. *p<0.01; **p<0.04; ***p<0.02; §p<0.001.

P2463

Effects of nebulizer therapy by hypertonic saline, gender and breastfeeding on evolution of acute bronchiolitis

Ekaterina Kutsia, Tina Ghonghade, Tamaz Zhorzhialian. PICU, M.Ashvili Children’s Central Clinic, Tbilisi, Georgia Infant’s Department, G. Zhvania Pediatric Clinic, Tbilisi, Georgia

Acute bronchiolitis is most common viral infection of lower respiratory tract in infants. In 90% it is caused by respiratory syncytial virus. The incidence of pneumothorax in patients with pulmonary MAC infection was as high as 2.4% (18 out of 746 all MAC patients), 2.1% in female and 3.0% in male patients.

Conclusions: The incidence of pneumothorax in patients with pulmonary MAC infection is unexpectedly high, especially in elderly, male, and progressed MAC disease. It is often difficult to treat and to easy to recur.

P2464

Inhaled colistin in elderly patients with bronchiectasis and chronic bronchial infection with pseudomonas aeruginosa

Eva Tabernero1, Ramon Alizka1, Pilar Gil1, Javier Garros1, David Cantero, Juan L. Artola1, Luciano Ramos. 1Pneumology, Hospital Santa Marina, Bilbao, Spain; 2Dermatology, Hospital Galdakao, Galdakao, Spain

Bronchiectasis is the end result of several different illnesses and a frequent cause of admission in hospitals for elderly people and chronic diseases. Although many guidelines recommend treatment with inhaled antibiotics in non cysitic fibrosis (CF) bronchiectasis in chronic bronchial infection with pseudomonas aeruginosa, there is limited evidence for elderly patients

Aims: To assess the effectiveness of inhaled colistin in elderly patients with non CF bronchiectasis and chronic bronchial pseudomonas infection

Methods: Prospective, controlled, randomized and open. We included patients with HRCT diagnosed bronchiectasis, after an acute exacerbation admission and appropriate antimicrobial therapy. We collected data on demographics, clinical and functional characteristics, admissions and sputum microbiology. We followed the patients for one year, evaluating microbiological results, functional tests, readmissions and exuhs.
Results: We included 25 patients, 13 treated with inhaled colistin and 12 in control group. Four patients stopped the treatment because of adverse effects. Main results are shown in the table.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>Colistin (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.2</td>
<td>75.6</td>
</tr>
<tr>
<td>Charlson</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>FEV1%</td>
<td>41.1%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Persistence of Pneumonia</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Change in FEV1</td>
<td>-1.2%</td>
<td>+5.6%</td>
</tr>
<tr>
<td>Hospital stay 1 year</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>Exitus 1 year</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Statistically significant.

Conclusions: Significant more patients in the treatment group achieved Pseudomonas eradication; but we could not demonstrate clinical or functional benefits in our elderly patients. These results may be due to small sample size. Side effects were frequent.

P2465

Changes in the lower airway bacterial community of from adult non-CF bronchiectasis population are significantly associated with exacerbations and the presence of *Haemophilus influenzae*

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Background: The aim was to investigate the polymicrobial communities in sputum samples derived from an adult non cystic fibrosis bronchiectasis (nCFB) population using culture independent methods. The cohort consisted of 70 individuals with HRCT proven nCFB. Twenty patients presented at the clinic for sputum collection with symptoms consistent with exacerbations, the remainder were clinically stable.

Methods: DNA was extracted from sputum samples of all patients (n=70). Universal primers for 16S and 28S rDNA, the resulting fragments were analysed by denaturing gradient gel electrophoresis. Demographic and culture data were used in constrained ordination analyses to identify any significant association between these data and changes in the sputum microbiota.

Results: The microbiota was significantly correlated with a reduced lung function. Bacterial profiles indicated a significantly different community was present in exacerbating patients compared to those that were clinically stable (P = 0.0002). *H. influenzae* carriage also produced significant changes (P = 0.004) in community structure. Moreover, *H. influenzae* was never found in samples that harboured *P. aeruginosa*. Bacterial communities appeared to be randomly assembled. Fungal taxa were scarce.

Conclusions: Bacterial communities from adult non-CF bronchiectasis patients have distinct differences between exacerbating and clinically stable episodes. Persistent colonisation by *Haemophilus influenzae* is significantly associated with reduced lung function, and is negatively correlated with *H. influenzae* carriage.

P2466

Rapid detection of *Mycoplasma pneumoniae* IgM antibodies using ImmunoCard Mycoplasma kit compared with complement fixation (CF) tests and clinical application

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Purpose: *Mycoplasma pneumoniae* is a leading cause of community-acquired pneumonia. For a rapid diagnosis of *M. pneumoniae* infection, we often use ImmunoCard Mycoplasma kit (IC), a 10-min-card-based enzyme-linked immunosorbent assay (ELISA) for IgM antibodies to *M. pneumoniae*. However, widespread clinical application of this test is hampered by an inability to identify pathogen directly with adequate sensitivity and specificity. Therefore, we examined the clinical usefulness of IC test retrospectively.

Method: We evaluated 316 samples which were measured by IC from October,2008 to March,2009. We also compared IC with the complement fixation (CF) test, and estimated false positive and negative rate based on the clinical course and other laboratory findings.

Results: Among 316 samples, 69 (21.8%) were positive of IC and 247 (78.2%) were negative. Sixteen cases were also measured by CF test with the paired serum, and in 5 (31.3%) cases of these, there was a discrepancy between the result of IC and that of CF test. On the basis of a clinical diagnosis, IC gave the false positive rate of 80.0%, false negative rate of 31.3%.

Conclusions: IC has so far been attributed to the rapid diagnosis of *M. pneumoniae* infection because it is unnecessary to use paired serum and possible to judge the infection rapidly. But a positive result of IC does not always indicate acute infection because the result of IC were not always concordant with that of CF test. According to our results, it seems that the interpretation of the result of IC is very difficult in order to use it clinically.

P2467

Legionella pneumonia in patients hospitalized with community-acquired pneumonia (CAP) in Norway

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Background: The aim was to investigate the frequency of *Legionella pneumonia* among hospitalized CAP-patients in Norway.

Methods: Adult patients with radiologically confirmed CAP were prospectively included at the main acute care hospitals of two counties in Norway (Telemark and Østfold) during a 20-month study period in 2007-2008. Microbiological analyses included culture of blood and sputum, urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1, real time polymerase chain reaction (PCR) of a throat swab for atypical agents, and serology for *L. pneumophila* serogroup 1-6.

Results: A total of 374 patients were included in the study. *Legionella pneumonia* was identified in 21 cases (6%). Eight cases were identified by a non-ICU department stay by urinary antigen testing, and 13 cases were identified later by serology, of whom four were classified as probable cases (single high convalescent titre). Three of the patients were part of a small outbreak of *Legionella* and another two patients probably were infected from the same source. Two of the patients may have been travel-associated. Otherwise, *S. pneumoniae* was the most common etiological agent detected (20%), followed by *Haemophilus influenzae* (6%).

Conclusions: *Legionella pneumonia* seems to be more prevalent than previously recognized in Norway, and testing for *Legionella* should be considered more frequently than currently practice.

P2468

Bronchiectasis in Auckland, New Zealand: Ethnic differences in severity

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Introduction: Bronchiectasis is more prevalent in Maori and Pacific Islanders (PI) than Europeans. The aim of this study was to evaluate differences in severity and microbiology between ethnicities.

Methods: Records of 250 patients (66% female, mean age 62yrs, FEV1% predicted 64.6%) attending the bronchiectasis clinic at Auckland District Health Board were retrospectively reviewed. Demographic and clinical variables were recorded. Ethnicity was compared to NZ Department Statistics 2006 census data for central Auckland.

Results: PI (23%) and Maori (12%) are over-represented in this cohort; European (44%) and Asian (16%) under-represented. Mean FEV1%predicted was higher in Europeans (70.7%) than Maori (63%) and PI (54%), p < 0.001 and remained so when corrected for smoking status p<0.001. Similar statistically significant differences were seen in FVC%predicted. Maori patients were younger (mean age 56yrs) than PI (66yrs) and Europeans (66yrs), p=0.02. There was a trend to later diagnosis in Maori and PI compared to Europeans. 124 patients had at least one sputum sampled that year with Haemophilus 29%, Pseudomonas 13.7%, Aspergillus 4.8%, Pneumococcus 2.4% and non tuberculous mycobacteria 2.4%.

There was no significant difference in sputum microbiology by ethnicity. Conclusions: Maori and PI are over-represented in the bronchiectasis clinic and tend to be younger with more severe disease than other ethnicities. Disease severity is independent of smoking status, microbiology and gender suggesting other factors such as genetic susceptibility or socioeconomic status influence outcome.

P2469

Pneumonia and Clostridium difficile infection: Hospital acquired infection in a non-ICU department

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Introduction: European studies have reported that *Legionella pneumonia* accounts for 0-10% of the cases of CAP in hospitalized patients. In Norway, data on the etiology of CAP in hospitalized patients is limited, and *Legionella pneumonia* has been considered a rare disease.

Aim: To investigate the frequency of *Legionella pneumonia* among hospitalized CAP-patients in Norway.

Methods: Adult patients with radiologically confirmed CAP were prospectively included at the main acute care hospitals of two counties in Norway (Telemark and Østfold) during a 20-month study period in 2007-2008. Microbiological analyses included culture of blood and sputum, urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1, real time polymerase chain reaction (PCR) of a throat swab for atypical agents, and serology for *L. pneumophila* serogroup 1-6.

Results: A total of 374 patients were included in the study. *Legionella pneumonia* was identified in 21 cases (6%). Eight cases were identified by a non-ICU department stay by urinary antigen testing, and 13 cases were identified later by serology, of whom four were classified as probable cases (single high convalescent titre). Three of the patients were part of a small outbreak of *Legionella* and another two patients probably were infected from the same source. Two of the patients may have been travel-associated. Otherwise, *S. pneumoniae* was the most common etiological agent detected (20%), followed by *Haemophilus influenzae* (6%).

Conclusions: *Legionella pneumonia* seems to be more prevalent than previously recognized in Norway, and testing for *Legionella* should be considered more frequently than currently practice.

The antibiotic use for pneumonia treatment contributes to the worldwide spreading of Clostridium difficile infection (CDI). Among all hospital acquired infections, CDI is an emerging cause of hospital morbidity, mortality and costs. We investigated the prevalence of CDI acquisition rates in patients hospitalized with pneumonia and compared all causes of inhospital mortality among patients.
Aims and objectives:
To determine whether there are clonal strains within the non-CF bronchiectasis.

In total 50 non-CF bronchiectasis population in Northern Ireland.

(CibeRes, CB06/06/0028), Barcelona, Spain; 4Servicio de Enfermedades Elena Prina¹,², Miquel Ferrer¹,³, Eva Polverino¹,³, Catia Cilloniz ¹,³,

It is well-known that antibiotic therapy for pneumonia, mainly based on newer fluoroquinolones, b-lactams and macrolides, combined with high-dose or long-term use of proton pump inhibitors drugs increase the risk of CDI. Our data suggest that CDI could be a very common etiology of hospital acquired infection also in non-ICU and non-outbreak setting with low endemic rate.

P2470 Clonal typing of Pseudomonas aeruginosa strains in non-CF bronchiectasis
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Introduction: Pseudomonas aeruginosa is the most clinically significant infecting organism in non-CF bronchiectasis.

Aims and objectives: To determine whether there are clonal strains within the non-CF bronchiectasis population in Northern Ireland.

Method: In total 50 Pseudomonas aeruginosa isolates from 26 patients were analyzed by pulse field gel electrophoresis (PFGE).

Results: There were 10 individual strains identified by PFGE band pattern after DNA macrorestriction. 350 isolates were unique novel strains from 5 separate individuals. There were two dominant strains in this cohort. BELFCITPA-1 in 14/50 isolates in 5 patients. 12/50 isolates in 7 patients were identified as BELFCITPA-5. Stable patients were found to have one strain per sample whereas there was greater diversity within the samples collected from patients with an exacerbation. 12 strains on average.

Conclusion: There are a number of common strains of Pseudomonas aeruginosa found in the sputum of non-CF bronchiectasis patients. Although there are at least 2 clonal strains identified in this small cohort, it is unclear whether this is because they are common environmental strains in the region or because of cross-infection between individuals.

P2471 C-reactive protein in community acquired pneumonia – Correlation with main clinical indices
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Background: C-reactive protein (CRP) has a significant role as a factor, correlating with main clinical indices of the community acquired pneumonia (CAP).

Aim: To evaluate the relationship between CRP-levels and main clinical signs of CAP – severity, length of stay, complications, outcome.

Results: At admission the levels of CRP were increased up to 434 mg/dl, mean value 83.41 mg/dl (normal range 0-5mg/dl). Most of the patients (54%) had score 3 concerning CURB65. Followed by 2 – 24% and 4 – 20%. 62% of them have had concomitant diseases, mainly cardiovascular – in 44% of the cases. The most frequent used antibiotic was ceftriaxone – in 92% of cases. 72% of the patients were treated with two antibiotics, 12% - with three. The duration of antibiotic treatment was average 7.2±1.69 d (from 5 to 12 days). The length of stay was 8.4 d (from 7 to 12 days). Significant relationship was established between CRP and: severity of CAP (CURB65 p<0,05, r=0,38, the duration of intravenous antibiotic treatment p<0,05, r=0,32; antibiotic prescription at leaving hospital day p<0,05; r=0,39; complications; length of stay p<0,05; r=0,30; outcome p<0,05; r=0,50.

Conclusion: CRP is a sensitive and reliable factor, correlating with the severity of CAP, length of stay and outcome.

264. Respiratory infections: prognosis and outcome

P2473 Prediction of prognosis in healthcare-associated pneumonia
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Rationale: Healthcare-associated pneumonia (HCAP) is a new category of pneumonia. Since patients with HCAP are at risk for infection with drug-resistant pathogens and increased mortality compared to patients with community-acquired pneumonia (CAP), predicting their prognosis is an important issue in HCAP.

Purpose: To apply prognostic scoring systems of CAP (PSI, CURB-65 and Japanese A-DROP systems) in prospectively collected patients with CAP and HCAP.

Methods: Patients admitted in three educational hospitals in Japan were analyzed. Receiver operator characteristic curve (ROC) analyses were performed for the three scoring systems in CAP and HCAP. Further, better system was sought in HCAP.

Results: 927 cases with CAP (mean age 73.2 years) and 469 cases with HCAP (81.8 years) were enrolled. Compared to HCAP, CAP showed larger values of area under the curve (AUC) in all scoring systems (CAP vs HCAP: PSI 0.77 vs 0.64, CURB-65 0.76 vs 0.65, A-DROP 0.80 vs 0.65). To develop a better scoring system for HCAP, candidate factors for predicting prognosis were extracted by univariate analysis followed by stepwise method. By logistic regression analysis, serum value of albumin (Alb) was related to the prognosis. Each of AUC in prognostic ROC
Thrombocytosis is a marker of poor outcome in community-acquired pneumonia.

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Background: Thrombocytosis, often considered a marker of normal inflammatory reaction of infections, has recently been associated with increased mortality in community-acquired pneumonia (CAP).

Methods: We evaluated 2,423 hospitalized patients with CAP. We excluded patients with immunosuppression, neoplasm, tuberculosis or haematological disease. The aim was to assess characteristics and outcomes of patients with CAP and thrombocytosis (platelet count $>400,000$ mm$^{-3}$) compared with thrombocytopenia (platelet count $<100,000$ mm$^{-3}$) and normal platelet count.

Results: Fifty-three patients (2%) presented thrombocytopenia, 204 (8%) thrombocytosis and 2,166 (90%) a normal platelet count. Patients with thrombocytosis were younger ($p<0.001$), while those with thrombocytopenia more frequently had chronic heart and liver disease ($p<0.001$ both). Patients with thrombocytosis more frequently presented respiratory complications such as complicated pleural effusion/empyema ($p<0.001$). Patients with thrombocytosis were more likely to be admitted due to chronic diseases ($p<0.001$), had a longer duration of mechanical ventilation ($p=0.001$) and ICU admission ($p=0.011$). Patients with thrombocytosis had longer hospital stay ($p=0.004$), higher 30-day mortality ($p=0.001$) and readmission rate ($p=0.001$) than those with a normal platelet count.

Conclusions: Thrombocytosis in CAP is associated with poor outcome, complicated pleural effusion/empyema. Therefore thrombocytosis in CAP should encourage us to rule out respiratory complications and could be considered for severity evaluation.

P2474

Thrombocytosis is a marker of poor outcome in community-acquired pneumonia

Elena Prina 1,2, Miquel Ferre 1,3, Ovatio Tavares Ranzani 1,4, Eva Polverino 1,5, Catia Cilfone 1,6, Encarnación Moreno 1,7, Josep Menesà 8, Beatriz Montull9, Rosario Menéndez 10, Roberto Cosenìni 11, Anton Ferre 11,12, Servies de Pneumologia, Institut del Tonus, Hospital Clinic, IDIIBAPS, Universitat de Barcelona, Spain; 2Emergency Medicine Department, IECCS Fondacion Ca Grupo, Ospedale Maggiore Policlinico, Milan, Italy; 3Centro de Investigación Biomédica en Red-Enfermedades Respiratorias, (CibeRes, CB06/06/0028), Barcelona, Spain; 4Respiratory Intensive Care Unit, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, SP, Brazil; 5Servicio de Enfermedades Infecciosas, Hospital Clinic, IDIIBAPS, Barcelona, Spain; 6Servicio de Neumología, Hospital Universitario La Fe, Valencia, Spain

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Results: Fifty-three patients (2%) presented thrombocytopenia, 204 (8%) thrombocytosis and 2,166 (90%) a normal platelet count. Patients with thrombocytosis were younger ($p<0.001$), while those with thrombocytopenia more frequently had chronic heart and liver disease ($p<0.001$ both). Patients with thrombocytosis more frequently presented respiratory complications such as complicated pleural effusion/empyema ($p<0.001$). Patients with thrombocytosis were more likely to be admitted due to chronic diseases ($p<0.001$), had a longer duration of mechanical ventilation ($p=0.001$) and ICU admission ($p=0.011$). Patients with thrombocytosis had longer hospital stay ($p=0.004$), higher 30-day mortality ($p=0.001$) and readmission rate ($p=0.001$) than those with a normal platelet count. Multivariate analysis confirmed a significant association between thrombocytosis and 30-day mortality (OR 2.588 95% CI 1.502-4.460 $p=0.001$).

Conclusions: Thrombocytosis in CAP is associated with poor outcome, complicated pleural effusion/empyema. Therefore thrombocytosis in CAP should encourage us to rule out respiratory complications and could be considered for severity evaluation.

P2475

eCURB outperforms CURB-65 and A-DROP for predicting 30-day mortality in pneumonia

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Rationale: Severity assessment tools that use objective data available in the electronic medical record include CURB-65, eCURB, and A-DROP, an electronic version of CURB-65 using continuous variables (Jones et al. Chest. 2011;140:156-163). Our aim was to compare eCURB, CURB-65, and A-DROP versus 30-day mortality in a contemporary, emergency department pneumonia cohort.

Methods: We identified pneumonia patients by ICD-9 code plus code compatible radiograph in 7 emergency departments Dec 1, 2009-Dec 1, 2010. Patients with community-acquired pneumonia (CAP) and health-care acquired pneumonia (HCAP) were included. We extracted initial clinical features and triage information from the electronic medical record. We determined mortality from the Utah Population Database. Receiver operator characteristic (ROC) analysis of mortality was conducted.

Results: We studied 2394 patients. 30-day mortality was 3.5% for 2061 patients with CAP and 16.2% for 333 patients with HCAP. The table shows areas under the curve (AUC) versus 30-day mortality.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>CAP Patients</th>
<th>HCAP Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>eCURB</td>
<td>0.85</td>
<td>0.87</td>
<td>0.74</td>
</tr>
<tr>
<td>CURB-65</td>
<td>0.81</td>
<td>0.83</td>
<td>0.74</td>
</tr>
<tr>
<td>A-DROP</td>
<td>0.82</td>
<td>0.83</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Conclusion: eCURB outperformed CURB-65 and A-DROP for mortality prediction in patients with CAP. For HCAP patients, all mortality predictors performed poorly.
Background: The CURB-65 score predicted hospital mortality better than IDSA/ATS minor criteria in low-mortality-rate settings is not clear. The purpose of this study was to determine the speculation.

Methods: 1230 adult patients admitted to our hospital from 2005 to 2009 for CAP were reviewed retrospectively.

Results: The hospital mortality was 1.3%. Percentage mortality increased significantly with CURB-65 score and the increasing number of IDSA/ATS minor criteria present. The number of CURB-65 criteria or IDSA/ATS minor criteria patient had significant increased odds ratios for mortality of 7.547 and 2.711, respectively. The sensitivities of a CURB-65 score of ≥ 3 and the presence of at least 3 minor criteria in predicting mortality from CAP was only 25% and 37.5%, with specificities of 92.2% and 96%, respectively. However, the sensitivities and specificities of a CURB-65 score of ≥ 5 and the presence of ≥ 2 minor criteria were 75% and 62.5%, and 91.8% and 86.5%, respectively. The area under the receiver operating characteristic curve for CURB-65 was 0.915 for predicting mortality, and the corresponding area for IDSA/ATS minor criteria was 0.805.

Conclusions: CURB-65 score predicted hospital mortality better than IDSA/ATS minor criteria, and a CURB-65 score of ≥ 2 or the presence of 2 or more minor criteria might be more valuable cut-off values for severe CAP in a low-mortality-rate setting.

P2482

Thrombin generation test – As a potential marker of severity and outcome of severe pneumonia with pulmonary sepsis

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Background: There is an important interaction between inflammatory mechanisms and coagulopathy in severe pneumonia (SP) with pulmonary sepsis. The aim. Determine the prognostic role of thrombin generation test (TGT) as a marker of severity in patients with SP with sepsis.

Materials and methods: 35 adults (18 years old or above) with SP and pulmonary sepsis were enrolled in the study. All patients were divided into two groups: survivors – 30 patients (85.7%, group 1) and died – 5 (14.3%, group 2) and stratified according to APACHE II score.

Results: According to TGT, the greater number of patients (84.6%) showed reduction in intensity of thrombin generation. We observed lengthening of Lat time.
of thrombin, reduction of Peak thrombin, and increase in tPpeak, and in general - reducing endogenous thrombin potential (ETP) (table 1). Analysis of the average of the absolute values of thrombin generation curve showed that mean values of ETP and Peak thrombin remain below the reference in both groups, and Lag time and tPpeak - higher than in control. In group 2, in comparison with the first one, peak thrombin was lower at 82.9%, tPpeak was shorter by 15.1%, and ETP was reduced by 3.9-fold.

When comparing patients according to severity, in group with APACHE II > 20 (compared with APACHE II <10), reduced Peak thrombin by 71.8% and ETP by 58.2% were defined, while lengthening lag time at 70.7% and increasing tPpeak by 234.4%.

Conclusion: According to our preliminary data, reducing the intensity of TGT in SP with pulmonary sepsis is associated with more severe course of the disease and can be regarded as a predictor of poor outcome.

P2483

Developing hospital admission criteria for electronic pneumonia decision support
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Rationale: Severity assessment tools that use objective data available in the electronic medical record to predict mortality include CURB-65, <CURB (an electronic version of CURB-65 using continuous variables), and A-DROP. We developed an electronic decision support tool for the emergency department that recommends admission for patients with 1) CURB 30-day mortality estimate ≥5% 2) ≥3 severe community acquired pneumonia criteria (2007 IDSA/ATS), or 3) PaO2/FiO2 ratio ≥280. Our aim was to compare the tool’s admission rule to the mortality predictors.

Methods: We identified pneumonia patients by ICD-9 code plus radiograph in 7 emergency departments Dec 1, 2009-Dec 1, 2010. We extracted initial clinical features, triage information and mortality from the electronic medical record; physician review identified multilobar infiltrates from radiograph reports. Simple agreement with hospital triage (outpatient versus inpatient) and mortality were compared.

Results: 57% of all patients were admitted (54% CAP and 76% HCAP) with a 30-day mortality of 5.5% (3.5% CAP, 17% HCAP). Table shows simple agreement with triage and mortality. While the actual admission rate was 57% with 13 outpatient deaths, the admission rule would have resulted in a 48% admission rate with 9 outpatient deaths.

% Agreement

<table>
<thead>
<tr>
<th>Admission</th>
<th>All (N=2994)</th>
<th>CAP (N=2060)</th>
<th>HCAP (N=934)</th>
</tr>
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<tbody>
<tr>
<td>Triage %</td>
<td>Mortality %</td>
<td>Triage %</td>
<td>Mortality %</td>
</tr>
<tr>
<td>Admit Rule</td>
<td>76</td>
<td>57</td>
<td>77</td>
</tr>
<tr>
<td>CURB-65 ≤3</td>
<td>70</td>
<td>58</td>
<td>71</td>
</tr>
<tr>
<td>A-DROP ≤1</td>
<td>78</td>
<td>48</td>
<td>78</td>
</tr>
<tr>
<td>A-DROP &gt;1</td>
<td>63</td>
<td>78</td>
<td>64</td>
</tr>
</tbody>
</table>

Conclusion: The tool’s admission rule agreed accurately with observed triage and might lower admission rate with improved patient safety.

P2484

Risk factors predicting mortality in patients with lung abscesses
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Introduction: Lung abscesses continue to express high mortality in patients hospitalised with the disease.

Objectives: To identify the factors associated with increased mortality in patients diagnosed with lung abscesses.

Methods: Retrospective study performed via hospital records on patients admitted with lung abscesses between January 2009 and January 2011 at the largest state-owned tertiary care centre in Karachi, Pakistan. Of 41 patients hospitalised, 17 could not survive and were evaluated for factors to determine association with heightened mortality.

Results: Mortality due to lung abscess stood at 41.46% (17/41). Adult male patients were found to have a higher mortality with 13/17 (76.5%) expired patients being male. Majority (21/41, 51.2%) of the cases belonged to the 41-60 year old age group with highest mortality (9/17, 52.9%). Number of patients with blood sugar levels of >200 mg/dl who succumb to disease was 9/17, 52.9%. Patients with history of smoking, diabetes mellitus, and alcohol intake expressed mortality rates of 70.6%, 58.8%, and 17% respectively; while 29.4% of the mortalities were positive for Pseudomonas aeruginosa on sputum culture. A significant association was found between elevated mortality and low haemoglobin levels at time of admission; mortality was 76.5% (13/17, p < 0.013) in patients with Hb between 7-10 mg/dl.

Conclusions: The risk factors involved with heightened mortality included male gender; older age; history of smoking, and diabetes. High blood sugar levels and detection of Pseudomonas aeruginosa on sputum cultures were also implicated. Hb level of <10 mg/dl was a statistically significant predictive factor for increased mortality.
P2488

Weight of CURB-65 criteria for community-acquired pneumonia in a very low-mortality-rate setting

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Background: The CURB-65 score is a simple well validated tool for the assessment of severity in community-acquired pneumonia (CAP). Weight of each criterion in very low-mortality-rate settings is not clear.

Objective: To determine the weight.

Methods: 1230 adult patients admitted to our hospital from 2005 to 2009 for CAP were reviewed retrospectively.

Results: 30-day mortality rose sharply from 0%, 1%, 8.2% and 16.7%, respectively, for patients with CURB-65 scores of 0, 1, 2 and 3 to 100.0% for patients with the scores of 4 (p < 0.001). Confusion had the strongest association with mortality.

Table 1. Association of CURB-65 criteria with 30-day mortality (n=1230)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Alive (%)</th>
<th>Dead (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>88 (81.8)</td>
<td>4 (18.2)</td>
<td>22.148 (6.516–75.288)</td>
</tr>
<tr>
<td>Urea &gt; 7 mmol/L</td>
<td>70 (49.7)</td>
<td>8 (10.3)</td>
<td>16.343 (5.957–44.838)</td>
</tr>
<tr>
<td>Respiratory rate ≥ 30 breaths/min</td>
<td>28 (93.3)</td>
<td>2 (6.7)</td>
<td>6.051 (1.313–27.896)</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>172 (97.7)</td>
<td>4 (2.3)</td>
<td>2.019 (0.644–6.333)</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>322 (95.8)</td>
<td>14 (4.2)</td>
<td>19.391 (4.383–85.789)</td>
</tr>
</tbody>
</table>

Low blood pressure was not associated with mortality. Confusion, urea > 7 mmol/L and age ≥ 65yrs showed independent relationships with mortality (Odds ratio, 11.537, 5.988 and 10.462; respectively). Urea > 7 mmol/L was most strongly associated with sequential organ failure assessment (SOFA) scores. Confusion was in closest relation to hospital length of stay. Age ≥ 65yrs had the strongest association with costs.

Conclusions: The individual CURB-65 criteria were of unequal weight in predicting 30-day mortality, SOFA scores, hospital length of stay and costs in a very low-mortality-rate setting, and low blood pressure was not associated with mortality.

P2489

Pulmonary CT findings of visceral larva migrans due to Ascaris suum

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Objective: To retrospectively evaluate the CT findings of pulmonary involvement in patients with visceral larva migrans due to Ascaris suum.

Methods: Institutional review board approval was obtained, and informed consent was waived. Chest CT scans obtained between January 1994 and December 2007 in 35 patients with Ascaris suum were retrospectively evaluated by three chest radiologists. In 4 patients who underwent surgical or transcortical biopsy, comparisons of the CT images with the actual specimens were performed.

Results: On CT scans, abnormal findings were seen in 30 patients. The most common abnormality consisted of nodules (n=20) in which the majority had a halo of ground-glass attenuation (n=18), followed by ground-glass attenuation (n=19), and interlobular septal thickening (n=15). These abnormalities were predominantly seen in the peripheral lung (n=25). Of the 7 patients who underwent follow-up CT scans, nodules (n=6) and ground-glass attenuation (n=5) had migrated in 4 patients. Pathologically, these findings corresponded to marked eosinophilic infiltration into the interstitium.

Conclusions: These CT findings are considered to be suggestive of thoracic involvement in patients with visceral larva migrans due to Ascaris suum.

P2490

Community acquired pneumonia in the emergency department: Comparison of clinical indication to in-hospital treatment and severity scales predicting mortality

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Introduction: Severity scoring systems (SSS) are used to predict risk, to help decisions about management strategies. The most notable scales in clinical use for Community acquired pneumonia (CAP) in the Emergency Department (ED) are CURB65 and CRB65.

Objective: To analyze cases in which the clinical judgement to admit and treat in-hospital a Patient with CAP disagreed with the low risk profile established by SSS.

Materials and methods: Observational clinical study in the ED of a university teaching hospital, enrolling every adult Patient with CAP related hospitalization in 4 months period.

Results: 73 Patients were emergently admitted: 172 resulted in high-intermediate risk class according to SSS. We compared high-intermediate versus low risk groups. The first were higher in mortality. Dimler, urca, creatin, CK, CKMB, LDH, NTproBNP, dyspnoea, neurologic dysfunction, need for mechanical ventilation or management in High Dependency Unit; and lower in SpO2 and rate of antibiotic treatment previously started. When the decision to admit showed discordance between SSS risk profile and clinical judgement, some elements were often involved: social and welfare aspects, chronic diseases, previous treatment failure, laboratory abnormalities, respiratory failure, chest Xrays characteristics.

Discussion: In the ED, careful clinical judgement is still irreplaceable in decision and management processes, beyond by SSS. New studies will define which parameters to develop to increase the value of some pivotal aspects in the triage process of CAP in the ED, to focus on the real need for hospitalization in the single Patient.

P2491

The influence of respiratory infection on bronchial asthma

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Acute respiratory infection (ARI) intensify the severity of inflammation reaction of bronchial asthma (BA).

Aim: To study the influence of ARI on the level of the control over BA and the immunology of this combination and the possibilities of treatment.

Method: The clinical monitoring over 316 patients with bronchial asthma for a year, the immunological research and the results of treatment with affine purified antibodies for gamma-interferon of the human (48 cases).

Results: During the observation there were fixed 4,±±0.3 episodes of ARI for each patient. Analyzing the graph of frequency of ARI with BA, some differences with seasonal virus ARI attract our attention. There is no traditional apex of seasonal virus ARI in the February, the reduction of tension is seen only by May, with seasonal virus ARI attract our attention. There is no traditional apex of seasonal virus ARI in the February, the reduction of tension is seen only by May, with seasonal virus ARI attract our attention. There is no traditional apex of seasonal virus ARI in the February, the reduction of tension is seen only by May,
the cellular immunity, the increase of the level of IgG to 9.88±0.41 I/ml with the following return to the previous level, and also the real reduction of the level of IgE to 69.2±6.5 mg/ml among the patients with exogenous asthma.

P2492

Risk factors, etiology and prognosis of adult patients with hospital-acquired pneumonia in Shanghai

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Objective: To investigate clinical features, risk factors, drug resistance, and clinical outcomes of hospital-acquired pneumonia (HAP) in Shanghai.

Methods: From November 2007 to December 2009, HAP was observed and prospectively studied in Shanghai seven large general hospitals. Clinical data and etiology of pneumonia were recorded. Blood and sputum cultures, identification of bacteria in specimen and drug sensitivity test were performed.

Results: We included 204 patients (mean age 68.07±16.61 years (± SD), 58.3% more than 70 years old) mainly from surgical wards, surgical ICU, medical wards, and medical ICU. Patients were complicated with cerebral vascular disease (19.61%), diabetes mellitus (14.22%), or abdominal surgery (11.76%). Ventilator-associated pneumonia were demonstrated in 20.6% of the cases. Total mortality was 15.69%. Increased heart rate, decreased arterial PH, hypoxia, high glucose, increased plasma creatinine and vasopressor use were associated with the poor outcome in patients with HAP. In all bacterial isolates from HAP, 64.90% were gram-negative bacilli bacteria, including Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli. 26.5% of the isolates were Staphylococcus aureus and the rate of MRSA was 65.4%.

Conclusion: The elderly, cerebrovascular diseases, and diabetes are risk factors of HAP. The major pathogen is the most serious complication associated with poor prognosis of HAP. In this setting, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, and Staphylococcus aureus (MRSA 60%) should be considered as the common etiologic pathogens of HAP.

P2493

Bacteriological analysis of lower respiratory tract in patients with rheumatoid arthritis complicated with either colonic or pulmonal diseases

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Background: Lower respiratory tract infections (LRTI, bronchiectasis, bronchitis and broncholithis) are common comorbidities in patients with rheumatoid arthritis (RA). According to the recent advances of the treatment modalities of RA and other collagen vascular diseases (CVD) including anti-inflammatory biological agents, an aggressive diagnosis of LRTI including non tuberculous mycobacteriosis (NTM) is becoming more important.

Patients and methods: From April 2008 to August 2011, patients with RA and other CVD with suspicion of NTM were enrolled. Additionally, patients with non-CVD with suspicion of NTM were also enrolled as controls. Bronchial washing were performed. Scores, biomarkers and risk factors in respiratory infections

265. Scores, biomarkers and risk factors in respiratory infections

P2494

CUREB 65 or CURB (S) 65 for community acquired pneumonia?

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The CURB-65 score (confusion, blood urea >42.8 mg/dl, respiratory rate >30/min, blood pressure <90/60 mm Hg, age >65) is quite a practical method for determining the need for hospitalization in community-acquired pneumonia. On the other hand, it is a known fact that CURB-65 is rather more sensitive for determining patients with severe illness, and lacks sensitivity towards other factors dealing with milder cases. The purpose of this study is to investigate factors that determine the need for hospitalization in patients not requiring hospitalization according to CURB-65.

The study was undertaken on 54 patients diagnosed with pneumonia and were recorded to the TTD pneumonia database between 2010-2012. Nineteen (35.2%) of the patients were female while 35 (64.8%) were male. The mean age was 67.5. The total treatment time, duration of hospitalization, saturation (SpO2), partial arterial oxygen pressures (PaO2) and mean pneumonia severity index (PSI) values were compared between 15 patients receiving 0.1 CURB-65 points (27.8%) (Group 1) and 39 patients receiving 2 or more CURB-65 points (72.1%) (Group 2). According to the data, the mean PSI score in Group 1 (74.93±30.45) and in Group 2 (106.61±37.41) were statistically different (p<0.003) even though their SaO2, paO2, hospitalization and treatment time were similar (Group 1 SaO2: 89.8±8.45, PaO2: 53.8±6.72, Group 2 SaO2: 89.23±5.94, PaO2: 54.6±8.48; p<0.05).

The study shows that although the PSI are different, low SaO2 levels in both groups show that hypoxemia is the main factor for hospitalization in patients with CURB65 indexes. Therefore we propose that the CURB(S) 65 hypotetic index is a better determinant than CURB 65 for hospitalization.

P2495

Do physicians use urinary pneumococcal antigen test (UPAT) appropriately?

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Introduction: UPAT is a useful test to identify the pneumococcal aetiology of pneumonia. The specificity and sensitivity are high in moderate to severe pneumonia. Most common antibiotic regimen guided by the results. We did this study to look at the utility of the test and how it altered clinical management.

Method: We conducted a retrospective analysis of medical records of all patients who had UPAT in a 6-month period between December 2007 and May 2008. The study was performed in a 1000 bed tertiary teaching hospital in United Kingdom. BTS CURB-65 scoring was used as a measure of severity of pneumonia.

Results: One hundred and eighteen patients had the test in the 6-month study period but only 37 patients met criteria for moderate to severe pneumonia (MSP). Rest of the patients had non-severe pneumonia, infective exacerbation of asthma and COPD. The most important use of the test is in modifying the antibiotic regimen according to the result. We analysed the test results and how it altered clinical management.

Conclusion: UPAT is used inappropriately and the test results are not effectively used in modifying management.

P2496

A clinical, radiological and microbiological profile of lung abscesses

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Introduction: Lung abscesses continue to be a frequent presentation for physicians in Pakistan With little local data available on the clinical correlations of the disease, there is a pressing need to describe the various factors associated with the condition.

Objectives: To evaluate the clinical,radiological and microbiological profile of lung abscesses.

Methods: A retrospective case study was done through studying hospital records of 41 patients admitted with lung abscess at a tertiary care hospital in Karachi, Pakistan. Demographical data, clinical symptoms, risk factor assessment, radiological findings and culture reports were studied to outline a relevant profile.

Results: Over half the cases comprised of adult, male patients. Clinically, 90.2% presented with productive cough, followed by 82.9% with fever, and 58.5% with haemoptysis. A significant association of 65.3% was found with smoking. Among other risk factors, poor oral hygiene was found in 50.6% of the cases, diabetes mellitus in 43.9%, pneumonia in 22%, and malignancy was diagnosed in 4.9%. Radiographically, 56.1% showed bilateral and 51.2% had right lower lung zone involvement. Sputum Gram staining revealed Gram negative rods and Gram positive cocci in 36.6% of the cases. ABF smear was positive in 22%. Sputum cultures showed Pseudomonas aeruginosa was present in 29.3%. No growth on blood cultures was seen in 86.6% and only 9.8% exhibited growth of E. coli.

Conclusion: Lung abscess was found to be more common in adult men,and was significantly related to smoking. The other common risk factor was found to be poor oral hygiene,while the right lower lung zone was the main site of abscess formation. Pseudomonas aeruginosa was the major pathogen implicated on sputum cultures.
P2497
The comparison of different methods of etiologic diagnosis of community-acquired pneumonia
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The aim of our study was to compare different laboratory methods of the CAP etiological factor identification. 30 patients (20 male and 10 female) with non-severe CAP were enrolled in the study (50,5±3,4 years). We have performed: microbiological test and polymerase chain reaction (PCR)-based study of induced sputum and peripheral blood samples, serological tests to evaluate the level of IgM and IgG antibodies to C.pneumoniae and M.pneumoniae in peripheral blood.

Results: With all laboratory tests the etiologic agents were determined in 76,7% of patients, mostly of S.pneumoniae. In sputum there were 30 positive results in PCR and 19 - in microbiological study. PCR study of sputum revealed in 10 patients monobacterial flora, 5 - bacterial mixture, 4 - virus-bacterial mixture while in microbiological study in all 19 patients there was monobacterial flora. The frequency of S.pneumoniae was comparable both in the PCR study, and in microbiological studies (46.6%). Frequency of K.pneumoniae and H.influenzae identification was the highest in the PCR study of sputum (13,3 and 26,7%).

Conclusion: The comparison of different methods of etiologic diagnoses is the most appropriate way for non-severe CAP.

P2498
Prevalence of MRSA nasal carrier rate in hematology patients of Benghazi Medical Center using PCR-based method; first study in Libya
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Introduction: Carriers of multi drug resistant staphylococcus aureus (MRSA) may spread or develop infections if not discovered and properly treated. Knowing MRSA carrier status would be useful especially for hematology patients on chemotherapy.

Aim and objective: The aim of the study was to determine prevalence of nasal MRSA carrier rate in hematology patients of Benghazi Medical Center (BMC).

Method: Hematology patients admitted to hospital or under regular follow up in clinic were included and consent obtained. Nasal swabs (AFTACA) were taken in standard way. Samples were analyzed for the presence of MRSA by using PCR based system (Gene expert machine-GXMRSA-120). The following data were collected: age, gender, weight, height, underlying hematological diagnosis, history of chemotherapy, hospital admission or MRSA swab in the previous 6 months and long term intravenous device insertion.

Results: 107 patients were screened. 49 (45.7%) were males. Mean age was 48 years. The race index was 25 kg/m². 5 out of 107 patients tested positive for nasal MRSA. 4 out of 5 had lymph proliferative disorders and all received chemotherapy. The rest of results are outlined in table.

<table>
<thead>
<tr>
<th>Age (mean)</th>
<th>MRSA positive, n=5 (5%)</th>
<th>MRSA negative, n=102(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>52 years</td>
<td>47 years</td>
</tr>
<tr>
<td>Mycoplasmolrophic disease</td>
<td>3 (60%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Blending disorder</td>
<td>0 (0%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Other disease</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>MRSA (H/O)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intravenous device</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Conclusion: 4.5% of patients screened in hematology department of BMC were nasal carriers for MRSA. This is the first study in Libya using PCR based method.

P2499
Influence of age in the clinical differentiation of atypical pneumonia in adults
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Background and objective: The Japanese Respiratory Society (JRS) scoring system is a useful tool in the early and simple presumptive diagnosis of atypical pneumonia, Mycoplasma pneumoniae and Chlamydia pneumoniae pneumonia. However, it has been suggested that it seems to be difficult to diagnose atypical pneumonia in the elderly using this system. In the present study, we evaluated the accuracy and usefulness of the JRS scoring system in the different age groups.

Methods: We analyzed 262 cases of M. pneumoniae, 98 cases of C. pneumoniae and 364 cases of common bacterial pneumonia.

Results: The comparison of co-morbid illnesses and higher risk classes in the elderly (age ≥60 years) group was significantly higher than those of non-elderly patients (age <60 years) in both atypical pneumonias. One or more additional etiological factors were found more frequently in the elderly group than in non-elderly patients. The diagnostic sensitivity and specificity for atypical pneumonias were 39% and 88% for the elderly group and 86% and 88% for age non-elderly group, respectively. When the diagnostic sensitivity was analyzed for different ages stratified into 10-year groups, the sensitivity was highest in the 18-29-year-old group and decreased in order from the youngest to the oldest age group.

Conclusions: Our results indicate that it is difficult to distinguish between atypical pneumonias and bacterial pneumonias in the elderly using the JRS scoring system. When treating patients aged ≥60 years, physicians should choose fluoroquinolones or β-lactams + macrolides as empirical first-choice drugs, so as to always include potential antibiotic cover for atypical pathogens.

P2500
Clinical features and prognostic factors in elderly patients with aspiration pneumonia
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Background: The aims of this study were to investigate the clinical features, risk factors, and outcomes of patients with aspiration pneumonia and to identify the prognostic factors contributing to mortality in these patients.

Method: Following a retrospective review of clinical data and radiographic findings between 2006 and 2010, 176 patients were enrolled in this study.

Results: The median age of patients was 75 years (range, 66-81), and 125 (71%) patients were male. 89 (51%) were admitted to the medical ICU and their clinical course was fulminating as a result of acute respiratory failure requiring mechanical ventilation in 79 (45%), septic shock in 36, ARDS in 20, and multi-organ failure in 26. Overall in-hospital mortality was 22.7% (40/176) with a median survival of 18 (range 9-43) days. Comorbidities or risk factors associated aspiration included cerebrovascular accidents (n=79), bedridden (n=57), malignancy (n=29), dementia (n=25), alcoholism (n=18) and Parkinson’s disease (n=14). The leading pathogen considered to be associated with pneumonia in patients (n=60), followed by A. baumannii (n=24), K. pneumonia (n=19), and P. aeruginosa (n=17). Independent predictive factors of in-hospital mortality included septic shock (HR 7.1, 95% CI, 2.6-19.3, P<0.001), dyspnea (HR 5.3, 95% CI, 1.5-19.1, P=0.030), hypoxemia (serum albumin ≥2.5 g/dl) (HR 2.7, 95% CI, 1.1-6.9, P=0.038), and CVA (HR 2.6, 95% CI, 1.1-6.5, P=0.036).

Conclusion: Aspiration pneumonia has a high mortality rate and poor prognosis, particularly in patients with septic shock, dyspnea, hypoxemia, CVA.

P2501
Incidence of ventilator associated pneumonia (VAP) and assessment of sereral estimation of procalcitonin levels as a prognostic marker in cases of VAP in a tertiary centre in India
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Introduction: Patients developing VAP have higher mortality rates and longer ICU stays. Various markers have been used for prognosis in patients who develop VAP. We studied serial estimation of procalcitonin (PCT) levels in VAP as a prognostic marker.

Aims & objectives: To calculate incidence of VAP per 1000 ventilator days and assess role of PCT as a prognostic marker in VAP.

Material & methods: All consecutive patients intubated in the ICUs were assessed for development of VAP using CPIS score. In patients who developed VAP during the study period, there serum PCT levels were collected on day 0, 3 and 7 of developing VAP.

Results: We studied 351 patients, 25 developed VAP. Incidence of VAP was 63.3/1000 ventilated days. (Incidence/1000 ventilator days= No. of VAP cases/Total ventilator days C 1000). Patients having higher initial levels of & in whom the levels decreased subsequently showed better survival as compared to less initial values and a marginal fall/rise in subsequently values. Mean value of PCT in survivor group on 0.3 & 7 days were 45.72, 21.01 and 7.26 respectively (standard error of mean of 34.71, 15.28 & 4.95) while the levels in non-survivor group were 1.94, 2.11 & 1.99 respectively (standard error of mean of 0.72, 0.80 & 1.25). The PCT levels remained low/steady on serial monitoring in the non survivor.

Conclusions: Our study further re-enforces the role of serial estimation of PCT as a prognostic marker in patients with VAP. Though further studies with larger number of patients is required to make its estimation as a standard protocol.
P2502
Procalcitonin and proadrenomedullin in COPD patients: Stable state versus exacerbation difference in mortality rate?

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Rationale: Little is known about proadrenomedullin (pro-ADM) and procalcitonin (PCT), biomarkers in COPD, in relation with mortality. Stolz. D et al. (Chest 2008;134:263-272) suggested that pro-ADM at hospitalization for an acute exacerbation of COPD (AE-COPD) predicts survival. In our cohort of well defined COPD patients (the COMIC study) we wanted to study the association between PCT and pro-ADM levels in stable state and at hospitalization with mortality.

Methods: PCT and pro-ADM levels were determined in 187 patients who provided a plasma sample during stable state and at hospitalization for AE-COPD. The mean follow-up after inclusion was 46 months ±20. Date of death was verified from the municipal administration.

Results: The PCT and pro-ADM levels were significantly increased at hospitalization compared to stable state. Patients who died had a significantly higher level of PCT and pro-ADM both during stable state and hospitalization.

Table 1. Pro-ADM and PCT results

<table>
<thead>
<tr>
<th>Pro-ADM nmol/l (mean ± (SD))</th>
<th>PCT ng/ml (median (IQR))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable state</td>
<td>Exacerbation</td>
</tr>
<tr>
<td>Died (N=82)</td>
<td>0.93 (±0.41)</td>
</tr>
<tr>
<td>Alive (N=104)</td>
<td>0.72 (±0.25)</td>
</tr>
</tbody>
</table>

Conclusions: Both PCT and pro-ADM could be a marker for mortality in COPD.

P2504
Plural fluid C-reactive protein concentration in discriminating uncomplicated from complicated parapneumonic pleural effusion

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Parapneumonic pleural effusions (PPE) are the second most common cause of exudates after malignant effusions. The early discrimination between uncomplicated parapneumonic effusions (UPPE) from complicated parapneumonic effusions (CPPE) is important for adequate management of PPE. Oversight in distinction between these two groups with classical recommended markers (pH, lactate dehydrogenase (LDH) and glucose) require alternative tests. The aim of this study was to determine the role and value of plural fluid C-reactive protein (CRP) in discrimination between UPPE from CPPE. The study was including 60 patients: 30 with UPPE and 30 with CPPE. CRP concentration was measured with Ektachem Clinical Chemistry tests on analyzer Vitros 250. LDH and glucose were performed on analyzer Vitros 350. Pleural fluid was aspirated from pleural cavity with ultrasound guidance. Receiver-operating curve were to assess the sensitivity and specificity of plural biochemical parameters. CRP was statistically higher in CPPE (118.97±31.04 U/L) than in group with UPPE (40.24±22.30 U/L) (t=11.26; p<0.005). According to Spearman’s correlation, positive correlation was between levels of plural CRP concentration and CRP in serum (r=0.635; p<0.01). Positive correlation was between pleural concentration of CRP and LDH (r=0.811; p<0.01). Significant negative correlation was between levels of CRP and pH (r=-0.813; p<0.05), and of CRP and glucose in pleural fluid (r=-0.826; p<0.01). The CRP cut-off value of 73.43 mg/l differentiated CPPE from UPPE with a sensitivity and a specificity of 100%.

Conclusion: CRP may be used as a good marker in discrimination from UPPE from CPPE and management of patients with PPE.

P2505
Lung and serum biomarkers of tissue lesions due to acute exacerbation of COPD

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Introduction: In COPD are common respiratory tract infections, resulting in exacerbation of disease. Laboratory findings are normal or slightly abnormal, such as inflammatory biomarkers: WBC, CRP, LDH, ALP. What is going on with pathological processes in lung tissue? Aim: Analyze tissue damage topical and serum biomarkers.

Methods: 56 COPD pts in exacerbation underwent bronchoscopy. Tissue damage topical biomarkers (LDH, CRP, ALP, bronchus pH acidity) were analyzed from the bronchial aspirate.

Results: Average pts age is 64.6 y. Lung LDH mean value (L-LDH) was 150.88±18.4, and in serum 181.66±79.64 U/L. Lung ALP mean value was 58.5±37.75 U/L, and in serum (S-ALP) 78.76±28.66 U/L. Lung CRP mean value (L-CRP) was 0.06±0.78 mg%, and in serum 56.54±17.45 mg%. L-CRP was detected in 10 pts only (in 76 not).

Mean lung acidity (pH) was 7.89±0.82. The most common organism causing COPD exacerbation was: H. influence, with biomarker values of L-LDH X=1746.30 U/L, and S-LDH=188.4 U/L. The second most common was P aeruginosa, with biomarker values of L-LDH X=1456.61 U/L, and S-LDH=201.8.

Conclusion: In pts with COPD, serum inflammatory biomarkers are not consistent index of COPD exacerbation, nor its severity. Lung LDH values are extremely increased, and serum LDH values are rarely pathological. These facts indicate severe lung tissue damage, although S-LDH values are not significant for pathological process. In contrast, L-CRP was found only in trace in few pts, whereas serum values are always increased. In bacterial lung inflammation pH is alkaline (X=7.89), however, it is not comparable with blood pH values, since the measuring method was different.

P2506
Elevated creatinine is a sensitive severity marker in community acquired pneumonia

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Background: It is recognised that acute kidney injury (AKI), as classified by the International Kidney Disease Group Improving Global outcomes staging classification, is associated with increased 30-day mortality in patients with community acquired pneumonia (CAP). This study aimed to determine if increases in serum creatinine not meeting the criteria for AKI were associated with increased 30-day mortality.

Methods: A retrospective study of patients admitted over a 6 month period, with radiologically confirmed CAP. Baseline creatinine, admission creatinine, AKI severity and 30-day mortality were recorded.
Results: 210 patients (52% male, 48% female) were included in the study with a median age of 76 years. 26 (12.4%) patients met the criteria for AKI. 57 (27.1%) patients had rises in creatinine above baseline, but not meeting AKI criteria. As expected AKI scoring was associated with increased 30 day mortality.

Table 1. Incidence of AKI and 30 day mortality rates

<table>
<thead>
<tr>
<th>AKI staging</th>
<th>Number of Patients</th>
<th>30 Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>185 (87.1%)</td>
<td>28 (15.1%)</td>
</tr>
<tr>
<td>1</td>
<td>15 (7.1%)</td>
<td>4 (26.6%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (3.8%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (1.4%)</td>
<td>2 (66.7%)</td>
</tr>
</tbody>
</table>

Greater than 20% rises in creatinine above baseline were strongly associated with a higher 30 day mortality rate.

Figure 1: Elevated creatinine and 30-day mortality.

Log rank test p<0.002.

Conclusions: Creatinine rises as low as 20% above baseline in patients with CAP are associated with higher 30 day mortality rates than for patients without creatinine rises.

P2507
Admission hyperglycaemia is associated with increased risk of diabetes mellitus following hospitalisation with community acquired pneumonia

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Background: Hyperglycaemia has previously been shown to correlate with adverse outcome in community acquired pneumonia (CAP). The aim of this study was to assess whether hyperglycaemia is associated with increased risk of diabetes mellitus (DM) following admission with CAP.

Methods: We conducted a prospective observational study of patients who had survived hospitalisation with CAP. All patients had random serum glucose measured on admission and were categorised into normoglycaemia (4.0-6.0 mmol/L), mild hyperglycaemia (6.1-7.0 mmol/L), moderate hyperglycaemia (7.1-14.0 mmol/L) and severe hyperglycaemia (>14.0 mmol/L). Patients with pre-existing DM or those who were hyperglycaemic on admission were excluded. The outcome of interest was diagnosis of diabetes mellitus within one year of hospital discharge.

Results: 1202 patients were included with 85 (7.1%) diagnosed with DM within one year of follow-up. Rates of diabetes diagnoses according to admission glucose level and normoglycaemia group 3.9%, mild hyperglycaemia group 6.4%, moderate hyperglycaemia group 9.8% and severe hyperglycaemia group 64.7%. On multivariable analysis, adjusting for age, gender, smoking status, cardiovascular disease and pneumonia severity, there was a graded increase in association of hyperglycaemia and subsequent diabetes diagnosis: mild hyperglycaemia (OR 1.55 (0.78-3.09) p=0.2), moderate hyperglycaemia (OR 1.69 (1.25-2.29) p=0.0007), severe hyperglycaemia (OR 3.0 (2.04-4.46) p<0.0001).

Conclusions: Moderate to severe hyperglycaemia on admission with CAP is associated with increased risk of subsequent DM diagnosis within one year of hospital discharge.

P2509
Study on human tracheal bronchial epithelial cells secreting cytokines in vitro by nontypeable haemophilus influenzae

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Obstructive To study the interaction of nontypeable haemophilus influenzae strain ATCC49247 with primary human bronchial epithelial cells (HBEc) and the NTHi-induced release and expression of proinflammatory cytokine in the HBEc.

Methods: HBEc were isolated by low temperature protease digestion and cultured in serum-free medium. Confluent epithelial cell cultures were incubated with NTHi, NTHi + erythromycin(0.1mg/L), NTHi + gentamicin(100mg/L), NTHi + dexamethasone(100µM)and normal untreated control cells after 24h. Release of IL-8 and TNF-a into the supernatant was assayed by enzyme-linked immunosorbent assay. The expression of ICAM-1 was examined by immunohistochemistry staining.

Results: (1) Some HBEc's were transformed and died after 24h. (2) HBEc: NTHi-induced cells released significantly greater amounts of IL-8 and TNF-a (p<0.001). (3) NTHi + erythromycin(0.1mg/L), NTHi + gentamicin(100mg/L), NTHi + dexamethasone(100µM) significantly reduced the total number of ICAM-1 positive cells from 10±5% (in control untreated cultures) to 8±3% (p<0.001). Similarly, incubation of HBEc with 0.1mg/L erythromycin and gentamicin significantly induced release of IL-8, TNF-a and the expression of ICAM-1, which was blocked by 10µg/ml erythromycin and 100µM dexamethasone.

Conclusions: HBEc can release IL-8 and TNF-a. NTHi may increase significantly release and expression of proinflammatory cytokine. Gentamicin have no anti-inflammatory effects. Erythromycin may have anti-inflammatory effects. Dexamethasone has distinct anti-inflammatory effects.

P2510
Comparision of procalcitonin and CURB-65 in pneumonia

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CURB-65 score, pneumonia and hospital admission decision as well as useful and simple clinical scoring model for prediction of pneumonia. CURB-65 score, =+2 is recommended for patients with inpatient treatment. The other hand, procalcitonin (PCT), a marker for determining prognosis of pneumonia. CURB-65 score and PCT levels were compared in this study.

In this study 58 patients were admitted to our clinic due to common acquired pneumonia. Patients, the clinical and laboratory findings were recorded. CURB-65 score was calculated. CURB-65 score in patients with Group-I (score, <+2) and Group-II (score, >=+2) as divided into 2 groups. (Normal value: Procalcitonin<0.1, CRP <0.5).

In our study, median age 68 (18-96) was found. The most frequent clinical symptoms were cough (83%), dyspea (71%) and fever (67%), respectively. In group-I, mean PCT level was 3.6±7.7, in Group-II PCT was 9.2±0 (p = 0.028). The average white blood cell was 12±8.6 and was 13±6.2 ± 2. (p > 0.05). CRP level of 18±4.1, and 19±4.1 (p > 0.05), respectively. Total 11 (19%) patients died. The median value of PCT was significantly higher in patients who died (2.2 ± 0.45, p = 0.012). Similarly, CRP was significantly higher in patients who died (33 vs. 14, p = 0.016). PCT levels were positively correlated with the CURB-65 score (r = 0.296, p = 0.024).

As a result, PCT levels correlated with a CURB-65 score in pneumonia. Initial PCT level may be considered in patients with pneumonia.
P2511

Bacterial infection in acute exacerbations of chronic obstructive pulmonary disease
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Introduction: Infections are major causes of acute exacerbations (AE) of chronic obstructive pulmonary disease (COPD) which increase mortality rate and impair quality of life of patients.

Aim: Determine the bacterial profile in patients hospitalized in our department for AE of COPD caused bronchopulmonary-infection.

Methods: Retrospective study including 100 patients hospitalized for AE of COPD. Bronchopulmonary infection was considered because of clinical, radiological and/or bacteriological criteria.

Results: Mean age of patients was 63 years and mean duration of the disease was 11 years. Regarding to GOLD classification, 63% of patients had COPD stage II, 34% stage III and 3% stage IV. Infection agent was identified in 69 patients with sputum culture. Isolated pathogens were: Haemophilus Influenzae (28), Streptococcus Pneumoniae (8), Streptococcus (3), Enterobacter (12). Pseudomonas Aeruginosa (10), serratia (2), Klebsiella (2) and 4 patients had mixed infections (staphylococcus and Haemophilus). Modification of sputum colour is the most parameter correlated with bacterial infection. Duration of COPD more than 10 years, severe dyspnea and impaired respiratory function (FEV1 < 35%) were significantly associated with more aggressive pathogens (negative gram bacilli).

Conclusion: Bacterial infection is major cause of AE of COPD and is considered as a worsening lung function factor. In patients with lower FEV1, AE is caused by more aggressive pathogens.

P2512

Influence of lung infection on the course and outcome in patients with stroke
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Purpose: Occurrence of acute bacterial lung infections affects the course of disease and outcome in stroke patients. Aim of the study was to explore the frequency of hypostatic and aspiration pneumonia, their risk factor and their effect on outcome in patients with acute stroke.

Methods: In this retrospective study, we evaluated patients with stroke who were hospitalized in the Department of Neurology in Niš, between January - December 2011. There were a total of 1312 patients with stroke. 824(62.80%) had ischemic stroke, and 488 (37.20%) had haemorrhagic. Patients were evaluated and had the same investigations with anamnestic, clinical, neurological, biochemical analyses, physical examination by a specialist for pulmonary diseases, lung X-ray, Doppler of the neck blood vessels, EEG, CT of lung, CT/MRI of brain, MRA angiography.

Results: Of a total of 1312 patients with stroke, 59 patients (4.49%) of them had pulmonary complications within 10 day from the event. There were 36 male and 23 female patients, age from 41 to 82 years. Pulmonary infections in all of the patients was confirmed by x-ray imaging and biochemical analyses. 28(47.46%) patients had lobar pneumonia, 23(38.98%) had bilateral broncho pneumonic changes and 13(5.56%) had pleural effusion. All of the patients were highly febrile, with increased sedimentation and leucocitosys with dominant neutrophiles. Despite the intensive antibiotic treatment, using two or more antibiotics in combination, 14 patients have died.

Conclusion: Hypostatic and aspiration pneumonia are frequent complications of stroke associated with poor outcome. Regarding to this fact, an intensive prevention of complications is necessary immediately after hospitalization.

266. Prognostic indices in respiratory infections

P2513

Nontypeable haemophilus influenzae leads to activation of the NLRP3 inflammasome – A possible trigger of chronic bronchial inflammation in COPD
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The inflammasome is a cytosolic protein complex which is involved in a variety of inflammatory diseases. Since it represents a heterogeneous group of proteins, we elucidated which specific set of proteins is recruited after stimulation with nontypeable Haemophilus influenzae (NTHi). In view of the fact that IL-1β is a central early phase inflammatory cytokine, we investigated whether inflammasome inhibition affects other cytokines like IL-8 and TNF-α.

Murine macrophages and human lung tissue were stimulated with NTHi 10 cfu/ml for 24-48h. To assess the relevance of the inflammasome for the inflammatory response, a caspase-1 inhibitor (CI) was added after in vitro stimulation. The inflammatory response was measured by cytokine ELISA and Western Blot. Western Blot analysis showed the activation of caspase-1 after NTHi infection and moreover the expression of the NO-like receptors NOD1 and NLRP3. In cell culture and human lung tissue experiments IL-1β production was significantly induced (RAW control 24h beneath lowest standard vs. NTHi 24h 408±546 pg/ml, n=6, p<0.01). The inhibition of caspase-1 led to a significant reduction of IL-1β levels and also to a decrease of IL-8 and TNF-α production (IL-8: NTHi 24h 408±64 pg/ml vs. NTHi+CI 24h 174±12 pg/ml, n=6, p<0.05). For the first time we demonstrated the participation of the NLRP3-inflammasome in NTHi-induced inflammation in pulmonary cells and tissues. Our findings concerning caspase-1 mediated IL-1β-suppression emphasize the role of the inflammasome in respiratory tract infections. These results may provide new insights into the pathogenesis of persistent airway inflammation in COPD.

P2514

The role of galactomannan in exhaled breath condensate in detecting pulmonary aspergillosis in patients with exacerbated COPD
Cristina Felisi 1, Laura Trovato , 2 Raffaele Campisi 1, Salvatore Oliveri 2, Giuseppe Di Maria 1, 3, Dipartimento di Medicina Bio-molecolare e Clinica, Università di Catania, Italy; 2Dipartimento di Scienze Biomediche, Università di Catania, Italy

Introduction: Growing evidence suggests that patients with severe COPD are at a higher risk of pulmonary aspergillosis (PA), especially during an acute exacerbation. The levels of GM in exhaled breath condensate (EBC) might allow earlier diagnosis and extend the diagnostic yield of noninvasive mycological tests.

Methods: Evaluate the role of GM in EBC for early diagnosis of PA in severe COPD patients at exacerbation.

Methods: Serum and EBC were collected from 15 severe or very severe COPD patients at exacerbation and tested for GM using a Platelet® Aspergillus Ag test. Sensitivity of EBC fluids with an index >0.5 were considered positive. Double diffusion in agrose gel (DD) for antibody response to Aspergillus was also determined.

Results: Two patients had probable, 7 possible and 6 had no evidence of PA according to the criteria proposed by Bulpa. Serum positive GM assay was observed in two samples of the patients with probable PA and in one sample of two patients with possible PA. In patients with probable PA also serum precipitins was positive (A. fumigatus). EBC analysis yielded GM positive results (range, 0.8–7.5 pg/ml). In one patient with probable PA and in 2 patients without PA. In a patient with probable PA, positivity of the GM in EBC, preceded that of the serum of 4 days. GM in EBC was negative in 5 out of 7 cases with possible PA and in 5 out of 6 without PA. The sensitivity of GM in EBC was lower for the diagnosis of probable and possible PA compared to serum GM. However, considering the discordant results in serum and in EBC of four patients with possible PA we suggest that EBC GM levels can expand the diagnostic yield of PA.

P2515

Clinical features of patients with pneumococcal urinary antigen positivity, in a cohort of hospitalised community acquired pneumonia
Chamra Rodríguez, Thomas Bewick, Sonia Greenwood, Wei Shen Lim. Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Streptococcus pneumoniae accounts for up to 50% of hospitalised community acquired pneumonia. Diagnosis of pneumococcal disease has always been a challenge. Urinary antigen testing provides a non-invasive, sensitive and specific diagnostic tool. We investigated the clinical features of patients with pneumococcal urinary antigen positivity in patients admitted with community acquired pneumonia. We conducted an observational, prospective cohort study in two large UK teaching hospitals, from September 2008 to September 2010. Consecutive adult patients (aged over 16), admitted with community acquired pneumonia (CAP) were recruited. A standardised proforma was used to collect clinical information. Urine samples were tested using the Binax NOW® immunochromatographic test. A total of 920 urine samples were available for analysis. 205(22.3%) had a positive antigen test.

Patients with a positive antigen test were more likely to be hypertensive (16.8% of antigen positive vs. 6.8% of antigen negative patients, OR 2.8, 95% CI 1.7-4.8, p<0.05) and tachypnoeic at presentation. Incidence of parapneumonic effusion and critical care admission rates (OR 2.2, 95%CI 1.4-9.3, p<0.01) were also higher in the antigen positive group. These associations were maintained when adjusted for age and pneumonia severity. Patients with a positive pneumococcal antigen test were more unwell at presentation with a greater likelihood of complications. This is likely to be due to the higher bacterial load in patients with a positive antigen test. Thus, urinary antigen testing appears to add prognostic value in addition to its diagnostic capabilities, when used in pneumococcal disease.
P2516
Effect of Cryptococcus neoformans on the immune system of immunocompetent patients
Jinhui Wang, Yingfeng Luo, Xiaoqiu Wei, Yangping Zai, Shuyue Li. The State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Guangzhou, Guangdong, China

On one hand the host immune system regulates the susceptibility and resistance to cryptococcal infection, on the other Cn can also affect T-cell activation and polarization during infection. Cn may potentially interfere with the differentiation of Th1 cells, which may be an escape mechanism of evade host defense and contribute to the cryptococcal infection in immunocompetent patients. However, most of these effects on T-cell biology were only found in cell and animal studies so far.

Objectives: To determine the effect of Cn on the immune system of immunocompetent patients.

Methods: Twenty immunocompetent patients with pulmonary cryptococcal infection were enrolled. Blood plasma concentrations of IFN-γ, IL-4 and IL-12 were measured using Elisa. PBMC were then isolated and incubated with or without Cn (3×10⁶ CFU/mL) for 6 and 24 hours, followed by the assay of IFN-γ and IL-12 concentration in the supernatant.

Results: Plasma IFN-γ was greatly decreased in the patients when compared to the healthy controls. No significant differences in plasma IL-4 and IL-12 were observed between these two groups, the increment for cryptococcal infection patients was much lower (3.1-fold) compared with that from healthy controls (7.4-fold). IL-12 treatment had no observed effect on the IL-4 production of PBMC.

Conclusions: Cryptococcal infection can damage the host immune system, leading to a deficient response to the IL-12 stimulation and an impaired Th1 polarization. This may explain the persistence of Cn in the immunocompetent patients.

P2517
Exhaled breath biomarkers in patients with ventilator associated pneumonia (VAP)
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Volatile organic compounds (VOC) in breath have been described as biomarkers of metastatic, oxidative stress and cancer. This pilot study was intended to find out whether VAP related breath biomarkers could be recognized by means of a smart and rapid combination of VOC sample preparation and analysis.

20 mechanically ventilated patients (10 with pneumonia, 10 controls) were investigated. In NTME, 1.0 μL of alveolar gas were withdrawn from the respiratory circuit. VOCs were pre-concentrated by means of needle trap micro extraction (NTME) at the bedside and identified/quantified by means of gas chromatography-mass spectrometry (GC/MS). Results were analysed using ANOVA on ranks. Expired concentrations of VOCs ranged from (400 pptV to 3000 pptV (0.02 to 14.2 nmol/L). Exhaled acetone concentrations were higher in control patients (median 2895 pptV vs. 187 pptV, p=0.037). VAP patients exhaled lower concentrations of CS aldehydes (median 2.061 pptV vs. 19.683 pptV, p=0.013) than control patients. Exhaled pentane showed a tendency to higher concentrations in VAP patients (median 9.507 pptV vs. 6.040 pptV).

The NTME-GC/MS assay enabled reliable detection of volatile substances from ventilated patients in trace amounts. Elevated pentane concentrations indicate oxidative stress in VAP, reduced aldehyde concentrations may be due to chemical quenching of ROS in NTME. NTME appears to be a promising tool for pneumonia patients.

Analysis of exhaled oxygenated compounds bears the potential of non invasive monitoring and recognition of pathological pulmonary processes.

P2518
Copetin predicts early clinical deterioration and persistent instability in community-acquired pneumonia
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Optimal risk prediction of early clinical deterioration in CAP remains unresolved. We prospectively examined the predictive value of the new biomarkers copeptin and proadrenomedullin (MR-proADM) in comparison to clinical scores and inflammatory markers to predict early high risk prognosis in CAP.

Methods: 51 consecutive hospitalised adult patients were enrolled. We measured CRP-65- and P5I-scores, the ATS/IDSA 2007 minor criteria to predict ICU admission and the biomarkers CRP, procalcitonin, copeptin and MR-proADM on admission. Predetermined outcome parameters were combined mortality or ICU admission after 7 days and clinical instability after 72 hours.

Results: Copetin was the only biomarker significantly elevated in patients with either adverse short term outcome (p<0.003). In ROC-curve analysis copeptin predicted ICU admission or death within 7 days (AUC 0.81, cut-off 35 pmol/L, sensitivity 78%, specificity 79%) and persistent clinical instability after 72 h (AUC 0.74). In Kaplan-Meier-analysis patients with high copeptin showed lower ICU-free survival within 7 days (p=0.001). The diagnostic accuracy of copeptin was superior to the CRB-65 score and comparable to the PSI-score and the ATS/IDSA minor criteria. If copeptin was included as additional minor criterion for combined 7-day mortality/ICU-admission, the diagnostic accuracy of the criteria was significantly improved (AUC 0.85, p=0.045).

Conclusion: Copeptin predicts early deterioration and persistent clinical instability in hospitalised CAP and improves the predictive properties of existing clinical scores. It should be evaluated within a biomarker guided strategy for early identification of high risk CAP patients.

P2519
Correlation of Mycobacterium tuberculosis-specific and non-specific quantitative T cell IFN-γ responses with mycobacterial load in a HIV-prevalent high burden setting
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Background: Measures of bacillary load in patients with tuberculosis (TB) may be useful for predicting and monitoring response to treatment. The relationship between quantitative T-cell responses and mycobacterial load is poorly studied. We hypothesised that, in a high burden setting, the magnitude of mycobacterial antigen-specific and non-specific T-cell IFN-γ responses would correlate with (a) bacterial load and (b) culture conversion in patients undergoing treatment.

Methods: We compared the magnitude of purified-protein derivative (PPD) and RD1-specific (TSPOT.TB and QFT-GIT) peripheral blood IFN-γ T-cell responses with associations of sputum bacillary load [liquid culture time-to-positivity, smear microscopy grade, Xpert-MTB/RIF] and the presence of cavities on a chest radiograph in 513 individuals with suspected TB in Cape Town, South Africa. Serial IGRA responses were evaluated at 2 (n=35) and 6 months (n=13) post treatment initiation.

Results: PPD and RD1-specific IFN-γ responses were not associated with culture TTP (p-values for TSPOT.TB, QFT-GIT and PPD of 0.11, 0.07 and 0.09), smear-grade (0.42, 0.08, and 0.85), Ct values (0.70, 0.91, and 0.49) or the presence of cavities on the chest radiograph (0.12, >0.05, and 0.08). 2-month IGRA conversion rates (positive to negative) were negligible (<10% for TSPOT.TB (3/28) and QFT-GIT (1/29)) and lower compared to culture [60% (21/35); p<0.01].

Conclusions: In a high burden setting M. tuberculosis-specific and non-specific antigen-driven IFN-γ responses do not correlate with bacillary load and are not useful for prognostication or treatment monitoring.

P2520
LL-37 is produced intrapleurally in infectious pleural effusion
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LL-37 is an antimicrobial peptide produced by neutrophils, respiratory epithelial and mesothelial cells that has been studied for its broad spectrum activity against microorganisms. It also recruits inflammatory cells and promotes immune responses. It has never been measured in pleural fluid.

Aims and objectives: The objective of our study is to measure the pleural and serum levels of LL-37 in pleural effusion patients, and to compare these levels and the pleural-to-serum LL-37 ratio among pleural fluids of three frequent etiologies: infectious, malignant and congestive heart failure (CHF).

Methods: We obtained 42 pleural effusions and divided them into 3 diagnostic categories. LL-37 was measured in the pleural fluid and serum of 23 infectious effusions, 10 malignant effusions and 9 CHF effusions by ELISA. Statistical analyses were performed using software SPSS 17.0.

Results: Results are presented: mean ± Std. Deviation (median, minimum, maximum).

Pleural Fluid LL-37 levels: Infectious 3.77±4.81 ng/ml (1.64, 0.38-19.4) malignant 2.58±4.17 (0.87, 0.09-13.5), CHF 1.59±1.02 (0.99, 0.47-3.3) (p=0.04)

Serum LL-37 levels: Infectious 2.09±1.42 ng/ml(0.98, 0.06-16.5), malignant 3.44±4.1 (1.19, 0.17-12.6), CHF 3.44±4.3 (0.22, 0.6, 0.71-10.3) (p=0.13)

Pleural fluid-to-Serum LL-37 ratio levels: Infectious 1.33±1.88 (1.29, 0.10-4.3) malignant 0.60±0.92 (0.72, 1.11-2.1) CHF 0.46±0.93 (0.44, 1.12-2.4) (<p=0.001). Infectious vs malignant p=0.002, infectious vs CHF p<0.001, malignant vs CHF not examined the p value.

Conclusions: Pleural fluid-to-Serum LL-37 ratios are significantly elevated in infectious pleural effusions in comparison with malignant or CHF pleural effusions, suggesting that LL-37 is actively produced intrapleurally in infectious effusions.
Conclusion: Several new risk factors have been identified that may help identify exacerbation patients who are at risk of failure despite adequate antibiotics. These patients should be closely monitored during and after treatment of their exacerbation.

P2524
Colonization in advanced chronic obstructive pulmonary disease
Jessica Rademacher, Hendrik Suhling, Günter Auenhammer, Jens Gottlieb, Tobias Welte. Respiratory Medicine, Medical School, Hannover, Germany.

Background: Isolation of potentially pathogenic organism from the sputum is associated with at least one hospitalization for COPD exacerbation (Martinez-Garcia et al. Chest 2011; 140: 1130-1137). But there is still a lack of examinations in larger populations of patients with COPD and pathogenic colonization. Aims: This examination was performed to evaluate the colonization in patients with advanced COPD. Methods: In this single-center evaluation, 379 patients with advanced COPD (GOLD III and IV) in our pre-transplant outpatient clinic were screened between October 2008 and 2011 by lung function, exacerbation rate within the last 12 month and sputum analysis. Results: The median exacerbation rate within the last 12 months was 2 (IQR 1-3), 51.7% of the patients had expectation and 40.9% had none (7.4% remains unknown). We analyzed the sputum of 186 patients and had a positive sputum culture in 31.6% of the patients, which is 16.4% of the whole examination group. Patients with a positive sputum culture were significantly more often hospitalized due to exacerbation (p=0.02). 94 patients (24.3%) underwent lung transplantation in the observation period. 19% of the explanted lungs had a proof of pathogenic organism. In 71 patients (75.5%) analysis of the sputum before transplantation was concordant with the results of the explanted lung. 11 patients (11.7%) had a proof in the explanted lung and no positive sputum or expectation before. Conclusion: Even in patients with end stage COPD chronic bacterial colonisation does play a role only in a minority of the patients (16%). The proof of pathogenic organism correlates with significant more hospitalization due to exacerbations.

P2525
Biomarkers and severity in community-acquired pneumonia (CAP)
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Introduction: To evaluate the prognostic value of biomarkers in community-acquired pneumonia (CAP), we studied the correlations between C-reactive protein (CRP), procalcitonin (PCT), leukocyte count (WBC) and pradefomedemulin (proADM) with the widely used PSI severity score.

Conclusion: Several new risk factors have been identified that may help identify exacerbation patients who are at risk of failure despite adequate antibiotics. These patients should be closely monitored during and after treatment of their exacerbation.

P2523
Prognostic factors for short and long term outcomes of outpatient exacerbations in moderate-to-severe COPD
Rob Wilson1, Antonio Anzueto2, Marc Miravitlles3, Pierre Arvis4, Tobias Welte. Respiratory Medicine, Medical School, Hannover, Germany.

Introduction: Older patients with severe COPD, frequent exacerbations and co-morbidities are at higher risk of poor outcomes. Additional risk factors for short and long term outcomes are yet to be fully identified.

Methods: In the MAESTRAL study, COPD patients treated with 5-day moxifloxacin or 7-day amoxicillin/clavulanic acid for an Anthonisen type I exacerbation, stratified to oral corticosteroid treatment at the physician’s discretion. Predictive factors for clinical failure at end-of-therapy (EOT) and 8 weeks post-EOT were compared by post-hoc multivariate stepwise logistic regression analysis.

Results: Patients with frequent exacerbations, paroxysm, higher respiratory rate, low body temperature and bacterial resistance to study drug had a higher risk to fail at EOT. While patients who, in addition to frequent exacerbations and low body temperature, required systemic corticosteroids for their current exacerbation, were on LABA, suffered from sleep disturbances, had longer duration of chronic bronchitis, increased heart rate, low FEV1, low BMI and positive sputum culture at EOT were more likely to fail up to 8 weeks post-therapy.

P2522
Pseudomonas aeruginosa exacerbations in COPD patients
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Background: Pseudomonas aeruginosa is found in COPD patients sputum in 4-15%, mainly in those with advanced disease and/or in those requiring mechanical ventilation. Currently, there are no data to justify an empiric antibiotic therapy against Pseudomonas aeruginosa when a new COPD exacerbation occurs in a patient with a previous Pseudomonas aeruginosa exacerbation.

Methods: We conducted a retrospective study to analyse microbiological ecology exacerbations in COPD patients with at least one Pseudomonas aeruginosa exacerbation.

Results: Among the 243 COPD patients hospitalized during the study period (2007-2011), only 23 (9.5%) had at least one Pseudomonas aeruginosa exacerbation (exacerbations per patient: 1.1). They presented a new Pseudomonas aeruginosa exacerbation in 54% of cases. From one to other exacerbation, the Pseudomonas aeruginosa susceptibility changed, with a wild type Pseudomonas aeruginosa in 58% of cases during the first exacerbation and 42% during the next one. COPD patients with GOLD stage IV were rarely hospitalized for a wild Pseudomonas aeruginosa exacerbation (p = 0.01, 15% vs. 83% in GOLD stage II and III patients).

Conclusion: In this pilot study, the microbiological ecology of COPD exacerbation differed from one exacerbation to another, contrary to that observed in cystic fibrosis patients.

P2521
Usefulness of procalcitonin as a diagnostic marker of pleural effusion
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Pleural effusions are common and are associated with many diseases. We investigated the usefulness of procalcitonin (PCT) as a diagnostic marker for the cause of pleural effusion. The study was carried out on 54 patients with pleural effusions divided into groups: transudate (n=6), empyema (n=9), T.B (n=8), parapneumonic effusions (PPE) (n=9) and malignan exacerbations (n=22). Levels of procalcitonin were measured both in serum & pleural effusions. Pleural fluid PCT was highest in empyema 1.7±0.86 ng/ml, next highest in PPE (0.57±0.56 ng/ml), & lowest in transudative effusions (0.06±0.03 ng/ml). Pleural fluid & serum procalcitonin levels positively correlate in both empyema & PPE. The optimal discrimination of patients with empyema could be performed at a cut-off point of pleural fluid procalcitonin 0.09 ng/ml with area under the curve (AUC) of 0.93 (sensitivity 80%,specificity 60%). However, the optimal discrimination of PPE levels positively correlate in both empyema & PPE. The optimal discrimination of patients with empyema could be performed at a cut-off point of pleural fluid procalcitonin 0.07 ng/ml (sensitivity 78%, specificity 51%) and at a serum procalcitonin 0.07 ng/ml with AUC of 0.74 (sensitivity 89%,specificity 69%).The optimal discrimination of patients with PPE could be performed at a cut-off point of pleural fluid procalcitonin 0.065 ng/ml (sensitivity 78%, specificity 33%). The optimal discrimination of patients with (empyema & PPE) could be performed at a cut-off point of pleural fluid procalcitonin 0.075 ng/ml (sensitivity 83%,specificity 58%) and at a serum procalcitonin 0.07 ng/ml (sensitivity 83%,specificity 47%). In conclusion: Pleural fluid PCT is a good and early marker of infection in the pleural space and correlates with the serum PCT in patients with PPE or empyema. Pleural PCT had better diagnostic accuracy than the serum PCT in cases of PPE & empyema.
**Material and methods:** We prospectively studied 282 immunocompetent adults; patients hospitalized with CAP, calculated their PSI score and measured on admission the mentioned four blood biomarkers. Subsequently, we established the ROC curves to determine which of the biomarkers had a better discriminating power from mild CAP (PSI 1-3) to severe ones (PSI 4-5).

**Results:** PCT and proADM significantly discriminated severe from mild CAP, although the area under curve was significantly higher for proADM (0.757 vs. 0.581). The other two biomarkers did not reach statistical significance.

**Background:** Bronchiectasis (B.) is induced by different mechanisms, one of these is primary ciliary dyskinesia (PCD). Genetic aberrations lead to a lack of mucociliary clearance. The bacterial biofilm in B. of patients with PCD in comparison to CF was studied by fluorescence in situ hybridisation (FISH).

**Material and methods:** An explant and 2 middle lobe resections of 3 patients (age between 5 and 50 years) were investigated using conventional histology. Diagnosis of PCD was confirmed by transmission electron microscopy. For comparison 10 explants of CF patients were available. Of all cases, at least 2 locations were studied by FISH using a pan-bacterial and a Pseudomonas-specific probe.

**Results:** Histology revealed typical B. In all 3 PCD cases no bacterial biofilms were detected by FISH, although at least one case Ps. was detected by culture previously. In comparison all CF cases showed colonization with Ps.

**Conclusions:** Significant differences exist concerning bacterial biofilms in PCD versus CF. This might be of relevance for the clinical practice.
Inflammatory cells composition of bronchial brush-biopsies in dependence on least injured effects. *H.*influenzae, *Ch.*pneumoniae have more injured effects and *M.*catarrhalis infection (33.7 ± 0.7%). Dystrophical cells count was reliable high (p < 0.05) in *H.*influenzae, *Ch.*pneumoniae, *M.*pneumoniae infection (6.3 ± 1.0%, 7.4 ± 1.4%, 7.4 ± 1.6%) as compared with *S.*pneumoniae, *M.*catarrhalis infection (2.5 ± 0.9%, 2.2 ± 0.7%). Dystrophical cells count was reliable high (p < 0.05) in *H.*influenzae, *Ch.*pneumoniae infection (50.3 ± 1.5%, 50.2 ± 2.1%) than *S.*pneumoniae, *M.*pneumoniae *M.*catarrhalis infection (49.6 ± 3.0%, 47.4 ± 3.5%, 39.8 ± 4.3%). Macrophages quantity was reliable high (p < 0.05) in *M.*pneumoniae infection (55.1 ± 1.6%) as compared with *S.*pneumoniae, *H.*influenzae, *Ch.*pneumoniae, *M.*catarrhalis infection (33.7 ± 3.7%, 27.4 ± 3.0%, 25.2 ± 3.5%). Infection agent species influence on degree of bronchial mucosa damage. *H.*influenzae, *Ch.*pneumoniae have more injured effects and *M.*catarrhalis have least injured effects.

Cellular composition of bronchial brush-biopsies at COPD exacerbation age, mortality and hospital costs were higher compared to culture negative group. *Acinetobacter* was the most common isolated microorganism. In hospitalised COPD patients in our clinic, *Acinetobacter* infection (48.8%). Taking into account the results of received data there have been developed and carried out special NPCP aimed to increase the LMSK (lectures, discussions, printed issues). Comparative exercise was repeated 1.5 yrs later. Test showed the increase of LCA up to 60% (p < 0.05). We determined that NP-rate was statistically decreasing during NPCP (p < 0.05). It was fixed that the most difficult questions were the following: sources of NI agents, risk factors of NI, rationale antibiotic use, hand-hygiene and other NI-preventive measures, mortality rates under NI.

Conclusions: There is a necessity to carry out NPCP among surgeons in GSD to increase LMSK and to decrease NP level. Therefore, the most difficult questions require to be studied more deeply.

267. Viral infections and rare respiratory infections

**P2530**

**Cellular composition of bronchial brush-biopsies at COPD exacerbation**

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46 COPD exacerbation patients were examined. Cytological research of brush-biopsies were taken at bronchoscopy was made; for verification of infectious nature of COPD exacerbation the quantitative bacteriological sputum research, definition of diagnostic main IgG, IgM levels to *Ch.*pneumoniae, *M.*pneumoniae in serum by means immuno-assay method, definition of their genomes fragments in sputum by means of PCR method were made. Kruskal – Wallis criterion was used.

Infectious character of COPD exacerbation was confirmed at 36 patients. Typical cells count in H.influenzae, Ch.pneumoniae, M.pneumoniae infection was 14 ± 6.2%, 15 ± 5.2%, 15 ± 5.1%, that was reliable low (p < 0.05), than in S.pneumoniae, M.catarrhalis infection (32 ± 6.3%, 37 ± 5.1%); Reserved cells count was reliable high (p < 0.05) in M.pneumoniae (12 ± 0.2%, 6%), than in S.pneumoniae H.influenzae, Ch.pneumoniae, M.catarrhalis infection (5 ± 3.1%, 8.4 ± 1.0%, 8 ± 1.0%, 5 ± 0.2%, 7 ± 0.2%, 7 ± 0.2%); Squamous, neutrophil and ciliated cells count was reliable high (p < 0.05) in H.influenzae, Ch.pneumoniae, M.pneumoniae infection (6.3 ± 1.1%, 7.5 ± 1.2%, 7.4 ± 1.6%) as compared with S.pneumoniae, M.catarrhalis infection (2.5 ± 0.9%, 2.2 ± 0.7%). Dystrophical cells count was reliable high (p < 0.05) in H.influenzae, Ch.pneumoniae, M.pneumoniae infection (54.9 ± 2.1%, 50 ± 1.9%, 48.1 ± 1.2% accordingly) than in S.pneumoniae, M.catarrhalis infection (49.4 ± 1.9%, 46.9 ± 1.8%, 38.9 ± 0.9%). Macrophages quantity was reliable high (p < 0.05) in M.pneumoniae infection (55.1 ± 1.6%) as compared with S.pneumoniae, H.influenzae, Ch.pneumoniae, M.catarrhalis infection (33.7 ± 3.7%, 27.4 ± 3.0%, 25.2 ± 3.5%). Infection agent species influence on degree of bronchial mucosa damage. *H.*influenzae, *Ch.*pneumoniae have more injured effects and *M.*catarrhalis have least injured effects.

**P2531**

**Inflammatory cells composition of bronchial brush-biopsies in dependence on infectious agent species at COPD exacerbation**

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46 COPD exacerbation patients were examined. Cytological research of brush-biopsies were taken at bronchoscopy was made; for verification of infectious nature of COPD exacerbation the quantitative bacteriological sputum research, definition of diagnostic main IgG, IgM levels to *Ch.*pneumoniae, *M.*pneumoniae in serum by means immuno-assay method, definition of their genomes fragments in sputum by means of PCR method were made. Kruskal – Wallis criterion was used. Infection character of COPD exacerbation was confirmed at 36 patients. Typical cells count in H.influenzae, Ch.pneumoniae, M.pneumoniae infection was 14 ± 6.2%, 15 ± 5.2%, 15 ± 5.1%, that was reliable low (p < 0.05), than in S.pneumoniae, M.catarrhalis infection (32 ± 6.3%, 37 ± 5.1%); Reserved cells count was reliable high (p < 0.05) in M.pneumoniae (12 ± 0.2%, 6%), than in S.pneumoniae H.influenzae, Ch.pneumoniae, M.catarrhalis infection (5 ± 3.1%, 8.4 ± 1.0%, 8 ± 1.0%, 5 ± 0.2%, 7 ± 0.2%, 7 ± 0.2%); Squamous, neutrophil and ciliated cells count was reliable high (p < 0.05) in H.influenzae, Ch.pneumoniae, M.pneumoniae infection (6.3 ± 1.1%, 7.5 ± 1.2%, 7.4 ± 1.6%) as compared with S.pneumoniae, M.catarrhalis infection (2.5 ± 0.9%, 2.2 ± 0.7%). Dystrophical cells count was reliable high (p < 0.05) in H.influenzae, Ch.pneumoniae, M.pneumoniae infection (54.9 ± 2.1%, 50 ± 1.9%, 48.1 ± 1.2% accordingly) than in S.pneumoniae, M.catarrhalis infection (49.4 ± 1.9%, 46.9 ± 1.8%, 38.9 ± 0.9%). Macrophages quantity was reliable high (p < 0.05) in M.pneumoniae infection (55.1 ± 1.6%) as compared with S.pneumoniae, H.influenzae, Ch.pneumoniae, M.catarrhalis infection (33.7 ± 3.7%, 27.4 ± 3.0%, 25.2 ± 3.5%). Infection agent species influence on degree of bronchial mucosa damage. *H.*influenzae, *Ch.*pneumoniae have more injured effects and *M.*catarrhalis have least injured effects.

**P2533**

**Distinct bacterial species: Escherichia coli and staphylococcus aureus have specific microcalorimetric patterns**

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**Material and method:** Series of experiments were conducted for *E.Coli* (15 experiments) as well as for *S.Aureus* (13 experiments) and the obtained thermograms were then compared. Several heatflow curve parameters were identified and then used for comparison.

**Results:** The obtained microcalorimetric curves present 2 peaks, each curve providing different recorded parameters.

**Conclusion:** Microcalorimetry represents a method which can be used to objectively differentiate the 2 species (with differences being statistically significant). In our opinion, these parameters could allow a primary microcalorimetric characterization of the bacterial growth. Furthermore, by using this method, identification of bacterial species could be possible in the near future.

**P2534**

**Induction of protective T cell immunity against influenza using a novel peptide vaccine**

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Influenza vaccination remains an important cause of global morbidity in spite of current vaccine strategies which generate antibody responses to surface viral proteins. Recent studies have established that naturally occurring T cells which recognize highly conserved core viral proteins and limit illness against a range of viral strains. We aimed to demonstrate that induction of T cell memory using a novel peptide vaccine (Flu-V) could limit influenza severity using a human viral challenge model. 32 seronegative healthy males were randomised to receive 500μg of peptide vaccine or placebo. All subjects were challenged by nasal instillation of live A/Wisconsin/67/2005 (H1N2). Safety, tolerability, influenza severity and cellular immune data were collected.

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The vaccine was safe and well tolerated. No pre-existing T cell responses to the novel Flu-V vaccine were seen at baseline by IFN-γ release assay. All subjects in the treatment arm demonstrated strong induction of the peptide specific cellular response (fold rise 8.2±1.9 (Range 5.0–10.6) p<0.0005). The length of the induction of T cell response to Flu-V inversely correlated with influenza illness severity -symptoms r=-0.786, p=0.02 and viral shedding r=-0.821, p=0.01. Furthermore the peptide specific induced strong cellular responses against heterogenous strains, including H1N1pdm in vitro. Peptide vaccination can induce cellular immunity to influenza which correlates closely with disease protection in humans. T cell responses can be induced against a range of strains and therefore this approach carries potential for the induction of broad heterologous immunity required to protect against future pandemics.

**Results:**
During 2011, 217 sera samples were examined. Antibodies on Adenovirus were detected by Indirect Immunofluorescent Assay –Pneumoslide IgM.

**Material and methods:**
The clinical episodes of 141 non-immunosuppressed outpatients with seasonal influenza A during winter season 2010/2011, including 67 patients IgM and 74 patients IgG with a neuraminidase inhibitor alone and 74 treated with the combination therapy (mean age: 30 and 31 years, respectively), were analyzed.

**Conclusion:**
Although the effect of clarithromycin in non-elderly patients with seasonal influenza A was limited, further studies might be needed to determine the additional or preventive effect of clarithromycin during influenza virus infection for elderly subjects or patients complicated with serious underlying diseases.
We report underlying malignancy and chronic corticosteroid therapy in a multivariate analysis of community-acquired pneumonia (CAP) as independent risk factors for mortality.

Results: A total of 223 patients had been included, 89 (40.3%) with CAP and 132 (59.7%) with HCAP. Statistically significant differences favoring HCAP were observed in the following variables: older age (75.6 yrs, p < 0.001), presence of cerebrovascular disease (74.1%, p = 0.039), poor functional status (37.5%, p = 0.039), previous antibiotic treatment (53.9%, p < 0.001), higher mortality rate (68.4%) and initial empiric therapy (piperacillin/tazobactam plus aminoglycoside, 63.2%).

Conclusions: Our results confirm the greater severity and worse prognosis of HCAP. In this group the most frequent agents were the gram negative bacteria. Accordingly, the empirical antibiotic therapy should cover not only the usual CAP agents, but also the causative agents associated with nosocomial pneumonia.

We compared HCAP vs CAP regarding clinical and epidemiological characteristics, comorbidities, functional status, previous antibiotic treatment, risk stratification by Pneumonia Severity Index (PSI) and CURB 65 score, etiologic agents, therapeutic regimens, hospital length and mortality.

Background: Nocardia pneumonia has emerged as an important cause of mortality and morbidity in both immunocompetent and immunocompromised hosts. In this study, risk factors, clinical features, outcomes and factors associated with mortality in Nocardia pneumonia were reported.

Materials and methods: Clinical records of all cases diagnosed with nocardia pneumonia during 2001-2010 were reviewed. Identification of Nocardia species was based on positive Gram stain and positive modified acid-fast stain results, colonial morphology, and conventional biochemical reactions. Data was analyzed using SPSS version 17. Factors associated with mortality was assessed by univariate and multivariate analysis.

Results: Fifty Five cases were identified. Fever, cough and dyspnea were the most common presentations. Most important risk factors were chronic steroid administration (69%) and an underlying malignancy (24%). Most common complications observed were respiratory failure (27%) and septicemia (27%) 19(34.5%) patients died. Factors associated with mortality were smoking (p = 0.01), decreased appetite (p = 0.007), leukocytosis (t = 0.006), mechanical ventilation (p < 0.001) and septicemia (p < 0.001). Septicemia (OR 20 [95% CI 3.13 -130]) was found to be independent risk factor for mortality in multivariate analysis.

Conclusion: We report underlying malignancy and chronic corticosteroid therapy as a risk factor for development of nocardiosis in our patients. High mortality rate in this cohort were observed. Septicemia was found to be independent risk factor for mortality. Clinicians should keep a high index of suspicion for early diagnosis and management to decrease mortality.

Conclusions: We provide data on the etiology and clinical features of patients with nocardiosis. The most frequent agents were the gram negative bacteria. The relative risk of lethal outcome in those patients was 24.4 (95% CI 10.5 and 52.1). The diagnosis was delayed and the mortality was high. The results confirm the greater severity and worse prognosis of Nocardia pneumonia.

Background: Cytokines are important mediators in the host response to infection. Responses in patients with non-severe and severe CAP and to correlate these with pneumonia severity index (PSI) and other clinical parameters.

Methods: In a prospective study, 20 CAP patients and 10 healthy individuals were included. Upon admission, levels of interleukin (IL-6), IL-10, IL-1β, tumor necrosis factor (TNF), interferon (IFNy), IL-22, IL-17A and IL-4 were determined in bronchoalveolar lavage (BAL) fluid and serum by enzyme-linked immunosorbent assay (ELISA). Systemic cytokine levels were also measured on days 7 and 30.

Results: IL-6 and IFNy were significantly increased compared with healthy individuals, but no correlations with disease severity were found. Systemic levels of IL-6, IL-10 and IFNy were significantly higher in severe CAP patients than in non-severe CAP patients and healthy individuals. Moreover, these cytokines showed a strong correlation with the PSI. In the total group of CAP patients IL-6 and IL-22 levels were also increased compared with healthy individuals.

Conclusions: IL-6 and IFNy are important cytokines in both the local and systemic inflammatory response in CAP. Differences in disease severity upon admission are however only reflected by the systemic levels of these cytokines and IL-10.

Background: Acute respiratory distress syndrome (ARDS) – Manifestation of onset in an immunocompromised patient with pleuropulmonary tuberculosis (TB) has been reported. The aim of this study was to describe the active pleuropulmonary TB and compare the clinical and laboratory findings with previous reports.

Methods: The authors present a clinical case of pleuropulmonary TB and ARDS.

Results: Young patient, 38 years, smoker (25 pack-year), was hospitalized in emergency with fever 39.8 °C, tachycardia (heart rate = 120/min), left thoracic stabbing. Admission chest Xray: opacities highlight ulcerated nodular infiltrative nature and opacity right upper lobe and parietobronzial fluid excluded on left. At 6 hours after admission, the general condition worsens (SaO2 = 40%, PaO2 = 35mmHg), and chest Xray and CT scan shows multiple pulmonary infiltrates ("white lung"). Sputum exam for tuberculosis is negative in microscopy and culture is positive. Pleural biopsies reveal the presence of tuberculosis folicles. Test for HIV was negative. The patient was intubated and mechanically ventilated for 3 days, then improved clinical course and radiological image become the same as admission. After biopsy confirmation of TB patient received tuberculostatic treatment with favorable clinical and radiological evolution.

Conclusions: To improve the prognosis of ARDS of unknown cause we should think of tuberculosi syndrome, especially in patients with impaired immunity.
The clinical evaluation of respiratory tract infection caused by MRSA
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Background: Most of the MRSA detected in respiratory specimens were colo-
ized. However pneumonia due to MRSA becomes severe and improvement of outcomes were important.

Methods: Medical records of 11 MRSA pneumonia patients among 106 patients with MRSA detected in respiratory specimens from June 2010 to May 2011 at Kameda Medical Center were reviewed retrospectively. The following variables were studied: patient background, hospitalization, drug susceptibility, outcomes.

Results: Mean age was 73.5 ± 5.0. Eight patients were male, 3 were female. Eight were HAP, 3 were NHCAP (Nursing and healthcare associated pneumonia). Four patients have Chronic kidney disease, 3 have neurological disorder and 2 were under steroid administration. Nine patients (81.8%) were detected through microbial subsetting. Period from admission to detection was 41.9 ± 1.2 days, period from antimicrobail initiation to detection was 23.1 ± 2.1 days, numbers of antimicrobial agents were 2 ± 0.2. Nine patients (81.8%) have polymicrobial detection. Paeruginosa, 5. malophilia, K pneumonia were detected in 4 ± 3, 2 patients frequently. All of the anti MRSA agents administered were VCM. MIC of VCM were 1 with 2 patients, 0.5 with 1 patients, unexamined with 1 patients in the 4 patients at the introduction of broth microdilution method. Duration of administration was 12.8 ± 4.5 days on average. In 9 patients (84.6%) beta-lactum agents were administered in combination. Duration of hospitalization was 124.8 ± 7.2 days on average, 5 patients (45.5%) were died.

Conclusion: Use of MRSA detected in respiratory samples was HAP and polymicrobial detection. MRSA caused the prolonged hospitalization and poor prognosis.

P2545
Community-acquired pneumonia during the influenza pandemic A(H1N1) pdm09 and post-pandemic period in hospitalized patients, Russia
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Background: This was a retrospective study including all adults with CAP admitted to the Hospital Regional Hospital 1 during an influenza A(H1N1) pdm09 between November 1, 2009 and January 15, 2010 (group A) and post-pandemic period between January 1 and April 20, 2011 (group B). Group A: 94 patients, mean age 36.1 ± 13 (men, 39%), Group B: 109 patients, mean age 43 ± 15 (men, 46%).

Methods: Patients with laboratory confirmed influenza A(H1N1) pdm09 (gr. A) 45% vs (gr. B) 28% (p = 0.02). In gr. B compared with gr. A: were hospitalized less often (30% vs 58%, p = 0.003), decreased the proportion of obese patients (14% vs 25%, p = 0.05), less lung injury: 2-way process (55% vs 82%, p = 0.000) and lung injury: 2-way process (55% vs 82%, p = 0.000) and decreased the proportion of obese patients (14% vs 25%, p = 0.05), less lung injury: 2-way process (5% vs 82%, p = 0.000) and lung injury (6% vs 80%, p = 0.000) and rarely detected “glass matte” (2% vs 11%, p = 0.03). In gr. B decreased need for admitted in the ICU 40% vs 60% (p = 0.002), with a smaller proportion of them are pregnant (9% vs 49%, p = 0.01). The length of stay in the ICU, the need for mechanical ventilation and the patients with laboratory confirmed A(H1N1) pdm09 not significantly different. The frequency of deaths in the groups did not differ significantly and was 18% (gr. B) vs 21% (gr. A).

Conclusion: Among in-patients with CAP in post-pandemic period decreased: the numbers of patients infected with the virus A(H1N1) pdm09, the need for admitted in the ICU with a tendency to reduce the incidence of CAP in pregnant.

P245
Prevention of the recurrent acute respiratory viral infections in children Andrey Zaplatnikov1, Nina Korovina1, Irina Zakharova1, Elena Burtsveva2, Gulina Mingleamova1, Ludmila Zaplatnikova1, Irina Zak1, Lucia Vezzoli1, Chiara Paladini3,4.
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Background: It is known that recurrent episodes of acute viral respiratory infec-
tions (recurrent ARVI) are common for children attending nursery school.

Methods: To evaluate the efficacy and safety of interferon inducer (IFN-i - “Anaferon”) in prevention of recurrent ARVI in children.

Patients with laboratory confirmed influenza A(H1N1)pdm09 (gr. B) 45% vs (gr. A) 28% (p = 0.02). In gr. B compared with gr. A: were hospitalized less often (30% vs 58%, p = 0.003), decreased the proportion of obese patients (14% vs 25%, p = 0.05), less lung injury: 2-way process (5% vs 82%, p = 0.000) and lung injury: 2-way process (5% vs 82%, p = 0.000) and decreased the proportion of obese patients (14% vs 25%, p = 0.05), less lung injury: 2-way process (5% vs 82%, p = 0.000) and lung injury (6% vs 80%, p = 0.000) and rarely detected “glass matte” (2% vs 11%, p = 0.03). In gr. B decreased need for admitted in the ICU 40% vs 60% (p = 0.002), with a smaller proportion of them are pregnant (9% vs 49%, p = 0.01). The length of stay in the ICU, the need for mechanical ventilation and the patients with laboratory confirmed A(H1N1) pdm09 not significantly different. The frequency of deaths in the groups did not differ significantly and was 18% (gr. B) vs 21% (gr. A).

Conclusion: Among in-patients with CAP in post-pandemic period decreased: the numbers of patients infected with the virus A(H1N1) pdm09, the need for admitted in the ICU with a tendency to reduce the incidence of CAP in pregnant.

Purpose: The aim was to conduct a systematic review of randomized controlled trials (RCTs) of single-dose PFCE (pentaerythrityl tetraacetate) therapy and chronic intermittent PFCE therapy in transgenic sickle cell and control mice infected with Streptococcus pneumoniae (strain D39).

Methods: Mice were injected intravenously with single dose of saline or PFCE (3 ml/kg) +/- S. pneumoniae strain (D39) and harvested at 72 hours or on showing signs of 2+ lethargy. A second group of mice were injected with PFCE daily for 1 week. Histological analysis of lungs was performed using H&E sections and light microscopy. In addition, white blood cell analysis was performed using flow cytometry.

Results: S. pneumoniae-infected mice treated with PFCE died earlier than those treated with vehicle and were less able to clear S. pneumoniae from the bloodstream. In the absence of infection, mice treated with a single dose of PFCE showed mild inflammation changes in the lung. However, mice treated with PFCE for 1 week did not show any histological abnormalities. The inflammatory response in healthy mice injected with PFCE was significantly higher compared to sickle cell mice.

Conclusions: Single-dose PFCE therapy causes lung injury mice whereas chronic PFCE therapy does not. In addition, the inflammatory response to PFCE therapy is different in healthy and sickle cell mice. Further studies are required to determine mechanisms of inflammatory responses in sickle cell mice and whether supplemental oxygen therapy improves outcomes in mice infected with S. pneumoniae and treated with PFCE.
Prevalence and risk factors for pneumonia in a cohort with clinical suspicion of influenza A (H1N1)

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Due to the potentially life-threatening of H1N1 infection, mainly influenza pneumonia (IP), distinguishing IP from non-influenza pneumonia (NIP) is crucial to adequate the appropriate treatment.

Aim: 1. To determine the prevalence of IP and NIP in a cohort with suspected pandemic H1N1.

2. To evaluate the presence of risk factors for pneumonia in both groups.

Methods: Retrospective observational study undertaken in patients with clinically suspected influenza admitted to emergency room, from August to December of 2009. Nasopharyngeal swabs were obtained from patients and RT-PCR was performed. Episodes in patients under age 18, nosocomial acquisition and infections in health-care workers were excluded. Demographic variables, comorbidities, final diagnosis and administered treatment were recorded.

Results: 326 episodes were evaluated (59.8% women). In 141 cases (43.2%) pandemic H1N1 was confirmed. IP was diagnosed in 33/326 (10.1%) and NIP in 86/326 (26.4%). 84.8% of IP episodes required hospital admission (27.3% in ICU).

On the other hand, 79.1% of NIP needed hospitalization (17.4% in ICU). 24% of IP were classified as PSI class IV/V vs. 44.2% of NIP (p=0.04). Mortality in both groups was 9.1% vs. 10.5% respectively. Regarding to risk factors, statistical significant differences were found in age (47.5±15.9 vs. 58.7±19.5, p=0.002), asthma (18.2% vs. 5.8%, p=0.037) and COPD (9.1% vs. 30.2%, p=0.016). Obesity and pregnancy did not show significant differences.

Conclusions: 1. - The overall prevalence of pneumonia was 36.5% (10.1% for H1N1).

2. - Older age and COPD were risk factors associated with non-influenza pneumonia while asthma was associated with influenza pneumonia.

Nebulised therapy in pregnant with acute respiratory viruses infections (ARVI)

Janna Pahomova

Nebulised therapy in pregnancy did not show significant differences.

Results: 22 cases were found influenza A virus positive via DIEFA with a positive rate of 55%, while 12 cases were found influenza A virus positive via GICA with a positive rate of 30%. Compared with qRT-PCR detection, the specificity, sensitivity and consistency of DIEFA were 85.7%, 78.9% and 82.5% respectively, while the GICA’s sensitivity, specificity and consistency were 42.8%, 84.2% and 62.5% respectively. The data showed that DIEFA had apparent superiority of sensitivity over GICA in rapid influenza A virus detection.

Conclusions: DIEFA can be an optimal approach for rapid detection of influenza A virus with the advantage of higher sensitivity and specificity, adapting for screening influenza A virus rapidly in influenza A virus epidemic conditions.

268. Management of pneumonia due to hospital pathogens

P2553

The role of inflammatory markers in the diagnosis and management of patients with community-acquired pneumonia

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The aim of this study was to determine whether there is a significant difference between the values of C-reactive protein (CRP) and white blood cells (WBC), in patients with serological proved atypical pneumonia and in serological negative atypical pneumonia.

Materials and methods: A total of 403 adult hospitalized patients with clinical and radiographic findings of pneumonia. Diagnosis of acute atypical pneumonia was established by serological confirmation of IgM and IgG antibody against Mycoplasma pn., Coxiella burnetii, Chlamydia pn. and Legionella pn. There were compared the values of the age, sedimentation, WBC, lymphocytes, neutrophils, CRP and aminotranspherases in patients with pneumonia with atypical infection (n=145) and in serological negative for atypical pathogen (n=258).

Results: The mean age of patients was 49.86 years, 209 (51.86%) were male and 194 (48.14%) females. Acute atypical infection was in 145 (35.98%), in 10 (2.48%) mixed etiology and 248 (61.54%) were negative for atypical pathogen.

The main value of the age in patients with positive result for atypical pathogen was statistically significance lower (t=4.43, p<0.05). The concentration of CRP was statistically higher in the group with negative result for atypical pathogen (146,7mg/l) then in atypical positive group (71.1mg/l) (t=4.46, p<0.05), while there was not statistical significance in value of WBC between the two groups (t=1.09, p=0.28).

Conclusion: Although nonspecific C-reactive protein as a parameter of inflammation, within the whole diagnostic protocol in patients with pneumonia, can be useful in their initial differentiation on atypical or not atypical.

P2554

Comparison of laparoscopic sleeve gastrectomy pulmonary complications comparing to laparoscopic adjustable gastric banding

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Introduction/rationale: Major changes in gastric anatomy and physiology following Laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG) may increase the risk of esophageal regurgitation, increasing possibility of long-term pulmonary complications.

Methods: A retrospective case-control study was performed including all patients undergoing bariatric surgery, LAGB or LSG, over a 10-year period (2000-2010) at Meir Medical Center, Israel. Two groups were defined: patients who underwent LAGB or LSG. Data included all perioperative management and were recorded in hospital computer database. All patients were thoroughly examined and questioned about pulmonary complaints, such as: shortness of breath, persistent cough, pneumonia, infected bronchietasis. The data were analyzed using Mann Whitney test for independent samples and Chi square test, with p < 0.05 considered significant.

Results: The patients underwent either LAGB (n=193, mean age 43.1 yrs., +11.3 yrs., 144 (76.6%) females, 21(10.5%) with previous lung disease) or LSG (n=114, mean age 45.5, ±11.3 yrs., 83 (73%) females, 12 (10.5%) with previous lung disease). The LSG patients had significantly lower rates of mencing cough and postprandial cough than did the LAGB patients: 14 (12.3%) vs. 115 (59.6%), p<0.001, 12 (10.5%) vs. 112 (58.0%), p<0.001, respectively, similar rate of complications (2 cases in each group) was noted follow the surgery. Mortality was zero.

Conclusions: Follow-up data demonstrated relatively less postoperative pulmonary complications after LSG comparing to LAGB. Additional follow-up is required to define long-term safety.
A retrospective infection in intensive care unit: Enterococci
Mohammed Emran Akkovayn1, Yasemn Akkovayn2, Tarun Adani3
Method: This study investigated direct costs and related factors for hospitalised CAP. Patients hospitalised with CAP major determinants of costs were length of hospital stay, use of antimicrobial antibiotic combination, use of antibiotic within 3 months and two or more hospitalisation days within 3 months.

Comparison of invitro antimicrobial susceptibility tests of patients admitted in a tertiary respiratory center intensive care unit with their clinical symptoms related to ventilator associated pneumonia (in vivo results)
Mahb Malkomehmad1, Mohammadreza Hashemian1, Parisa Adimi Naghan2, Helenar Fajraliszadeh1,2, Makan Sadr3, Hamidreza Jamaati1.

Background: Ventilator associated pneumonia (VAP),is the most common nosocomial infection in ICU admitted patients. There is no study about comparison of clinical response to routine VAP treatment and susceptibility of microorganism to antibiotics in VAP suspected patients.
Methods: In this cross-sectional retrospective study, the files of 99 mechanically ventilated patients in a respiratory center ICU were assessed. Patients demographic data, underlying diseases, Clinical Pulmonary Infection Score (CPIS), in vitro (culture) results, antibiogram and antibiotic regimen were recorded.The change in CPIS was considered as positive in vivo. The result of culture of secretion (especially tracheal secretion) was considered as in vitro result.
Results: From 99 patients, 59 (60%) were male with a mean age of 42 years.14 patients (14%) had positive in vivo result and 19 patients (19%) had positive in vitro result. 60% of patients had given VAP antibiotic regimen. Comparison between results are seen in 56% of patients with both positive results of in vivo and in vitro had resistant antibiotic susceptibility test in antibiogram. Near to half of patient with both negative results of in vivo and in vitro had given antibiotic regimen for VAP.
Conclusion: More attention to clinical condition of patients (CPIS) than laboratory results is necessary for beginning of VAP antibiotic treatment.
P2560  
Microbial contamination of single- and multiple-dose vials after opening in a pulmonary teaching hospital  
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Introduction: Intravenous therapy is a complex procedure usually requiring the preparation of the medication in the clinical area before administration to the patient. Breaches in aseptic technique may result in microbial contaminations of vials which is a potential cause of different avoidable infections.  

Aims: We aimed to investigate the prevalence and pattern of microbial contamination of single- and multiple-dose vials (SDVs and MDVs) in the largest pulmonary teaching hospital in Iran.  

Methods: In a period of 2 month, opened SDVs and MDVs from different wards were collected by a pharmacist. The name of the medication, ward, labeling of the vials, date of opening, and storing temperature were recorded for each vial. Remained contents of each vial were cultured using appropriate bacterial and fungal growth media.  

Results: Microbial contamination was identified in 11 of 205 (5%) of vials. The highest contamination rate was 14.29% for vials used in interventional bronchoscopy unit. The most frequent contaminated medications were Insulin and potassium chloride. Gram-positive bacteria (81.82%) were more significantly involved than gram-negative ones (9.09%) and fungi (9.09%), with the highest frequency for Staphylococcus epidermidis.  

Conclusions: Use of safe injection practice is critical to prevent microbial contamination of these medications. A training program for health care workers in aseptic techniques and written guidelines for aseptic handling of intravenous solutions are required.

P2561  
Comparison of scoring systems use for estimation of severity of community acquired pneumonia  
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Introduction: Estimation of Community acquired pneumonia (CAP) severity is important for patient management. Some scoring systems for estimation are: Pneumonia severity index-PSI, CURB, CURB-65 and CRB-65 index and A-DROP system.  

Aim: Aim of this study was to compare predictive values of these scoring systems regarding severity of CAP.  

Method: Study was done at Clinic for pulmonology, Belgrade, in 100 hospitalized patients with an admission diagnosis of CAP, which were categorized into PSI, CURB, CURB-65 and CRB-65 index and A-DROP system.  

Results: The study included 100 patients (men 65, women 35), age range 23-87 years. The patients rates with PSI risk class I, II, III, IV and V were 15%, 16%, 21%, 28%, 14% respectively. Using CURB index rates were 34%, 49%, 9%, 6% and 2% for scores 0, 1, 2, 3, 4 respectively. CURB-65 index was 36%, 31%, 34%, 6%, 2%, 1% with score 0, 1, 2, 3, 4 and 5 respectively. Patients rates for CRB-65 scores 0, 1, 2, 3 and 4 were 44%, 43%, 9%, 3%, 1% respectively. The patients rates for A-DROP characteristics were 24%, 30%, 36%, 13%, 2%, 1% for scores 0, 1, 2, 3, 4, 5 respectively. 9% of patients were died. 28% of patients had chronic obstructive pulmonary disease (COPD).  

Conclusions: Patients were hospitalized more common then that was indicated by scoring systems (some were hospitalized for social reasons). PSI is more additive for estimation of CAP severity, but CURB, CURB-65, A-DROP and especially CRB-65 have the benefit of being easy to calculate and simple to use. CURB-65 and A-DROP show similar results for estimation of degree of the disease. Neither of these scoring systems use COPD as category for assessment (PSI and A-DROP only include arterial blood gas analyses).

P2562  
Community acquired pneumonia: Can physiotherapists and occupational therapists help reduce the length of stay?  
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Introduction: Community Acquired Pneumonia (CAP) places a significant burden on healthcare budget. With an increasingly ageing population, an unmet need for measures to cut down on length of stay (LOS) from this diagnosis exists.  

Methods: We retrospectively analysed all cases of CAP admitted to our hospital for a period of six months. After adjusting for co-morbidities with charlson index, 40 cases of LOS over and above the expected LOS were identified. Their case notes were analysed in detail to identify potential remediable factors to help reduce overall LOS.  

Results: All of the 40 cases received timely diagnosis, review by senior clinicians and appropriate treatment in keeping with national guidelines. The average age was 79 years. Higher Charlson index correlated well with increased LOS. Overall, 42% (n=17) developed complications of pneumonia resulting in increased LOS. Out of these, 23% (n=4) continually deteriorated resulting in an overall mortality of 10%. Unmet occupational and physiotherapist needs resulted in an increased LOS in 45% (n=18) after time to clinical stability (TCS). In 10% (n=4) increased LOS was attributable to ongoing social needs whilst no documented cause could be ascertained in the last remaining case.  

Conclusions: Early institution of physiotherapy and occupational therapy interventions can potentially help reduce LOS from CAP and reduce economic burden on healthcare budget. A multi-disciplinary team approach to CAP, especially in elderly patients, should be considered.


P2563  
Smoking, haemophilus influenzae and hospital readmission  
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Background: Patients with chronic lung diseases are well known to have colonisation of lower respiratory tract with Haemophilus Influenza (HI). D Roberts et al have demonstrated increased growth of HI inviron the presence of nicotine. However, it is not known if that leads to increased risk of clinical infection requiring hospital readmission.  

Hypothesis: Smoking increases the risk of acute clinical infections and hospital readmission due to HI.  

Methods: Retrospective study of adult patients admitted with acute HI infection over a 2 year period in an acute teaching hospital setting.  

Results: N=133, mean age 60 years, male 57%, smokers 89%; Respiratory co-morbidities 83% (COPD 79%, Bronchiectasis 7%, Asthma 7% and Combined 7%).  

Current smokers had increased risk of recurrent admissions 17/29(59%) compared to Ex-smokers 33/89(37%).  
P = 0.05 Fisher’s exact test.  

Patients with >40 pack years smoking history had increased risk of recurrent admissions 34/6(54%) compared to <40 pack year group 15/30(50%). P=0.01 Fisher’s exact test.  

Smokers with background chronic lung disease had a tendency to have a higher number of recurrent admissions (46% vs 25%), but this was not statistically significant. P=0.09 Fisher’s exact test.  

Conclusions: This study shows a significant association with smoking and increased HI related hospital readmissions. Smokers should be informed of this risk and strongly advised to quit smoking.


P2564  
Community-acquired complicated parapneumonic effusions in adults without associated comorbidity – A study from India  
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Methods: Retrospective analysis of clinical, radiological, bacteriological, pleural fluid A-DROP scores and outcome of surgical intervention. The entry criteria for surgery was pleural fluid characteristics and treatment outcome of cases managed at a multispeciality hospital in rural India.  

Results: 17 cases in this study had 15 males and 2 females between 21 to 53 years of age. All presented with acute onset of fever, chest pain, pulmonary consolidation and leucocytosis. Mean duration of symptoms averaged 6 days prior to hospitalisation. 2 had mild effusion while moderate effusions was observed in the remaining 3 with them having multiloculation. Pleural fluid grew streptococcus pneumoniae in 5 and staphylococcus aureus in 2 cases. Blood and sputum grew streptococcus pneumoniae in 2 cases. Pleural pus was present in 11 cases and in the remaining pleural fluid revealed polymorphonuclear leucocytosis with glucose below 50 mg/dl. Pleural fluid gram stain was positive in 8 cases. All cases received appropriate antibiotics. Pleural drainage with 24 F chest tube was instituted in 11 cases while in the remaining with 12 F pigtail catheter. 3 cases with multiloculation required instillation of intrapleural streptokinase and placement of pigtail catheters at two different sites for an effective pleural drainage. Amount of pleural fluid drained varied from 450 ml to 2400 ml with mean chest tube dwell time of 6.5 days. All patients responded well to therapy. 2 cases had residual pleural thickening without functional abnormality.  

Conclusions: ACCP category 4 effusion was the commonest with infection by streptococcus pneumoniae predominating among them. Early institution of pleural drainage along with appropriate antibiotic therapy resulted in excellent outcome.
P2565 Multilobar x-ray shadowing is an independent predictor of community-acquired pneumonia severity and mortality
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Introduction: National guidelines for community-acquired pneumonia (CAP) recommend the CURB65 score to assess severity and determine antibiotic therapy. CURB65 does not factor the radiographic extent of consolidation on chest x-ray. The aim of this study was to determine the prognostic value of classifying CAP into unilobar and multilobar consolidation.

Methods: A retrospective study of patients admitted with CAP was performed over 6 months. CAP was confirmed as a new radiographic infiltrate. The primary outcome of the study was the 30-day mortality.

Results: 210 patients (52% male) were included. Median age was 76 years. 62% (no=131) were classified as unilobar pneumonia compared to 38% (no=80) with multilobar CAP. A positive correlation was observed between multilobar consolidation and mortality by Kaplan meier analysis (p=0.01 by log rank test).

Conclusion: Multivariable analysis, after adjusting for confounders, revealed that multilobar consolidation was independently associated with 30-day mortality (odds ratio 2.25 95% CI 1.03-4.92, p=0.02). This relationship persisted for 90-day mortality (odds ratio 1.99 95% CI 1.01-4.02, p=0.04).

P2566 Nitric oxide (NO) in exhaled breath helps to distinguish the origin of lung infiltrate
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Introduction: Determination of pulmonary infiltrates is necessary not only to evaluate the general condition of a patient, but also to determine needs and duration of antibiotic therapy. Well-recognized methods of diagnosis (physical examination, blood tests and x-rays) are not enough helpful in determination of the pulmonary infiltrate’s origin.

Objective: To distinguish the origin of lung infiltrate using NO in the exhaled breath.

Materials and methods: Prospective non-randomized study was carried out in the Centre of pulmonology and allergy, Paul Stradins Clinical University Hospital, Riga, Latvia. The study is approved by Riga Stradins University Ethics Committee. Patients with lung infiltrate of inflammatory (due to pneumonia) and congestion (heart failure) origin were involved to the study. Community-acquired Pneumonia/CAP was confirmed in 6 (from 10) patients. Heart failure (HF) with small blood circuit congestion and lung infiltration was confirmed in 4 patients. Exhaled NO, X-Ray, clinical pattern were processed. The NO level was measured by chemiluminescence’s analyzer (Aerocrine). The data were processed under SPSS 20.0 for Mac.

Results: CAP patients (no=7) demonstrated 24.67 ppb. HF patients (no=4) demonstrated 3.65 ppb (p<0.05). Normal range for exhaled NO is less than 4 ppb.

Conclusion: The data show that is increased NO production in pneumonia patient. The lung infiltrate origin might be evaluated using NO in the exhaled breath.

P2567 Community acquired and health-care associated pneumonia: Should we own follow guidelines?
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Treatment of healthcare-associated pneumonia (HCAP) according to published guidelines recommend initial broad-spectrum antibiotics and de-escalation based on culture results.

This study aims to investigate the in-hospital and 30-day mortality and LOS in both CAP and HCAP non-immunocompromised (NIC) and HCAP immunocompromised (IC) related to the empirical antibiotic therapy started at admission, before microbiological data availability. All patients admitted to a university tertiary care hospital in Milan with a diagnosis of pneumonia from 2005 to 2011 were prospectively enrolled. CAP, HCAP and immunocompromised were identified on the basis of the existing criteria. Therapies of two periods (T1: 2005-2007 and T2: 2010-2011) have been compared.

Ongoing Results
A total of 275 patients, 135 HCAP, were included in the analysis. T1 accounted for 240 CAP, 40 HCAP-NIC and 80 HCAP-IC. T2 (partial results) accounted for 20 CAP, 4 HCAP-NIC, 11 CAP-IC.

During T1, culture positive were 23.3% and culture negative 55%. The majority of CAP was started with monotherapy (51.7%), while the most of HCAP with dual-therapy (NIC 45%, IC 41.3%). Triple-therapy was addressed for 9.2% of CAP, 12.5% of HCAP-NIC and 25.0% of HCAP-IC. During T2, culture positive were 17.1% and culture negative 80%. The majority of CAP and HCAP-IC started a dual-therapy (55% and 54.5%), while 50% of HCAP-NIC had a monotherapy. Triple-therapy was started in 5% of CAP, 25% of HCAP-NIC and 18.2% of HCAP-IC.

In CAP of both periods none of the patients treated with triple-therapy died, and there were no differences for mortality between mono and dual-therapy. HCAP with dual therapy had less mortality than both monotherapy and triple-therapy.

P2568 Multidrug-resistant bacteria: a serious growing public health threat.
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Introduction: Multidrug-resistant bacteria (MRB) are a seriously growing public health threat.

Objectives: Characterize patients with MRB isolations, namely their risk factors. Evaluate frequency of MRB species. Assess influence of antibiotic (AB) therapy towards length of hospital stay (LOS) and mortality.

Methods: Retrospective identification of patients with MRB isolations admitted to Respiratory Insufficiency Unit (RIU) from Feb/10 to Jun/11, followed by medical records’ analysis.

Results: MRB were isolated from 32 patients: male sex – 56.3%; mean age – 74.5 years; chronic respiratory disease – 81.3%; comorbidities – 93.8%; of which 65.6% were immunocompetent. Some (37.5%) were transferred to RIU with an average previous LOS of 42.3 days. At RIU admission 96.9% were under treated on AB and 40.6% had been discharged, in the previous month. 71.9% underwent invasive techniques. There were 44 MRB isolations: MRSA – 45.5%; Acinetobacter baumannii – 29.5%; Escherichia coli; Klebsiella pneumoniae, Pseudomonas aeruginosa and Enterococcus faecium – 9.1% each. Pathogen directed-AB was introduced in 29 isolates (65.9%), but only 11 (37.9%) underwent post-AB control and only 3 of these (27.3%) became negative. There were 14 (43.8%) deaths, 78.6% due to infectious causes, of which 54.5% were attributed to MRB. We found no statistically significant differences between death and survival groups, however LOS was significantly longer in patients who had >1 isolation and whose post-AB control remained positive.

Conclusions: Every patient had at least 1 risk factor for infection. MRSA predominated. MRB were difficult to eradicate and responsible for a high mortality rate.

P2569 Implementation of IDSA/ATS and national guidelines for community acquired pneumonia by Greek chest physicians
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Background: The implementation of practice guidelines for CAP by Greek physicians and their impact on cost and patients’ outcome remain unknown.

Material & methods: A prospective observational study incorporating 350 immunocompetent hospitalized pts with CAP. The aim was to investigate whether the 2007 IDSA/ATS and the Greek national guidelines for CAP are implemented by chest physicians in “Sotira” General hospital in Athens, Greece. We: a) assessed whether the decision of hospital admission was correct or not and b) evaluated whether the administered antimicrobial regimen was in accordance to guidelines. Fine score (PSI) was applied by the authors to determine the severity of CAP.

Results: The mean age was 56.3±22.2years and the duration of hospitalization 10.9±11.8days. 218 (62.2%) pts were male and 132 (37.7%) female. The mortality rate was 12.29%. 167 (47.71%) pts were admitted to the hospital, despite they were classified as risk class I or II and therefore could be treated as outpatients. Implementation of CAP guidelines as far as the initial antimicrobial regimen is concerned was poor (211pts, 60.29%). Patients treated with an initial antimicrobial in accordance to guidelines performed statistically significant lower mortality and
a trend towards shorter length of hospitalization compared to pts receiving initial regimen in discordance to guidelines (p=0.04 & p=0.006 respectively).

Conclusion: The implementation of CAP guidelines by chest physicians in the major Greek hospital for thoracic diseases is poor. Improvement of adherence may improve patients’ outcome, shorten the length of hospitalization and reduce the financial burden for the national health system.

P2571
Clinical presentation and evolution of community acquired pneumonia in older patients
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Introduction: Community-acquired pneumonia (CAP) is an important threat to the health of older adults with almost 40% of them requiring hospitalization. CAP in the elderly has a different clinical presentation and evolution than CAP in other age groups.

Aim: Comparing the characteristics, severity and outcomes of CAP in elderly and younger patients (control group).

Methods: An observational, retrospective study of consecutive CAP patients >65 years old was performed during two years in two respiratory clinics. Exclusion criteria were immunosuppression and suspicion of aspiration.

Results: Of 180 cases of CAP, 116 patients were >65 years old, with a mean age 75±10.3 years. Most elderly patients (76%) had comorbid conditions, including cardiac (35%), COPD (42%), diabetes mellitus (27%) and neurologic diseases(17%). Two-thirds (68%) of elderly patients belong to CURB65 III -IV classes comparing to 12% of the controls. An acute altered mental status was included in 30% of elderly patients comparing to 11% of the others and 80.5% classes comparing to 12% of the controls. An acute altered mental status was detected in 53.6 days.

Period: 1 month and microbiological initiation to detection was 40.6 days. The numbers of antimicrobial agents were 3.5 on average. MDRP were detected in 6 patients with hematological disorders. Sixty three patients have polymicrobial detection. S.marcenses, MRSA, MSSA, K pneumoniae were detected in 12, 12, 11, 11 patients frequently. Fifty nine were judged as colonization. Forty one were causative organism of pneumonia. Three were CAP.

Conclusions: Paeruginosa were detected in patients with chronic respiratory disease and long hospitalization. More than half of detections were bacterial colonization. HAP were frequent and Paeruginosa caused the prolonged hospitalization and poor prognosis.

P2572
The clinical evaluation of patients with Pseudomonas aeruginosa detected in respiratory specimens
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Introduction: The present study aims to clarify the clinical picture of patients with Pseudomonas aeruginosa detected in respiratory specimens.

Methods: Medical records of patients with Pseudomonas aeruginosa detected in respiratory specimens from April 2010 to March 2011 at Kameda Medical Center were reviewed retrospectively. The following variables were reviewed: patient background, duration of hospitalization, drug susceptibility, outcomes.

Results: One hundred patients were detected with P. aeruginosa in respiratory specimens totally. Mean age was 75.0 y.o. Sixty seven patients were male, 33 were female. Twenty eight patients have chronic respiratory disease. Fifty three patients were detected through microbial substitution. Period from admission to detection of P. aeruginosa was 53.6 days. Period: 1 month and microbiological initiation to detection was 40.6 days. The numbers of antimicrobial agents were 3.5 on average. MDRP were detected in 6 patients with hematological disorders. Sixty three patients have polymicrobial detection. S.marcenses, MRSA, MSSA, K pneumoniae were detected in 12, 12, 11, 11 patients frequently. Fifty nine were judged as colonization. Forty one were causative organism of pneumonia. Three were CAP.

Conclusions: Paeruginosa were detected in patients with chronic respiratory disease and long hospitalization. More than half of detections were bacterial colonization. HAP were frequent and Paeruginosa caused the prolonged hospitalization and poor prognosis.

P2573
Serum level of vitamin D3 before and after treatment in pulmonary tuberculosis
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Vitamin D3 is known to have potent immunomodulatory effect and it has been suggested that the low serum level of vitamin D3 increases the risk of tuberculosis. Serum levels of 25 hydroxyvitamin D3 (25HOD3) were measured in 168 drug sensitive pulmonary tuberculosis (PTB) before and about 6 months after the treatment by using high performance liquid chromatography, and were compared with those of 197 healthy normal controls (HNC). Deficiency of vitamin D was defined by the serum level below 15 ng/mL of 25HOD3. The sputum AFB smear grade was quantified from 1 to 4 according to ATS criteria. Heavy AFB smear was defined as 3 and 4 grades.

The mean level of 25HOD3 in PTB before treatment was significantly low compared with HNC (18.7±8.33 vs. 13.1±8.6 pg/mL, p<0.05). The mean level of 25HOD3 in PTB after treatment was also significantly low compared with HNC, but did not show difference compared with the level before treatment. The numbers of vitamin D deficiency before treatment were significantly higher in the PTB compared with HNC, and the numbers did not show significant change after treatment. The numbers of heavy AFB smear were also significantly higher in the vitamin D deficiency patients in the PTB (p<0.05).

These results strongly suggest that vitamin D deficiency increases the risk of tuberculosis, and is related with more severe form of PTB.

P2574
Supplementary cholecalciferol in recovery from pulmonary tuberculosis
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Vitamin D is known to have important for immune homeostasis. In vitro work suggests that l-alpha-25-(OH)2-D modulates host cell responsiveness to the T cell cytokine, interferon gamma (IFNγ). IFNγ is one of the key mediators of protective immunity against Mycobacterium tuberculosis infection therefore; vitamin D may enhance the host immune responses against the pathogen. The objectives of this study were to determine whether supplementation of vitamin D in patients with Tuberculosis could impact recovery.

Methods: 266 patients were randomized to receive either 600,000 IU of Intramuscular vitamin D3 or placebo for 2 doses. Clinical assessments were done...
at 4, 8 and 12 weeks from baseline. Blood samples were obtained at 0 and 12 weeks. Statistical comparisons between outcome variables at 0 and 12 weeks were performed:

**Main Results:** 259 patients completed the study. At the end of 12 weeks, the vitamin D arm demonstrated significantly greater mean weight gain: + 4.02 (95% CI 3.38,4.86) v/s + 2.61 (95% CI 1.99,2.23); p = 0.007 and increases in BMI: + 1.48 (95% CI 1.17, 1.78) v/s + 0.96 (95% CI 0.72,2.10); p =0.008 as compared with the placebo arm. There was a significant difference in chest radiographic improvement in the vitamin D group; number of zones involved -2.21 (95% CI -1.91, -2.51) v/s -1.77 (95% CI -1.51, -2.03); p = 0.01 and resolution of cavitation 73(65.7%) v/s 60 (55%) v/s 60, p = 0.05.

No differences were seen in TB score or sputum smear conversion. At follow up Conclusions: Vitamin D supplementation significantly impacted clinical improvement in patients with pulmonary TB.

P2575

**Prevalence of hypovitaminosis D in TB patients in an East London population**

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**Introduction:** There is a well-established link between vitamin D (25(OH)D) deficiencies and TB, although in vivo association is still contentious.

**Aims:** This retrospective case control study aimed to compare the prevalence of hypovitaminosis D in cases diagnosed with TB in 3 East London boroughs to controls, who were defined as non-occupational inpatients who were not on vitamin D supplements and in whom 25(OH)D assay was performed during the study period.

**Methods:** We compared 25(OH)D levels in patients diagnosed with active TB with controls during a twelve month period from 01/09/10-31/08/11. Hypovitaminosis was defined by two thresholds for 25(OH)D concentrations: deficiency < 30nmol/L and insufficiency 30-79 nmol/L.

**Results:** There were 211 TB cases of whom 75 (35%) had 25(OH)D levels measured. All 75 had hypovitaminosis D of whom 60 (80%) had 25(OH)D deficiency and 15 (20%) were insufficient in 25(OH)D.

There were 323 controls, 87 of whom were taking supplements and so were excluded. Of the remaining 236 controls, 6.8% were vitamin D replete (vs. 0% in TB cases), 52.1% had vitamin D deficiency (vs. 80% in TB cases) and 41.1% were vitamin D insufficient (vs. 20% in TB cases). Mean 25(OH)D levels were significantly lower in the study group as compared to the control group (18.11 nmol/L vs 34.98 nmol/L, p < 0.001).

**Conclusions:** The prevalence of hypovitaminosis D in both the study as well as the control groups is alarmingly high but importantly 100% of TB cases who had 25(OH)D levels checked were either deficient or insufficient. We hypothesize that this may be a unique finding in our ethnically-diverse population and thus may have implications for nutritional supplementation offered to active TB patients.

P2576

**Factors influencing change in baseline vitamin D level in mycobacterial infection**

Gemma Hawthorne1, Alice Turner1, Heinke Kunst1, Martin Dedicoat2

1School of Clinical and Experimental Medicine, University of Birmingham, United Kingdom; 2Department of Respiratory Medicine, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

**Background:** Vitamin D may be an agent, of broad relevance in the treatment of infectious disease because of its immunomodulatory properties.**Methods:** In an ongoing open label observational trial, baseline bloods, vitamin D levels, sputum smear and culture results, radiological changes and TB score were recorded in patients with mycobacterial infection. Each patient was supplemented with 100,000 units of cholecalciferol at 0, 8 and 16 weeks.

**Results:** The mean age of patients recruited (n=42) was 36 years (M:F 27:15), 16 weeks. The mean age of patients recruited (n=42) was 36 years (M:F 27:15), with pulmonary disease (n=29) or extra pulmonary disease (n=13). There was a significant difference in vitamin D levels between the groups. Pre supplementation median vitamin D levels were 11.9 nmol/L (mean 16.96 nmol/L, 92.9% with 25(OH)D levels <50nmol/L. At week 8 post supplementation levels had risen to median 44nmol/L (mean 43.9 nmol/L). There was a significant difference in vitamin D levels pre and post supplementation (p=0.00), with a significantly higher percentage rise in vitamin D levels in patients who were severely deficient (<20nmol/L) (p=0.01).

There was no correlation between vitamin D and DBP, antimicrobial product (LL37) levels or TB score at baseline measurement.

**Conclusions:** Supplementation with 100 000 units of cholecalciferol does not result in sufficient levels (>50nmol/L) at 8 weeks in all patients with just 65% attaining levels >50nmol/L. However, there is a statistically significant rise in levels of vitamin D in those supplemented between week 0 and week 8.

Patients with mycobacterial infection with vitamin D deficiency may benefit from higher initial doses to obtain sufficiency.

P2577

**Does relationship exist between severity of vitamin D deficiency and development of active TB?**

Adeel Tariq Sahal, Joyutpal Das, Sushil Agarwal, Karunvir Singh, Martin Dedicoat, Alice Turner, Heinke Kunst

Respiratory Medicine, Heart of England NHS Trust, Birmingham, United Kingdom

**Introduction:** Deficient serum vitamin D levels have been associated with impaired mycobacterial immunity and incidence of active tuberculous (TB). However, the significance of level of vitamin D in LTBI and the risk of progression to active disease is less clear.

**Methods:** A retrospective review of vitamin D levels of all patients with active TB and LTBI was undertaken between January 2010 and December 2010 at Heart of England NHS foundation trust, Birmingham. We compared vitamin D levels in cases with active and latent TB to explore a relationship between severity of vitamin D deficiency and incidence of active/latent TB.

**Results:** 148 cases with LTBI and 113 with active TB were included in the study. 117 out of 148 patients with LTBI and 108 out of 113 active TB cases had a Vitamin D level performed. Median Vitamin D level in patients with TB was 5.7ng/ml (Range 2-46.4). Median Vitamin D level for LTBI was 7.8ng/ml (2.95-30). The difference in Vitamin D levels between latent and active TB cases was statistically significant with P =.003 (calculated Using Mann Whitney U Test). Subgroup analysis, Median Vitamin D levels of non-white TB and LTBI population were 5.2 (Range 2.00 - 36.20) and 6.5ng/ml (Range 2.00 - 43.40) respectively, P value 0.01. Median Vitamin D levels of white TB and LTBI cases were 17.0 (Range 2.50 - 46.40) and 22 ng/ml (Range 7.30 - 95.30) respectively, P value 0.29 (cohort of white population much smaller than non-white).

**Conclusions:** Vitamin D levels were significantly lower in active compared to latent tuberculosis cases suggesting that degree of vitamin D deficiency may influence development of active TB. We feel prospective study is needed to evaluate it further.

P2578

**Ethnic differences in the vitamin D levels of foreign-born tuberculosis patients in south London not reflected in patients born in the UK**

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Vitamin D deficiency is more common in tuberculosis (TB) patients, and within certain ethnic groups. 70% of TB in the UK occurs in foreign-born persons. We investigated the roles of ethnicity and immigration on the vitamin D levels of TB patients in south London.

We analysed the vitamin D levels of all patients at the time of diagnosis. We compared results by country of birth, ethnicity, age and length of residency in the UK.

There were 470 patients; the mean serum 25(OH)D level was 29.1nmol/L (95% CI 27.2-31.0) and 90.6% had insufficient (<30nmol/L) 25(OH)D levels. Patients born in the Horn of Africa and Indian subcontinent had significantly lower vitamin D levels compared to patients born in the rest of Africa (P<0.001) and Asia (P<0.01). Patients born in Europe had significantly higher vitamin D levels than patients born in Africa (P<0.05) and Asia (P<0.05). Children born in the UK had the highest vitamin D levels (mean 57.4% 95% CI 45.6-69.2); this was significantly more for than children born outside of the UK (mean 19.5% 95% CI 12.5-26.5, P<0.001).

**Mean Serum 25(OH)D by country of birth showing particularly low levels in those from the Horn of Africa and the Indian Subcontinent [normal value >50nmol/L]**

TB patients born in the horn of Africa and the Indian subcontinent have an increased risk of very low vitamin D levels. As there is little difference in ambient sunshine this raises the possibility of significant differences in diet or genetics. Children born in the UK had high levels of vitamin D not attributed to ethnicity.
Conclusion: We found that majority of the LTB patients had low 25[OH]D levels. In general, patients with low 25[OH]D levels tend to react more strongly during TST. One limitation of our study is that the impact of BCG vaccination was not taken into account. Nevertheless, this study further highlights the impact of 25[OH]D as an immuno-regulator in vivo.

P2582
Adverse drug reactions and outcomes of tuberculosis treatment using fixed-dose combination drugs

Methods: Clinical analysis of adverse reactions to second line anti TB drugs

Aim: To assess the effect of 25[OH]D level on the size of tuberculin skin test in household contacts of patients with active tuberculosis.

Methods: We performed a retrospective analysis of 25[OH]D levels and induration sizes during TST in 212 TST cases from 10/2009-10. 146/212 cases had both values (25[OH]D level and the induration size during TST) recorded. Only 3% (5/146) of them had normal 25[OH]D level (<20ng/ml) and normal induration size during TST. We also observed that the average increase of 25[OH]D levels with Adcal-D3, ergocalciferol and combination of these two agents were 14.6±5.4, 20.6±8.9 and 25.8±5.3 respectively. We found that the increase of 25[OH]D level with combination of two agents were greater than Adcal-D3 alone (p<0.001).

Conclusions: Does vitamin D level influence the size of tuberculin skin test in household contacts with latent TB infection?

Methods: Clinical analysis of adverse reactions to second line anti TB drugs

Introduction: Adverse reactions to second line anti TB drugs not only leads to permanent system damage and discontinuation of therapy, but also MDR/XDR treatment failure. This study was conducted to evaluate the impact of 25[OH]D levels on the size of tuberculin skin test (TST).

Objective: Evaluation of vitamin D replacement in the tuberculosis patients

Methods and results: We reviewed 113 TB cases from 2010 in our retrospective study. The study population was consisted of 68 males and 45 females. 25[OH]D levels were checked in 96% (65/68) and 98% (44/45) of male and female patients respectively. 25[OH]D levels were 25[OH]D deficient. 53/56 males and 38/40 females, who were 25[OH]D deficient, received 25[OH]D replacement therapies with Adcal-D3 (cholecalciferol, vitamin D3), ergocalciferol (ergocalciferol, vitamin D2) or combination of these two agents. We then assessed the effect of these agents on the 25[OH]D level. Only 76% (20/26) of males and 87% (46/53) of females who received replacements, had their 25[OH]D levels repeated in 3-6 months. In both genders, 25[OH]D levels increased with the treatment (p<0.0001 in both genders). We also observed that the average increase of 25[OH]D levels with Adcal-D3, ergocalciferol and combination of these two agents were 14.6±5.4, 20.6±8.9 and 25.8±5.3 respectively. We found that the increase of 25[OH]D level with combination of two agents were greater than Adcal-D3 alone (p<0.001).

Conclusions: Consistent with other studies, we have noticed that most of the TB patients had low 25[OH]D levels. Majority of these patients responded to supplementation, regardless of the gender or the therapeutic agent(s).

P2581
Does vitamin D level influence the size of tuberculin skin test in household contacts with latent TB infection?

Methods: Clinical analysis of adverse reactions to second line anti TB drugs

Introduction: Adverse reactions to second line anti TB drugs not only leads to permanent system damage and discontinuation of therapy, but also MDR/XDR treatment failure. This study was conducted to evaluate the impact of 25[OH]D levels on the size of tuberculin skin test (TST).

Objective: Evaluation of vitamin D replacement in the tuberculosis patients

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Conclusions: Consistent with other studies, we have noticed that most of the TB patients had low 25[OH]D levels. Majority of these patients responded to supplementation, regardless of the gender or the therapeutic agent(s).
ing incidence. TB meningitis (TBM) is a rare form of extra-pulmonary TB, which carries disproportionately high mortality and morbidity rates. Barking, Havering and Redbridge University Hospitals Trust (BHRUT) serves an area in East London with a high incidence of TB. This study aims to evaluate the epidemiology, clinical presentation and outcome of patients diagnosed with TBM.

**Methods:** Individuals diagnosed with TBM between 2000 and 2010 were identified using the London TB Register. A prospective observational study was conducted reviewing medical notes, microbiology results and radiology. Data was collected for epidemiology, clinical features, risk factors, treatment regimens and outcome.

**Results:** 50 patients with TBM were identified and notes were available for 42. 82% were born outside the UK with the highest incidence seen in patients born in India. All patients were treated for at least 12 months with 92% receiving concurrent steroids. Other information is shown below.

<table>
<thead>
<tr>
<th>Table 1. Presenting clinical features</th>
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<tr>
<td><strong>Symptoms</strong></td>
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<td>&gt;1 week</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Fever</td>
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<td>Confusion</td>
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<tr>
<td>Focal neurology</td>
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<tr>
<td>Photophobia</td>
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<tr>
<td>Neck stiffness</td>
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<tr>
<td>Vomiting</td>
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</table>

**Conclusion:** TBM has a high mortality rate in East London with a high proportion of patients requiring treatment in intensive care or suffering long-term neurological sequelae. Confirming diagnosis is challenging as presentation is non-specific, potentially leading to treatment delay. Development of a diagnostic scoring system using clinical features, risk factors and CSF data to aid early diagnosis would prove extremely valuable.

P2585

**Miliary tuberculosis during treatment with anti TNF alpha – A report of three cases**

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The anti-TNFs have proven very effective in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn’s disease. Among the side effects is well known the risk of developing infections, particularly tuberculosis. We present three cases of miliary tuberculosis with mediastinal lymphadenopathy which occurred during treatment with anti-TNFs. Two male patients aged 56 respectively 41 years, were treated with infliximab for ankylosing spondylitis. One male patient aged 32 years was treated with adalimumab for psoriasis. All patients performed chest X-ray, tuberculin skin test, quantiferon TB test for latent TB. The clinical signs of disease were febrile syndrome, dyspnoea, cough and weight loss. In the first case, the positive diagnosis was concluded on lung biopsy and culture positive for BK in sputum. In the second case, were revealed AFB in bronchial aspirate. In the third case, the diagnosis was concluded on lung and mediastinal lymphnode biopsy.

In all cases we observe an aspect of miliary and mediastinal lymphadenopathy on chest CT. In the first case, we find a pulmonary embolism. All three patients developed hepatic cytolytic during anti TB treatment, requiring discontinuation in two cases. The evolution was slowly favorable after the reintroduction of treatment.

**Conclusions:** All three cases are severe forms of miliary tuberculosis associating necrotic mediastinal lymphnodes occurred during treatment with anti-TNFα.

P2586

**Clinical and radiological (CR) features of tuberculosis formed as a result of immunomodulatory therapy (IT)**

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Research objective was an analysis of features of pulmonary tuberculosis (PT) formed as a result of IT.

<table>
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<th>Table 2. Outcome</th>
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<tr>
<td><strong>ITU admission</strong></td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Long term neurological deficits</td>
</tr>
</tbody>
</table>

**Conclusion:** IT has a high mortality rate in East London with a high proportion of patients requiring treatment in intensive care or suffering long-term neurological sequelae. Confirming diagnosis is challenging as presentation is non-specific, potentially leading to treatment delay. Development of a diagnostic scoring system using clinical features, risk factors and CSF data to aid early diagnosis would prove extremely valuable.

P2587

A dilemma of skeletal tuberculosis diagnosis

Parvaneh Baghaei Shiva, Majid Marjani, Payam Tabarsi, Mohammad Reza Masjedi. Clinical Tuberculosis and Epidemiology Research Center, NRTLD, Tehran, Islamic Republic of Iran

**Objectives:** Skeletal tuberculosis reports 1-5% of all TB cases. The most common sites of involvement are spine, knee and hip. The diagnosis of extra-pulmonary TB is difficult. The aim of this study was to show up the different way of diagnosis and report this kind of TB in Iran.

**Method:** This study was done in Masih Daneshvari Hospital, a referral center of TB in Iran, from 2003 to 2011. In this retrospective study, we extracted all skeletal TB. Demographic information, the method of diagnosis, and other information were evaluated.

**Results:** Of 426 extra-pulmonary TB, 58(13.6%) patients were skeletal TB. The mean age was 45.72±20.26yrs. 31(53.4%) patients were male. One patient was HIV positive. New cases of TB, relapse and history of TB treatment were 51, 4 and 3 respectively. Median of duration of symptoms was 7 months. 28 patients had pulmonary TB (sputum smear or culture was positive). The kind of skeletal TB was: 2patients with pleural, one patient with CNS, one patient with lymph node concomitant with spine and 52 patients just spine. Two patients were arthri-tis (knee) tuberculosis. Diagnostic method was: positive granuloma 43.7%, PCR positive 31.2%, positive smear and culture 22%, positive sputum for TB 31% and diagnosed by clinical/magnetic resonance imaging 13.7%.

**Conclusion:** The diagnosis of skeletal TB is difficult and it will take time to detect it. Investigation of other involved site such as lungs, pleura or lymph nodes can help us early TB diagnosis.

P2588

Obstructive airway disease in pulmonary tuberculosis cases in relation to smoking

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**Introduction:** Tuberculosis (TB) is a long-standing & expanding threat to public health. People with treated pulmonary tuberculosis (PTB) are left with significant changes in lung anatomy & are at higher risk of pulmonary sequelae. Smoking is the major risk factor for airflow obstruction. Recent & early studies suggest association of prior TB with development of COPD. But whether smoking modifies this relationship is unclear.

**Aims:** 1) To study the effect of smoking & prior PTB on airflow obstruction 2) To assess the severity of obstructive abnormality in smoker versus non smoker patients of prior PTB. Settings: Tertiary care Institute in Lucknow, India. Period: From Jan 2011 to Jan 2012.

**Material & method:** 100 patients who visited OPD with history of prior PTB were divided into different categories on the basis of sex, smoking history, age etc. All patients were subjected to spirometry, sputum examination for acid fast bacilli, chest X-ray & their history were also evaluated. Diagnosis of COPD was based on GOLD criteria.

**Results:** Out of total 100 patients 53 were smokers and 47 were non-smokers.
Out of 53 smokers 38 (71.69%) had obstructive abnormality while out of 47 non-smokers 23 (48.93%) had obstructive abnormality (p<.05). Smoker with prior PTB developed more severe airflow obstruction (Mean FEV1 40.03%) as compared to non-smoker with prior PTB (Mean FEV1 45.43%).

Conclusion: Prior PTB is an independent risk factor for airflow obstruction irrespective of smoking status which may explain the higher prevalence of COPD in India. Prior PTB along with smoking is associated with more severe form of airflow obstruction.

P2589
Prevalence, features of the course and treatment efficacy airway obstruction in patients with newly diagnosed pulmonary tuberculosis

Airway obstruction (AO) is an important factor for ineffective treatment of pulmonary tuberculosis. The aim of research was studying prevalence AO, features of treatment and inhalation therapy in patients with newly diagnosed pulmonary tuberculosis (TB).

Methods: In a prospective study was examined by spirometry among 311 patients of 18-75 with TB. The effectiveness of treatment was identified among 125 patients by randomization. The first group consisted of 31 patients, who, besides chemotherapy, got ipratropium bromide and fenoterol (1 month); the second group consisted of 32 patients, who got fenoterol. The Control Group included 32 patients, who got only standard chemotherapy. Quality of life (QL) was evaluated using Short Form-36 (SF-36) at baseline and 1 month.

Result: The prevalence of AO among patients with TB was 62.70%. AO associated with greater frequency of shortness of breath (odds ratio (OR) = 11.78) and cough (OR=10.56) compared patients with non-obstructive pattern (p=0.01). The relative risk of developing endobronchial pathology in patients with AO is 2.01 times greater than without AO. In patients treated with inhalation therapy was observed greater improvements in HRQL by 5.6 scores for the physical component of SF-36, microscopic conversion of sputum to 16.17% cases and X-rays cavity closure to 11.81% cases more frequently compared with the Control group (p<0.05).

Conclusions: TB is often complicating by AO, short course of inhaled bronchodila-
tors and/or glucocorticoids improve results of a treatment for such patients.

P2590
Effect of tobacco on the pulmonary tuberculosis

Samiy Farah1, Manel Hadji2, Chiraz Aichaoui3, Manel Hdiji2, Chiraz Aichaouia3, Salsabil Dabboussi4, Zied Moetaattar1, Samira Mhamdi1, Abderrazek Haddaoui5, Moreh Khadraoui6, Rzek Cheikh9.

Introduction: Tobacco increases the risk of pulmonary infection, especially tuberculosis.

Objective: To determine the effect of pulmonary tuberculosis on clinical expression of the tuberculosis and its delay diagnosis.

Material and methods: It’s a comparative study between two groups of patients hospitalized in our department between January 2008 and June 2010.

Results: The first group was made of 37 smokers patients hospitalized because of confirmed pulmonary tuberculosis. The second group consists of 32 non smokers patients and also hospitalized because of confirmed pulmonary tuberculosis. Delay of diagnosis was shorter in the group of smokers (42 days versus 78 days). Cough and dyspnea were more found at the smoker’s (86% versus 82%). The biological investigations showed a high level of white blood cells with predominance of neutrophils especially in smokers (20 versus 10) and smokers were more likely to be smear-positive (21 versus 17). Chest X ray showed essentially nodules in both groups. These nodules were bilateral in the group of smokers (22 versus 14). The duration of the treatment was longer at the smokers (7 months versus 6, 5 months). Evolution after antituberculosis treatment was favourable for all patients. The complications as the lung fibrosis (2 versus 1) were more among smokers than non-smokers.

Conclusions: The Smoking was not associated with delay in the diagnosis and treatment of tuberculosis.

P2591
Anxiety and depression in tuberculosis hospitalized patients in comparison to healthy individuals

Ionela Ionel1, Dorin Vancea1, Zeno Flratia1, Ovidiu Buralcav2. 1Clinic of Pneumology, Victor Babes Hospital, Timisoara, Timis, Romania; 2Thoracic Surgery, Emergency Municipal Hospital, Timisoara, Timis, Romania.

Introduction: Very little is known about the psychiatric comorbidities in tuberculosis (TB), which must be recognized and managed in order to improve adherence to the treatment.

P2592
Screening and monitoring of tuberculosis in patients on biologics treatment

Sameh Farah1, Galina Lukina2, Lydia Gumapov2, Kochetkov Yakov1.

Background: The new class of drugs - biologics (B) - is high effective, but its use is limited due to different degree the risk of tuberculosis (TB).

Methods: 600 pts (rheumatoid arthritis - 264, ankylosing spondylitis - 257, psoria-
sis - 50, other - 29), 303 male and 297 female, 15-80 y.o. (95/CI 42,2, 43,3) were examined before (377 pts) and during (286 pts: infliximab - 159, adalimumab - 58, etanercept - 17, certolizumab - 28, abatacept - 11, tocilizumab - 21; 20 pts receive more then one B consecutively) B treatment. Clinical examination, X-ray (CT in any abnormalities), tuberculin skin test (TST), interferon-gamma release assays (IGRA), skin test with recombinant protein ESAT-6/CFP10 (developed in Russia as DIASKINTEST - DST) were performed.

Results: In all cases by primary screening active TB was rejected, but positive TST was obtained in 82.6%, IGRA in 34.6%, and DST - in 25.8%. Preventive TB treatment (PT) was administered in patients with residual TB changes (49) or defined latent TB infection (LTI) (positive both NST and IGRA/DST). During the B treatment active pulmonary TB was detected in 8 pts (all - on TNF-alpha inhibitors: etanercept - 17, certolizumab - 12, rituximab - 28, abatacept - 11, tocilizumab - 21; 20 pts receive more then one B consecutively) B treatment. Clinical examination, X-ray (CT in any abnormalities), tuberculin skin test (TST), interferon-gamma release assays (IGRA), skin test with recombinant protein ESAT-6/CFP10 (developed in Russia as DIASKINTEST - DST) were performed.

Conclusion: The procedure of TB screening and monitoring is the essential part of the B treatment program. The tests based on specific M tuberculosis antigens are very useful as the tools for LTB monitoring and enable to reduce PT at least three times.

270. Tuberculosis: clinical findings II

P2593
Predictive factors of relapse in pulmonary tuberculosis

Sonia Habibeb1, Ines Zendah, Nhadja Ayed, Leila Bayahi, Ibtihel Kouaja, Habib Chenitra. Respiratory Department I, Abdourhamen Mama Hospital of Respiratory Diseases, Ariana, Tunisia.

Background: Pulmonary tuberculosis (TB) relapse is a life-threatening condition. Revealing the factors that lead to relapse may help developing preventive measures.

Aim: The aim of this study is to reveal the main predictive factors of relapse in patients with pulmonary TB.

Methods: We compared the data reported during the first episode of TB of 22 non-HIV patients treated for pulmonary TB and who had a relapse with those of 36 non-HIV patients treated for the same disease without relapse. Files were selected if the follow-up period exceeds 3 years. Results are expressed as a percent or a mean with (C.I.95).

Results: Patients with relapsing disease, as compared to patients without relapse, are older (61[56-65] vs 37[33-41] years-old), with history of heavier smoking (40[29-51] vs 18[10-26] Pack-Years) and a lower proportion of TB-vaccinated patients (40% vs 80%; p=0.05). The 2 last findings are likely to be correlated to age. But independently of age, in patients with relapse, we found a higher proportion of patients who have a close contact with another TB-patient (63% vs 38%; p=0.01) and a more frequent right lung involvement (50% vs 36%; p=0.05).

Conclusion: From our data, relapse of pulmonary TB is more likely to occur in older patients, those exposed to contagious persons and those with a right lung involvement during the first episode of TB.

2012-09-03
P2594
Relapse rate of tuberculosis and related factors in Korea; by using the nationwide tuberculosis notification data
Hyungmin Lee1, Yoosung Park1, Sang-suk Shin1, Eun-hee Cho1, Sung-suk Shin1, Bo Youl Choi1, Division of HIV and TB Control, Korea Centers for Disease Control and Prevention, Osong, Korea, 2Department of Internal Medicine, College of Medicine, Catholic University, Seoul, Korea, 3Department of Preventive Medicine, College of Medicine, Hanyang University, Seoul, Korea

Background: The relapse rate of tuberculosis(TB) was one of the indicators that assess indirectly the level of TB control. In Korea proportion of relapse TB was reported in about 12%.

Aims: To estimate the relapse rate of TB and investigate the related factors with relapse of TB by using the nationwide TB notification data in Korea.

Materials and methods: Data source was the nationwide TB notification data in 2005. For them to check that TB patients had been reported again from 2006 to 2010. Related factors were analyzed by using multivariate logistic regression.

Results: Of 45,434 TB patients in 2005, 4.371(9.6%) were reported with TB again and 564 were reported two or more. So the cumulative relapse cases were 5.072(11.2%). A relapse rate was 4.8% in 2006, 2.4% in 2007, 1.6% in 2008, 1.4% in 2009, and 1.0% in 2010.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
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<td>Sex</td>
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<td>men</td>
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<td>Age</td>
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Conclusion: The five-year relapse rate was 9.6%. It was likely to be underestimated for death after failure or default were related strongly.

TAF = treatment after failure, TAD = treatment after default, TI = transfer in, pul = pulmonary.

P2596
Safety and benefit of adjunctive systemic corticosteroid therapy in the management of severe, smear positive pulmonary tuberculosis (SSP-PTB): an interim analysis of a randomized controlled trial
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Objective: To assess the safety and benefit of adjunct steroid therapy in SSPPTB.

Methods: SSPPTB patients were randomized to 2 groups. All were given standard category 1 anti-tuberculosis therapy (ATT). Test group was given a tapering 3 week course of oral prednisolone. Interim analysis done at 8 weeks.

Results: Steroid arm had 38 (36 males; mean age 49y) while control arm had 26 (19 males; mean age 46y) patients.

Conclusions: Adjuvant therapy with prednisolone in patients with severe, smear positive pulmonary tuberculosis is safe and obtainable cost-effective.

P2597
C-reactive protein in pulmonary tuberculosis-correlation with extent and severity of the disease
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Background: Pulmonary tuberculosis (PT) presents a broad clinical spectrum. C-reactive protein (CRP) has been identified as a possible marker of severity in this disease.

Aims: To assess the role of CRP in patients admitted for PT and its relation with radiological extent, bacterial load, hospital stay and mortality.

Methods: We retrospectively evaluated 201 adult patients admitted in a tertiary hospital for PT without HIV infection (2007-2011). Demographic, clinical, analytical and radiological data as well as hospital evolution were studied. Patients were categorized according to radiological extent (National Tuberculosis Association classification) and initial bacterial sputum load (ATS criteria). For statistical analysis, Spearman correlation coefficient, analysis of variance ANOVA and Bonferroni test were used, with SPSS18 support.

Results: Most were male (74%), mean age 53.5 yrs. Sputum smear on admission was negative in 39.8%; in these, CRP was significantly lower (mean: 82.1 mg/L) than in smear-positive patients (mean: 114.5 mg/L), p=0.003. However, CRP did not increase with higher bacterial load (p=0.113). CRP values increased significantly with more extensive disease on chest X-ray (Est.I: 61.7mg/L, Est.II: 109.9mg/L, Est.III: 170.8mg/L), p=0.000. A positive correlation between CRP value and hospital mortality was found (r=0.141, p=0.027) but not with duration of hospitalization (p=0.065).

Conclusions: CRP may play an important role as an indicator of the extent and severity of PT and showed prognostic value for short term mortality of the disease.
Studies including ambulatory patients may help defining its role in identifying those who need to escalate health care.

P2598

diagnosing value of closed-pleural biopsy in pleural tuberculosis

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Introduction: Thoracoscopy is the gold standard for diagnosis of pleural tubercular (PTB). However, pleural biopsy (PB) is a blind technique of investigation of simple first intention designed to make the histological diagnosis.

Aim: To evaluate the contribution of PB in the histological diagnosis of PTB.

Method: We study retrospectively 49 patients in whom PTB were diagnosed in our military department. PB was sent for culture and histopathological examination. Patients were excluded if they had positive bacilloscopy.

Results: The mean age was 32 years (12 to 78). 81% were male. A past medical history of tuberculosis was found in 25% of cases. The most frequent symptoms were chest pain, cough and constitutional symptoms. The TB effusions were all exudative with a mean lymphocyte fraction of 80%. PB was done in 89% of cases with a mild number of fragments was 4.5. Diagnosis was confirmed by closed-PB in 61.9% of cases, bones from the first biopsy in 53.3% of cases. Thus the sensitivity of the PB is 53%. No complications of PB were noted. The thoracoscopy confirm the diagnosis in 24.4% of cases. 4.4% of cases was histologically non diagnostic. Pleurisy is noted in 77.5% of cases associated with pericardial disease in 6.1% of cases. Histology found a tuberculous granuloma in 69% of cases with caseous necrosis in 50% of cases. Culture of pleural fragment was positive in 3 cases. In other cases the diagnosis is retained on elements of presumptions.

Conclusion: Necessity of PB depends on the extent of lesions and the experience of the operator. The PB is a minimally invasive and cost effective procedure for the early diagnosis of pleural tuberculosis before considering more invasive examinations.

P2599

Atypical pulmonary tuberculosis

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Introduction: Tuberculosis remains a common disease, but despite this, it is often diagnosed with long delay due to some atypical presentations. The aim of our work is to know unusual shapes because they may pose problems of differential diagnosis especially with malignant diseases.

Methods: We report 50 cases of pulmonary tuberculosis atypical between 2000 and 2009: 15 cases of endobronchial tuberculosis, 16 cases with basal localization and 19 cases of pseudotumoral form.

Results: The average age is 37 years. Smoking is found in 17 cases and diabetes in 12 cases. The clinical picture is dominated by bronchial syndrome. The chest rays show basal opacity in 16 cases, a pseudo-tumor opacity in 19 cases and a retraction opacity in 15 cases. Bronchoscopy visualizes endobronchial granuloma in 6 cases, tumor buds in 5 cases and bronchial stenosis with extrinsic compression in 8 cases. CT show suspected tubular process in 19 cases, mediastinal lymphadenopathy assessed in 12 cases and avascular opacity in 5 cases. Pulmonary tuberculosis is confirmed by bacteriology in 23 cases, bronchial biopsies in 8 cases, transmural biopsy in 7 cases, by thoracotomy in 6 cases and by lymph node biopsy in 2 cases. Antitubercular treatment was prescribed in all cases with good evolution in 36 cases (72%).

Conclusions: Pulmonary tuberculosis may mimic atypical, mainly malignancy hence the interest to recognize its various unusual shapes.

P2600

Features and treatment outcome in cavitary pneumonia

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Cavitary pneumonia is a clinical X-ray form of infiltrative TB or a complication of the acute progression of fibro-cavitary TB. Aim of study is evaluation of features and treatment outcome in CP. A retrospective study included 95 patients with CP. Most of them (84%), were new cases of infiltrative TB and 16% fibro-cavitary TB. New-onset TB were 70% cases, relapse cases were 21% after treatment failure 21% and after default 2%. Male/female ratio was 2/1, average age 42.6 yrs, unemployed 64%, diabetes 11%, with bad living conditions 72%, homeless 10%, with medium level of education 59%. Regarding the way of detection, all were detected passively, 63% were late detected (average time 6 weeks). Regarding clinical picture, 77% had well-defined respiratory syndrome and 85% intoxication syndrome. Co-morbidities had 40% (alcoholism 19%, hepatitis 7%, diabetes 7%, HIV-infection 4%). Hematological parameters included anemia in 61% cases, lymphocytosis 48%, lymphopenia 51%, increased ADA 42%. Radiological were revealed destructive lesions in 90% with bilateral localization in 89%, involving more 3 lobes in all cases. At the detection, smear positive for acid-fast bacilli were 85%, culture positive 84%. Primary drug resistance was identified in 34% cases. Conversion rate of smear positive patients at 2 months of treatment was 56%. DOTs received 91%, individualized treatment 9%, compliant with treatment were 84% cases. Treatment outcome: anti-TB treatment completed 61%, dead 23%, treatment failure 12%, default 4%. Features that affect the outcome of CP are: late detection, co-morbidities (especially for low economical status), previous anti-TB treatment, high rate of primary resistance, bilateral involving.

P2601

How do we diagnose tuberculosis in early childhood?

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Children are a special group when considering Tuberculosis(TB) diagnosis: they can develop disease quickly after primary infection, present severe forms and there is a lack of standardized case definition and difficulties in establishing a definitive diagnosis.

Aims: Understand reasons to initiate TB treatment in children under 6 years old and identify risk factors associated with treatment in the absence of laboratory criteria.

Methods: We reviewed TB records of patients younger than 6y reported in North-ern Portugal in 2000-09. Epidemiological, clinical, radiological, microbiological and treatment information were analyzed (univariate/multivariate analysis) using SPSS19.0 (p<0.05).

Results: In the last 10 years 132 children under 6y were diagnosed with TB; 60% male. Six children had co-morbidities: five HIV-positive and one diabetic. 90% were BCG vaccinated. Information about TB detection known in 130: 104 had symptoms (78.8%) and 26 were screened during contact investigation (19.7%). Laboratory criteria for TB obtained in 73 (56.2%): 31 culture-positive (23.7%). Having normal SPSS19.0 (C 1.45-15.45), positive tuberculin skin test-TST (OR 5.26, CI 1.92-14.29) and not having performed invasive tests-bronchoscopy/gastric fluid analysis (OR 5.95, 1.89-16.67) were independently related to the decision to treat without laboratory criteria. History of TB contact, existence of symptoms and co-morbidities were not associated to that decision.

Conclusion: Our confirmation rate among this age group was higher than in Europe (19% in 2009). Decision to treat was neither based on laboratory criteria nor on radiological finding consistent with TB, but on a positive TST. Criteria to initiate treatment in this group must be reviewed in order to prevent loosing cases and over-treatment.

P2602

Gender difference in sputum positive pulmonary TB cases

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Material and method: All sputum positive cases registered for two years (ie, 2003 & 2004) were included in the study. Sputum positive grade with gender and age was analyzed. Among the males there were no gender difference reported in this rate so far. Alappuzha district is one of backward district of South India. Females are usually of working class of manual labour group. We are trying to evaluate any difference from usual presentation in gender difference in sputum positive pulmonary TB cases from a backward district of South India.

Introduction: Incidences of tuberculosis among males are considered about dou-ble that of females. There was no geographical difference reported in this rate so far. Alappuzha district is one of backward district of South India. Females are usually of working class of manual labour group. We are trying to evaluate any difference from usual presentation in gender difference in sputum positive pulmonary TB cases from a backward district of South India.

Material and method: All sputum positive cases registered for two years (ie, 2003 & 2004) were included in the study. Sputum positive grade with gender and age was analyzed. Among the males there were no gender difference reported in this rate so far. Alappuzha district is one of backward district of South India.

Results: A total of 260 sputum positive cases registered during the study period. 215 were male and 45 were female. Among the females there were scanty cases and only 3 cases were 1+. 3+ cases were 33 among females and 156 among males.

Conclusion: A high incidence of sputum positive cases among males (1:5) may be due to low reporting of working class females. Late reporting is also common among females in backward areas.

P2603

Risk of serious adverse reactions during the treatment of new tuberculosis patients

Diana Ivanova, Sergey Borisov, Alexander Ryzhov. Clinical Department, Moscow Research and Clinical Center for TB Control, Moscow, Russian Federation

Background: Treatment of tuberculosis (TB) may be complicated by serious adverse reactions (SADR)s. Correct risk assessment before the start of treatment enables to choose the right preventive strategy and thereby to reduce a frequency of SADRs. The aim was to determine the rates of and risk factors for SADRs during treatment of new TB patients.

Methods: 200 HIV-uninfected new pulmonary TB patients admitted to Research
and Clinical Center for TB control 2009 to 2011 were monitored for ADRs during the intensive phase of treatment. The median age was 28.0 (IQR 22-44) yrs, 93 were female, 108 were smear-positive, 172 received only first-line anti-TB drugs. ADRs having NCI CTCAE Grade 3-4 were recorded as serious. Multivariate logistic regression was used for risk assessment.

**Results:** Seventy-six (37.8%) experienced at least one SADR, to a total of 95 events (47 - hepatitis, 19 – allergic reactions, 14 - hyperuricemia, 7 – deafness). Seventy-six (37.8%) experienced at least one SADR, to a total of 95 events (47 - hepatitis, 19 – allergic reactions, 14 - hyperuricemia, 7 – deafness). A cavity diameter (MM) < 32.9 (OR = 2.31, 95%CI: 1.56-3.45) and a history of drug/food allergy (OR = 2.94, 95%CI: 1.33-6.49) were identified as risk factors for developing a SADR.

**Conclusion:** During anti-TB treatment more than the third part of new TB patients experienced SADRs (more often hepatitis and allergy). Female sex, a history of drug/food allergy, low BMI, smear-positive TB and large cavities are the risk factors associated with SADRs.

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**P2606**

**Anti-tuberculosis therapy as a reason for ejaculatory disorders**

Ekaterina Kolchavenets, Elena Brzhuzhtayk, Denis Khloston, Alexander Osadchyi.

Introduction: The sexual life is an integral part full and happy life. Patient with tuberculosis (TB) suffers from this disease itself as well as from different complications. The aim was to estimate the frequency of ejaculatory disorders in men suffering from tuberculosis and to determine the effect of TB treatment on the ejaculation.

Material and methods: 98 pulmonary TB patients were enrolled in study. The intravaginal latency time before onset of TB was estimated retrospectively and in 3 months of anti-TB therapy.

Results: Before anti-TB therapy 14.3% of pulmonary TB patients had ejaculatory disorders; 10.2% had premature ejaculation, and 4.1% delayed ejaculation. The rest 85.7% of patients had normal ejaculation.

Conclusion: The months of the therapy with 4 anti-TB drugs (isoniazid, rifampicin, pyrazinamide and streptomycin) the proportion was changed significantly. The share of patients with normal ejaculation decreased to 61.2%. On contrary, frequency of premature ejaculation increased twice (20.4%), and delayed ejaculation – in 4.5 times (18.4%).

**P2607**

**Predictive factors for antituberculosis treatment failure**

Tatjana Lesnjic, Zlepca Vasile. Pneumopathology, State Medical and Pharmaceutical University “Nicolet Testemiten”, Chisinau, Republic of Moldova.

The effectiveness of DOTS achieved 59% in Moldova in 2011. The result of an inadequate treatment is the treatment failure. Its increasing rate (7.5% in 2011) leads to accumulation of MDR sources in the population and puts more problems to the National TB Control Program. Treatment outcome depends by the social categories of patients, TB extension and co-morbidities. Aim of study is evaluation of predictive factors for anti-TB treatment failure (TF).

Methods: We compared risk factors for TF in a study group (SG) of 110 patients with pulmonary TB failed after 5 months of DOTS and a control group (CG) of 100 patients cured with DOTS.

Results: Males 60% SG vs 50% CG, average age 35.6 SG vs 42.5 CG, unemployed 76% SG vs 48% CG, with bad living conditions 63% SG vs 48% CG (p<0.05). Were detected 80% of patients from both groups by passive way with known TB contact 26% SG vs 20% CG. All patients (100%) had destructive forms of TB with positive smear, but bilateral extension had 84% of SG vs 24% in CG (p<0.05). Susceptibility test detected primary resistance in 55% SG vs 12% CG. Co-morbidities had 56% of SG vs 24% in CG, most frequent alcoholism, malnutrition, diabetes, HIV infection, tuberculosis 20% from SG vs 100% compliance in CG. Treatment outcome in SG cured 42, 30% dead, 10% default, 18% continue another treatment regimen vs 100% cured in CG.

Conclusions: Predictive factors for TF: are treatment not adapted to susceptibility testing, noncompliance with treatment, low social status, extensive TB with co-morbidities.

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**P2608**

**Incremental yield of first, second and third spumum acid fast bacilli smear by microscopy in the diagnosis of pulmonary tuberculosis among patients referred to St. Paul Hospital Iloilo Public Private Mix directly observed treatment programme**

Kristine Kurz Gaven, Amne Lourdes Ponje, Ellice Solis, Rosario Toledo III. Department of Internal Medicine, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines Department of Internal Medicine, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines Public-Private Mixed DOTS, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines Public-Private Mixed DOTS, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines Department of Internal Medicine, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines Public-Private Mixed DOTS, St. Pauls Hospital Iloilo, Iloilo City, Iloilo, Philippines

Study included all TB suspects referred to St Paul Hospital Iloilo Public Private Mix DOTS for sputum microscopy who submitted 3 sputum specimens for 2 days before and at least 1 spumum positive for AFB by smear microscopy. 3922 TB suspects submitted 3 specimens each 18.62% suspects fulfilled the definition of having at least 1 positive smear result confirmed by 2nd smear examination.0.27% had at least one positive smear.93.8% of suspects had their first specimen positive for AFB.5.55% were positive on the second specimen but not on the first and 0.65% were positive on the third specimen but not on the previous two. The distribution of smear positives among TB suspects in successive specimens and year, in 2003, 116 TB suspects examined of whom, 28.4% were positive. For 2005, 481 suspects wherein 22.24% were positive. For 2006, 481 suspects, 21% were positive.
2007, 670 suspects,17% were positive. In 2008, 734 suspects,16% were positive. In 2009,401 suspects and 14% were positive. Result showed reliance on the first specimen detect 85% of the sputum positive patients in 2003,94% in 2004,91% in 2005,98% in 2006,95% in 2007,94% in 2008 and 91% in 2009. If the second morning specimen was taken into consideration,then 97% were detected in 2003 and 2004 and 100% were detected from 2005-2009. As shown in this study that almost 7% of cases can be detected with submitting 2 specimens, one of which is the early morning specimen, the DOTS could improve the compliance of sputum submission of the patients as well as reduce the cost.

P2609
Presentations and treatment response of pulmonary tuberculosis in type 2 diabetes mellitus
Safaa Wolfs. Chest Department, Assiut University Hospital, Assiut, Egypt

Introduction: The association between diabetes and tuberculosis and their synergistic role in causing human disease has been recognized for centuries. They have serious implications on each other.

Aim: The aim was to study the coexistence between Tuberculosis and Diabetes, and to determine whether diabetes alters the radiological manifestations of pulmonary tuberculosis.

Methods: Patients with both Tuberculosis and Diabetes(28patients), were compared with another TB patients without diabetes(30patients). All were subjected to sputum smear for AFB examination and X ray chest.Bronchoalveolar lavage and tuberculin test were performed in selected cases.

Results: Diagnosed in 48.5% of TB patients. The majority were old females(60.7%) with mean age51.80±11.32.All patients associated with diabetes had type 2 DM. Most of them had diabetes before TB infection(57.5%). TB caused uncontrolled diabetes in 71.4% of cases, while diabetes decreased the response to anti-TB drugs in 32.1%. In diabetic patients lesions of tuberculosis were found to be bilateral in 39.3%, followed by left lung. It was significantly different from control group as it affected either right or left lung. Lower lung zone affection was significantly higher among diabetic patients 71.4% vs 3.3%. Atypical radiological features were significantly common in diabetic patients. Cavitating lesion and pneumonia may delay the proper treatment.

Conclusions: DM and TB had an adverse affect on each other. The atypical radiological images masked the diagnosis of tuberculosis in diabetic patients, which may delay the proper treatment.

P2610
Cutaneous tuberculosis: Two cases report
Orlum Sanive Ingam1, Hatice Türker1, Merve Çiftçi2, Baran Gündogus1

Aim: The aim was to study the coexistence between Tuberculosis and Diabetes, and to determine whether diabetes alters the radiological manifestations of pulmonary tuberculosis.

Methods: Patients with both Tuberculosis and Diabetes(28patients), were compared with another TB patients without diabetes(30patients). All were subjected to sputum smear for AFB examination and X ray chest. Bronchoalveolar lavage and tuberculin test were performed in selected cases.

Results: Diagnosed in 48.5% of TB patients. The majority were old females(60.7%) with mean age51.80±11.32. All patients associated with diabetes had type 2 DM. Most of them had diabetes before TB infection(57.5%). TB caused uncontrolled diabetes in 71.4% of cases, while diabetes decreased the response to anti-TB drugs in 32.1%. In diabetic patients lesions of tuberculosis were found to be bilateral in 39.3%, followed by left lung. It was significantly different from control group as it affected either right or left lung. Lower lung zone affection was significantly higher among diabetic patients 71.4% vs 3.3%. Atypical radiological features were significantly common in diabetic patients. Cavitating lesion and pneumonia may delay the proper treatment.

Conclusions: DM and TB had an adverse affect on each other. The atypical radiological images masked the diagnosis of tuberculosis in diabetic patients, which may delay the proper treatment.

P2612
The situation of extrapulmonary tuberculosis in Japan: Affected organ and rate of bacteriologically detection
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Introduction: To bacteriologically confirm diagnosis of tuberculosis (TB) is desirable. However, extrapulmonary TB (EPTB) is difficult because collecting samples are not simple like sputum samples, and burden for patients and doctors. In addition, smear examination tend to be negative. In Japan, patients access to examination easily because of health system. That is why, EPTB may be more bacteriologically confirmed in Japan.

Objectives: It is interesting to look into % of EPTBs bacteriologically confirmed by organs, because it would be a good guide for national TB programmes in high-burden countries which type of EPTBs are more likely to be confirmed.

Methods: EPTB data were collected from public health centre from 2008 to 2010 in the whole country. Study variables were affected organ of by age group, gender, nationality, month of diagnosis, prefectural, occupational and treatment history.

Results: The total number of EPTBs in Japan from 2008 to 2010 was 14,711. The most affected organ was pleura (7,043 cases) followed by lymph node excluded hilar lymph node and mediastinal TB (2,882 and 1,433 cases, respectively). Overall 6% of bacteriologically confirmed EPTB was 30.6%. The organ which was highest % of all EPTBs was oculus (4.1%) followed by pleura and hilar lymph node (16.3% and 21.8%, respectively).

Conclusions: Our study demonstrated that 14,711 cases of EPTB were found in Japan from 2008 to 2010. The most affected organ was pleura, however, the % of bacteriologically confirmed pleural TB was only 16.3%.

P2613
Culture-positive pulmonary tuberculosis with a normal chest x-ray in the absence of HIV co-infection
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Aim: Normal chest x-rays (CXRs) have been found in those with culture-positive pulmonary tuberculosis, even without HIV co-infection. We wished to know how frequently this occurs, how frequently such patients are smear-positive and therefore infectious, whether contacts of these patients had evidence of tuberculosis and whether the site of disease can be identified by CT scan.

Methods: Records from the tuberculosis clinic at the Homerton Hospital, London, were reviewed for the period 2003-2012. All cases of culture positive pulmonary tuberculosis were reviewed and for those with a reported normal CXR the case notes were reviewed.

Results: 13 of 364 cases of culture positive pulmonary tuberculosis had a normal CXR. This included 6 of 34 (18%) with HIV co-infection. The frequency of a normal CXR was 3 of 233 (1.3%) with a negative HIV test. Data from one case without an HIV test and another with ++ smear but no culture are included.

Conclusions: Although 3 sputum samples were usually sent, often only one proved culture-positive. CT scans may not reveal active disease. Two with a positive smear had contacts who had forms of TB suggesting recent infection.

480s

271. Tuberculosis: clinical findings III

P2611
Tuberculosis and tumor necrosis factor alpha antagonist: Our experience
Nuria Maria Reina Martí, Ezpeletxeta Sanee de Tejada, Lidia López, Ana Milena Franco Torres, José Luis Velasco Garrido, Carmen Fernández Aguante, María Victoria Hidalgo Sajuga. Pulmonology Department, Virgen de la Victoria University Hospital, Malaga, Spain

Tumor necrosis factor alpha (TNF-alpha) antagonist are used for the treatment of chronic inflammatory disorders when they are refractory to standard therapy. Among its side effects are tuberculosis infection.

Objective: To evaluate the tuberculosis in patients treated with TNF-alpha antagonist.

Method: A retrospective review of patients treated with infliximab, etanercept and/or adalimumab in our hospital. We obtained 633 potential cases. We included patients with a positive culturing or histologic findings suggestive of Mycobacterium tuberculosis infection. Data collected: sex, age, underlying disease, prior immunosuppressive therapy, tuberculosis screening and prophylaxis, TNF-alpha antagonist used and location of the infection.

Results: Of the 633 patients, three developed active tuberculosis. Two men received prophylaxis with isoniaid and they were affected by psoriatic arthropathy treated with infliximab (previously with methotrexate). One of them, a 39-year-old man, developed pulmonary tuberculosis and the other one, a 53-year-old man, a genitourinary disease with a resistant germs to isoniaid. And a 58-year-old woman with rheumatoid arthritis treated with infliximab (and previously with sulphasalazine, penicillinamide, chloroquine and methotrexate), with unknown screening and prophylaxis, who developed pulmonary tuberculosis.

Conclusions: Screening and prophylactic measures cannot eliminate the risk totally. All the patient that developed tuberculosis disease were undergoing infliximab treatment and all of them suffered rheumatic disease. At least two of the developed tuberculosis diseases were not chemo prophylaxis treated. Two developed pulmonary tuberculosis disease and another one a genitourinary disease.
P2614
The factors associated to pulmonary impairment in patients with treated tuberculosis
Mikhail Chushkin, Valentina Aksenova, Elena Bogorodskaya, Vadim Koroev, Sergey Mandrykin, Dmitry Zhutikov, Eduard Tikhokhod, Sergey Smerdin. 
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Tuberculosis is associated with frequent pulmonary impairment. Low lung function is an independent predictor of all-cause or respiratory disease mortality. The aim of the study was to ascertain the factors affecting lung function in patients treated for pulmonary tuberculosis.

Methods: In 302 patients who were treated for pulmonary tuberculosis (188 men and 114 women between the ages of 20 and 82 years) and observed at local dispensaries pulmonary function tests were performed. 

Results: Out of 302 patients, 114 (37.8%) had low lung function (FEV1 < 80% predicted). According to ATS/ERS criteria we classified 8.3% of subjects as having mild impairment; 18.2% of subjects as having moderate impairment; and 11.3% of subjects as having severe impairment. Risk factors for low lung function were positive culture in the past (odds ratio [OR] 4.3; 95% confidential interval [CI] 2.9 to 6.0; p < 0.001), age more than 40 years, recurrence of tuberculosis (OR 2.6; 95% CI 1.3 to 4.9; p < 0.004); education less than 15 yrs (OR 1.7; 95% CI 1.05 to 3.05; p < 0.05). We did not find influence of gender (males vs females, OR 1.36; 95% CI 0.84 to 2.21; p > 0.05), smoking ever vs never (OR 1.21; 95% CI 0.74 to 1.97; p > 0.05).

Conclusion: Risk factors for low lung function were culture-positive pulmonary tuberculosis in the past, age more than 40 years, recurrence of tuberculosis which may increase the prevalence of low lung function in the patients treated for pulmonary tuberculosis.

P2615
Sensitivity and specificity of St. George’s Respiratory Questionnaire in predicting low lung function in patients treated for pulmonary tuberculosis
Mikhail Chushkin, Elena Bogorodskaya, Valentina Aksenova, Vadim Koroev, Sergey Mandrykin, Dmitry Zhutikov, Eduard Tikhokhod, Sergey Smerdin. 
1Pulmonary Physiology, Research Institute of Phthisiopaediatrics, M.I. Sechenov First Moscow State Medical University, Moscow, Russian Federation; 2Rehabilitation, Medical Center, Central Bank of Russian Federation, Moscow, Russian Federation

Tuberculosis is associated with frequent pulmonary impairment. This supports performance of pulmonary function tests in the course of treatment and after a cure but until now pulmonary function testing had not been included in tuberculosis treatment guidelines. The aim of the study was to assess the usefulness St. George’s Respiratory Questionnaire (SGRQ) for predicting low lung function in patients after treatment of pulmonary tuberculosis.

Methods: We investigated 226 patients older than 40 years who were cured for pulmonary tuberculosis (145 males and 81 females). Quality of Life was studied by SGRQ. Pulmonary function was studied by spirometry. Receiver Operating Characteristic (ROC) curve analysis was used for assessment of sensitivity and specificity.

Results: Out of 226 patients, 97 (42.9%) had low lung function (FEV1 < 80% predicted). According to ATS/ERS criteria we classified 8.8% of subjects as having mild impairment; 20.8% of subjects as having moderate impairment; and 13.3% of subjects as having severe impairment. According ROC curve analysis for low lung function, when 29% of Total SGRQ score was chosen as the cut-off, the sensitivity, specificity, positive value and negative value were 57.7%, 83%, 72%, and 72% respectively. Area under the ROC curve (AUC) was 0.75 (95% confidential interval [CI] 0.69 to 0.81; p < 0.001). AUC was a bit bigger in male than in female (0.79 vs 0.69).

Conclusion: Total SGRQ of 29% may be the best cut-off in low lung function detection. Higher Total SGRQ score was associated with higher probability of low lung function.
parameters of both pleural fluid and sputum were measured. Twenty patients showed positive pleural fluid AFB culture results while the other 20 patients were AFB culture negative. Four patients among 38 patients had positive PCR results for tuberculosis and all of them had positive pleural fluid AFB culture results. Thirty five patients (88.5%) were accompanied with pulmonary tuberculosis in chest radiography. Both sputum and bronchial washing AFB culture showed higher positive results in patients with positive pleural fluid AFB culture results (p=0.001) compared to the group with negative culture results. The patients with positive AFB culture in pleural fluid had greater RPT one year after initiation of antitubercular treatment compared with those with negative AFB culture. The mean RPT of pleural fluid AFB culture positive group and culture negative group were 1.5±2.27 and 0.63±2.75 (p=0.046), respectively. There were no differences in pleural adenosine deaminase levels, initial amount of pleural effusion, need for

P2621 Pulmonary tuberculosis presentation – Late diagnosis, advanced disease

Valeria Maria Augusto, Direza Bartolomeu Greco, Margarete Dalcolmo, Marina Augusto Neves, Helena Rachel Wemereich. Clínica Médica, UFMG, Belo Horizonte, MG, Brazil

Pulmonary TB is the disseminating form of the disease. Rates are particularly high in urban areas associated with poverty, crowded living, social instability and HIV infection.

Objective: To describe clinical and radiological manifestations of pulmonary TB in a big Brazilian city and to evaluate the time between beginning of symptoms and diagnosis.

Methods: Prospective descriptive study; patients with positive smear proceeding from the public laboratories of the city of Belo Horizonte were prospectively included between May 2006 and April 2008. Demographic data were investigated. Blood samples were drawn for HIV. Chest radiographs (CXR) – were examined. Sputa were cultured whenever possible.

Results: 224 cases were included, 150 (67.0%) of the male sex. Age was 39.3 (± 13.0). Pulmonary manifestations occurred in almost all cases and systemic manifestations in 90%.

Respiratory manifestations of pulmonary TB (n=224)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral cavity</td>
<td>96 (42.8)</td>
</tr>
<tr>
<td>Unilateral cavity</td>
<td>50 (22.3)</td>
</tr>
<tr>
<td>Bilateral not cavity</td>
<td>49 (21.9)</td>
</tr>
<tr>
<td>Unilateral not cavity</td>
<td>26 (10.3)</td>
</tr>
</tbody>
</table>

Time from beginning of symptoms and diagnosis was 16.26 (± 18.75) weeks. Cavitations were seen in 67.1% of cases.

Radiologic extension of pulmonary TB (n=218)

<table>
<thead>
<tr>
<th>Radiologic presentation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough/production</td>
<td>221</td>
</tr>
<tr>
<td>Wheezing</td>
<td>111</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>71</td>
</tr>
<tr>
<td>Throat/pain</td>
<td>165</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>146</td>
</tr>
</tbody>
</table>

MRTB occurred in 3/158 with culture (1.9%). HIV was positive in 5/222 (2.3%).

Conclusion: Pulmonary positive TB had a late diagnosis in this big Brazilian city. Clinical presentation was of advanced disease with frequent cavitary lesions. In multifocal TB, the radiologic manifestation is not prevalent. Faster diagnosis should become available for high burden cities counties.

P2622 Bacteriological confirmation in a series of patients with exudative pleural

collections, presumed of tuberculous origin

Raúla Daniela Vasilescu, Pneumology I, Hospital for Infectious and Tropical Diseases Dr. Victor Babes, Bucharest, Romania

We analised a series of 23 cases of pleurises diagnosed in 2011 in our pneumology department. There were 23 patients, 14 males and 9 females, aged between 21 and 80.

Pleural fluid analysis: exudate, 100% lymphocytes in 22 cases and with 90% neutrophils one case, with proteins 3.8 – 6.2 g/dl, LDH 274 – 1743 u/l and ADA 47.5 – 196 u/l. Ziehl – Neelsen smears for BAAR from the pleural fluid were negative in all cases.

We obtained bacteriological confirmation in 4 cases from 23 (17,4%) – cultures typical for Mycobacterium tuberculosis.

Bacteriological confirmation coming too late, the criteria for choosing an antituberculous treatment were – epidemiologic, the analysis of pleural fluid (lymphocytic exudate with high ADA) and exclusion of other etiologies after performing CT scans and bronchoscopy.

We administered a standard regimen with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol 7/7 in the first two months continued with HR 3/7. At the end of the hospital stay we obtained important resolution of the pleuritis in all cases and at the end of the treatment - normal chest X-rays at 20 patients, 3 having residual pachypleuritis.

We obtained bacteriological confirmation at one patient with liver cyrosis of viral (HCV) origin, one patient with 4 month pregnancy, one student with no other comorbidity and one patient with the contact.

In conclusion - bacteriological confirmation after cca 45 days of delay did not influence the therapeutic decision and the absence of confirmation didn’t change the type of treatment at that patients with favourable outcome. We must also consider a relative high prevalence of tuberculous pleurisy in a high endemic country as Romania.
P2623 Antituberculosis chemotherapy toxicity reduction
Yevelina Voronkova, Sergey Medvedev, Elena Pushkareva. Clinical Department, Novosibirsk TB Research Institute, Novosibirsk, Russian Federation

Increasing number of TB patients with co-morbidities (including hepatitis) affects the tolerance to treatment and - as a consequence - the efficiency of the treatment.

Purpose: To reduce the toxicity of TB treatment.

Method: A prospective study of 92 patients with pulmonary tuberculosis with drug-sensitive MTR. Study Design: "Case control". TB Patients were treated by standard chemotherapy regimens, including those in the study group (46 patients) - anti-TB medications lecithin-based ultra-emulsion.

Results: The application of anti-TB drugs in form of lecithin-based ultra-emulsion does not reduce the effectiveness of treatment in comparison with the conventional method, while significantly improves patient tolerance to chemotherapy. The analysis of tolerance demonstrated that adverse events were occurring with standard chemotherapy in 19 (41.3%) respectively, the application of the proposed method - only in 3 patients (6.5% < p<0.001, y2). We found that of development hepatotoxic reactions is 9.4 (p = 0.008, y2) in patients with the standard chemotherapy of pulmonary tuberculosis with chronic viral hepatitis. Hepatotoxic reactions were not registered in group with application of anti-TB medications lecithin-based ultra-emulsion.

Conclusion: The proposed method for the treatment of pulmonary tuberculosis prevents development of hepatotoxic complications. The patent of the Russian Federation has been obtained.

P2624 Tuberculosis in immunocompromised hosts: Pathogenic and pathologic peculiarities
Maryna Dzusmikeyeva 1, Dzmitry Gorenok 2. 1Laboratory Department, Republic Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk, Belarus; 2Surgery Department, Republic Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk, Belarus

Fast spreading of HIV-infection is one of the leading reasons of TB incidence increase. HIV-associated immunodeficiency leads to transition TB from infection to disease. Active TB strengthens HIV replication due to rapid synthesis of proinflammatory cytokines. In Belarus, the annual tendency to HIV-associated TB increase is observed. In 2002, a total of 35 HIV/TB patients was registered, whereas 265 in 2009. The purpose of study: to investigate pathogenic and pathologic peculiarities of pulmonary TB in patients with HIV/AIDS.

Methods: Morphological study of HIV/AIDS-associated TB was carried out on autopsy material of 11 patients died in center clinic in 2006-2010. The control group was 10 not HIV-infected TB patients.

The causes of death in HIV-infected patients were generalized TB with extrapulmonary manifestations in 2 cases, cases of pneumonia in 2 cases, acute progressive and disseminated TB in 3 patients. We distinguished following pathogenetic variants of associated HIV/TB pathology: HIV was primary, duration of observation before TB revealing 1-3 years, HIV/TB were revealed simultaneously. Peculiarities of TB course in AIDS patients compared with non HIV-associated TB were: loss of wavy TB coursing signs and specific inflammation features; monomorphism of TB inflammation foci; prevalence of necrotic suppurative foci; absence of productive inflammation elements on foci periphery; absence of localization and organizations signs of TB foci.

Morepathological peculiarities of HIV/TB determine diagnostics complexity and require histobiological study with Ziehl-Nielsen staining.

P2625 Spinal tuberculosis
Waan Ali, Abdelaziz Aichane, Zineb Berrada, Hicham Afif, 1Zoubida Bouayad, 2Department of Phthisiopulmonology, I.I.Mechnikov’ North–West State Medical University, St. Petersburg, Russian Federation; 1Laboratory of Genetic Methods of Research, The Research Institute of Phthisiopulmonology, St. Petersburg, Russia; 2Department of Phthisiopulmonology, I.I.Mechnikov’ North–West State Medical University, St. Petersburg, Russian Federation; 1Department of Phthisiopulmonology, I.I.Mechnikov’ North–West State Medical University, St. Petersburg, Russian Federation; 2Department of Phthisiopulmonology, The Research Institute of Phthisiopulmonology, St. Petersburg, Russian Federation

Introduction: Spinal tuberculosis is rare, but represents the most common form of atypical tuberculous in endemic countries.

Methods: From January 2000 to December 2010, we collected 16 cases of spinal tuberculosis. We analyzed clinical and radiological profile, means of confirmation and treatment.

Results: Spinal and chest pain were the most frequent signs. Four patients had neurological signs. The diagnosis was made by the detection of bacillus in the pus of paravertebral abscess in 6 cases, by histological study of vertebral biopsy in 5 cases, biopsy of another associated lesion in 1 case and in front of clinical and radiological (mainly CT and MRN) arguments with good clinical evolution under antibacterial treatment in 4 cases. The antibacterial treatment associating at least 4 drugs was tolerated and correctly followed by all patients. Surgical drainage was associated in 5 cases. The evolution was good in all cases.

Discussion: Diagnosis of spinal tuberculosis is late when there is no neurological sign. Imaging can make early diagnosis with MRN. Prognosis is good when treatment is early.

P2626 Hepatotoxicity of antituberculosis chemotherapy in patients with liver cirrhosis
Hong Joon Shin1, Chan Woo Park1, Sung Chul Lim1, 2In Jae Oh1, Kyu Sik Kim1, Yu Il Kim1, Young Chul Kim1, Jung Pil Jung1, Young Chun Ko2, Young Soo Kwon1, 1Internal Medicine, Chonnam National University Hospital, Gwangju, Korea; 2Internal Medicine, Gwangju Christian Hospital, Gwangju, Korea

Background: We compared liver cirrhosis (LC) and control patients who were received standard short-course antituberculosis (TB) therapy to evaluate the risk of drug induced hepatotoxicity (DHI) in LC patients.

Methods: Forty two LC patients with newly diagnosed active TB who were received isoniazid, rifampin, ethambutol, and/or pyrazinamide were included in the study. One hundred forty eight patients were selected as control subjects. DHI was defined as a liver transaminase level ≥ 120 IU/L.

Results: Of all LC patients, the etiology of LC consisted of alcoholic in 31 (74%), hepatitis B in 8 (19%), and hepatitis C in 3 (7%). Mean Child-Pugh score of all LC patients was 7.1±1.2 and Child’s A and B were 16 (38%) and 26 (62%), respectively. Pyrazinamide containing regimen were more commonly used in control patients (24 of 42 LC patients [57%] vs. 138 of 148 control patients [93%], p=0.001). Elevated liver enzyme including transient elevation of transaminase was more frequently found in LC patients (31 of 42 LC patients [74%] vs. 69 of 148 control patients [47%], p=0.002). DHI was also more frequently found in LC patients (6 of 42 LC patients [14%] vs. 6 of 148 control patients [4.3%], p=0.016).

In 5 out of 6 LC patients showed DHI, isoniazid and rifampin were successfully readministered and maintained until the end of treatment.

Conclusion: Our data suggested that LC patients with active TB should be closely monitored liver function tests due to more frequent hepatotoxicity during anti-TB treatment including isoniazid and rifampin.
P2629
Smear negative pulmonary tuberculosis in HIV: Over diagnosed or under investigated
Mandar Kubal1, Kavita Mody2, Ravindra Nath Sahay3, Amita Athavale2.
1Department of Medicine, Seth G S Medical College & K E M Hospital, Mumbai, Maharashtra, India; 2Department of Chest & EPRC, Seth G S Medical College & K E M Hospital, Mumbai, Maharashtra, India

Introduction: A significant proportion of HIV infected individuals with respiratory complaints and abnormal chest radiograph are labelled as tuberculosis and started on anti-TB treatment without detailed investigations.

Aims: The aim of the study was to verify the empirical diagnosis of smear negative pulmonary tuberculosis in HIV infected individuals using diagnostic modalities available at a teaching hospital in resource limited settings.

Methods: 50 HIV infected individuals with respiratory complaints, an abnormal chest radiograph, and negative sputum for AFB and labeled smear negative pulmonary tuberculosis underwent detailed history, physical examination, and a series of microbiological investigations. HRCT scans of the chest were performed to verify the chest x-ray findings. In the absence of definitive diagnosis on the initial sputum, the patients underwent bronchoscopy and sampling of respiratory secretions from the affected areas.

Results: Out of the fifty patients enrolled in the study, definitive diagnosis was reached in 47 patients of which 14 patients (28%) had bronchectasis, 13 patients (26%) had Pneumocystis jiroveci pneumonia, 5 patients (10%) bacterial pneumonia, and 8 patients (16%) had fungal pneumonia. 6 patients (12%) had non infective conditions like cardiomyopathy (3 patients), bronchial asthma (1 patient), non small cell carcinoma (1 patient), and interstitial lung disease (1 patient). Only 1 patient was confirmed to have tuberculosis on sputum AFB culture and also on bronchial washings AFB smears.

Conclusion: A wide variety of respiratory conditions other than tuberculosis can be definitively diagnosed in HIV infected individuals if investigated in detail.

P2630
Therapeutic drug monitoring of ionized, rifampin, and pyrazinamide in HIV infected patients with tuberculosis
Shadi Baniasadi1, Kavita Mody2, Ravindra Nath Sahay3, Amita Athavale2.
1Iran; 2India; 3Iran

Results: Twenty HIV-infected patients who received 4 first-line anti-TB drugs for active TB were eligible for the study. Venous blood was obtained 2 h after daily dose of INH (5mg/kg), RIF (10 mg/kg), and PZA (25 mg/kg). Serum levels of anti-TB drugs were analyzed using high–pressure liquid chromatography (HPLC) and compared with published normal ranges.

Conclusion: Of the 20 patients (mean age 36.25 years, range 30-57 years), 18 (90%) had a very low maximum concentration of INH (<1 μg/mL), and 2 (10%) had a low maximum concentration of INH (<2 μg/mL). All patients had a very low maximum concentration of RIF (<7 μg/mL) and 7 (35%) had a low maximum concentration of PZA (<20 μg/mL).

Further description of the study is available in detail.

272. Tuberculous and non-tuberculous mycobacterial infections: diagnostic tools
P2632
FcyRI and CR on blood monocytes in differentiation between sarcoidosis and tuberculosis
Anna Dubaniewicz1, Manta Saguldziska1, Monika Wybieralska2, Katarzyna Rogora1, Jan M. Slominski1, Piotr Kowalczykski1, Adam Sterman1.
1Department of Pneumonology, Medical University of Gdansk, Poland; 2Department of Clinical Immunology and Transplantology, Medical University of Gdansk, Poland

Results: Of the 20 patients (mean age 36.25 years, range 30-57 years), 18 (90%) had a very low maximum concentration of INH (<1 μg/mL), and 2 (10%) had a low maximum concentration of INH (<2 μg/mL). All patients had a very low maximum concentration of RIF (<7 μg/mL) and 7 (35%) had a low maximum concentration of PZA (<20 μg/mL).

Conclusion: Low serum concentrations of INH, RIF, and PZA, which may be related to poor compliance, are common in HIV-infected patients. TDM of anti-TB drugs may help to optimize drug therapy and improve TB cure rates.

P2631
HIV/TB co-morbidity epidemiology in Siberian Federal District 2008-2010
Svetlana Naryshkina1, Elena Pushkareva1, Sergey Medvedev2, Chul Ho Oak3, Tae Won Jang1, Bong Guen Chyun1, Hee Jae Cha3, Maan Hong Jung4.
1Virology Research Center, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran; 2Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran; 3Department of Clinical Immunology and Transplantology, Medical University of Gdansk, Poland; 4Department of Endocrinology and Internal Diseases, Medical University of Gdansk, Poland

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P2633
Over-expression of thyminol beta-4 in granulomatous lung lesions in active mycobacterial infections: diagnostic tools
Shadi Baniasadi1, Kavita Mody2, Ravindra Nath Sahay3, Amita Athavale2.
1Iran; 2India; 3Iran

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Purpose: We investigated the expression level of thymosin β4 in the various stages of pulmonary tuberculosis. We also examined the expression pattern of VEGF and HIF-1α and compared the expression pattern of thymosin β4 with VEGF and HIF-1α.

Material and method: Ten surgical samples of active pulmonary tuberculosis lesions were immunostained with rabbit polyclonal antibody to thymosin β4 (1:1,000 dilution, ALPCO Diagnostics, Windham, NH, USA), HIF-1α (1:100 dilution, Novus Biologicals, Littleton, CO), or VEGF (1:2,000 dilution, Abcam Inc., Cambridge, MA, USA) at 4°C for overnight. The expression levels were analyzed on the pathological stages of pulmonary tuberculosis.

Result: Thymosin β4 was highly expressed in both alveolar macrophages in granuloma and surrounding lymphocytes in early stage of granulomatous tissues but not expressed in late stages of fibrous tissues. The expression pattern of HIF-1α was similar with that of thymosin β4. VEGF was weakly expressed in alveolar macrophages in granuloma but highly expressed blood vessels surrounding granuloma. The expression pattern of VEGF was co-localized with CD31 (Platelet endothelial cell adhesion molecule, PECAM).

Conclusion: These data suggested that thymosin β4 is highly expressed and associated with HIF-1α and VEGF-mediated inflammation and angiogenesis in the granulomatous lesions of active pulmonary tuberculosis.

P2634

Altered imbalance between Th17 and regulatory T-cells and impaired Th1 response in the recovery of multidrug-resistant tuberculosis

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1Department of Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; 2Department of Chronic Infectious Diseases, Center for Disease Control and Prevention, Jiangsu Province, Nanjing, China; 3Department of Respiratory Medicine, The First Hospital of Jiangnan City, Zhongshan, Jiangsu, China

Objective: Multidrug-resistant tuberculosis (MDR-TB), a lethal global threat today, requires prolonged and expensive second-line drugs of heightened toxicity. A dysregulation of Cyt4 T cell subsets, found in the pathogenesis of TB, is a crucial question still unsolved in MDR-TB. Insights into MDR-TB immune responses are urgent for developing new solutions.

Methods and results: We phenotypically examined circulating TH17/Treg cells, regulatory T cells (Tregs), TH1/TH2 cells by flow cytometric detection in 26 MDR-TB patients, 26 drug-sensitive TB patients (DS-TBs) and 26 healthy subjects (HCs). The levels of circulating T cell subsets were further analyzed during before/post-treatment phase in MTB-TB patients.

Results: We found upregulation of circulating Th17 expression (7.45±1.54%) and decreased ratio of Treg/Th17 (0.42±0.01) in MDR-TB compared to HCs and DS-TBs. More remarkable suppression of Th1 cell activation was detected in MDR-TB patients than in DS-TBs compared to HCs. Although clinical signs of MDR-TB patients did not show obvious recovery after 7 month-chemotherapy, the circulating ratio of Treg/Th17 (0.88±0.13) and level of Th1(15.1±0.90) in MDR-TB patients tended to normal compared to their previous level before treatment (P<0.05).

Conclusions: These data provided evidence for an unbalanced immune status of Treg/Th17 and inhibition of Th1 type immunity in MDR-TB infection, and suggested a specific role of these T cell-induced immunities during the evolution of MDR-TB. Further study on the immune homeostasis restoration of MDR-TB patients may aid in improving adjuvant immunotherapies and developing potential therapeutic strategies.

P2635

Phagocytosis by blood monocytes in differentiation between sarcoidosis and tuberculosis

Anna Dukhaniewicz1, Monika Wysieralska1, Katarzyna Rogora2, Marlena Typiak1, Adam Serna1, Jan M. Slominski1, Piotr Trzonkowski2

1Department of Pneumology, Medical University of Gdańsk, Gdańsk, Poland; 2Department of Thoracic Surgery, Medical University of Gdańsk, Gdańsk, Poland

Due to clinical and histopathological similarities between sarcoidosis (SA) and tuberculosis (TB), we try to find some biomarker(s), which allow to a differential diagnosis between these disorders. We recently revealed increased frequencies of receptors for Fc fragment of IgG (FcγRII) and FcγRI (FcγRI) monocytes in both SA and TB but in contrast to SA, monocytes had increased FcγRIII expression with receptors for fragment of complement (CR) CR1 and CR4 deficiency. Abnormal expression of FcγRI and CR may cause of a disorder of the phagocytosis by monocytes and clearance of immune complexes (CIs) with following immunocomplexes, which concentration was higher in SA than in TB. Therefore, we have analyzed the key stages of phagocytosis blood monocytes from 22 patients with SA, 20 patients with TB and 20 healthy volunteers using the PHAGOTEST® kit by flow cytometry. Our study revealed increased percentage of monocytes in SA than in TB and the controls (p=0.003, p=0.002, respectively), but there was no difference between TB and healthy individuals. The percentage of phagocytizing monocytes was increased in SA than in the controls (p=0.03) and it was slightly elevated compared to TB. There was no difference between TB and the controls. In summary, current study revealed increased of phagocytic activity of monocytes in SA than TB and explained previously obtained results regarding higher frequency of FcγRI and CR deficiency on sarcoid than on tuberculosis monocytes. The increased phagocytosing of CIs and high antigen load with following persistent antigenemia may explain the presence persistent complexemia in our patients with SA. This study may be useful for differentiation of both diseases.

P2636

Serum and r32kd induced cytokine levels and expression in tuberculosis patients and controls

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Tuberculosis is a disease caused by Mycobacterium tuberculosis (MTB) whose interaction with the host may lead to a cell-mediated protective immune response. Several cytokines, including IL-6, IFN-γ and TNF-α, play important roles in mediating resistance against MTB. The aim was to investigate the candidate cytokines in active pulmonary tuberculosis patients of younger age (15 to 25yrs), their Household Contacts and controls. Levels were estimated by ELISA in pg/ml in serum(n=30) and PBMCs stimulated with r32-kd antigen of M.bovis BCG (n=30). Expression by qRT-PCR in 5 individuals from each group in culture supernatants were studied. In serum IFN-γ and TNF-A concentrations were elevated in patients compared with their contacts and controls(24.51±10.60, 20.45±4.93, 14.14±8.22 at p<0.002, (13.62±8.14, 11.34±5.30, 6.39±4.10 at p<0.003). In contrast, r32kd stimulated PBMCs produced less IFN-γ and TNF-A (36.21±16.9, 45.57±4.91, 56.37±5.37 at P<0.002, (59.74±6.51, 87.28±5.43, 109.2±8.56 at p<0.007), whereas IL-6 concentrations were elevated in controls both in serum and stimulated PBMCs(11.6±4.09, 1.20±0.0018 at 74.94±15.18, 61.21±11.87, 68.66±69.36 at P<0.01). Out of the 30 cases studied 6 contacts behaved similar to the patients in their clinical and Immunological aspects. The cell-associated mRNA in Ag85B-stimulated r32kd-activated PBMCs was significantly depressed in TB patients. On the other hand, Expression of IL-6 was high in patients. Therefore, in conclusion, IFN-γ, TNF-α and IL-6 production to r32-kd antigen could be used as biomarkers for the clinical status of TB patients and early diagnosis of their contacts.

P2637

Serum amyloid A is a sensitive marker of activity of the process in patients with pulmonary tuberculosis

Rajeshvili Kuzag, Kumineya Galina, Oksana Komissarova. Biochemistry Laboratory, Central TB Research Institute of RAMS, Moscow, Russian Federation

Aim: Study level of serum amyloid A (SAA) in blood serum of patients with active pulmonary tuberculosis (TB) and its comparison with level of C-reactive protein (CRP).

Materials and methods: We studied level of SAA and CRP in blood serum of 93 M tuberculosis patients in the age from 18 till 55 years (male – 38 and female – 55). Concentration of SAA was determined by ELISA and CRP by immunoturbidimetric method.

Results: It was established that the level of SAA increased in 99% of patients, whereas rate of CRP was increased in 80.7% of patients. The degree of increase SAA also was much higher: the levels of SAA over 100 mg/l were observed in 68.8% of patients, but CRP - only 11.1% of cases. The degree of increase SAA was directly related with the manifestation of tuberculosis intoxication, the quantity of M tuberculosis (MTB) in sputum, the spectrum of drug resistance of MTB, the extension of the lung process and the presence of destruction in lung tissue. A maximum value of SAA in patients with pulmonary tuberculosis was 247 mg/l. The level of SAA after 3 months of chemotherapy decreased by about half in patients with effective treatment, but remained significantly increased in comparison to the norm. In patients with inefficient of the treatment the level of SAA was not substantially changed.

Conclusion: SAA is a useful marker of activity of the process in patients with pulmonary tuberculosis and its sensitivity is higher than that of CRP.

P2638

The usefulness of antimonycytobacterial antibodies detection in TB diagnosis

Elena Ciocanu1, Codrin Popa2, Irina Luciana Dumitru1, Bogdan Gruza1, Cristian Cogorc1 

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Aim: Due to the high number of cases, it could be useful a rapid and cost effective test for early diagnosis of tuberculosis. We planned to evaluate if a test based on detection of anti-lipoarabinomannan antibodies in serum is suitable for diagnose the tuberculosis (TB)

Methods: The test used is based on detection of anti-lipoarabinomannan antibodies
from the sample using plastic combs. The test is positive if a colored spot appears on plastic comb. We used a randomized lot of patients addressed to Clinic of Pulmonary Diseases, Iasi, Romania.

Results: We have tested 46 patients from June 2011 to January 2012 from Iasi County. The final bacteriological results are available for 27 patients in present (February 2012). All the data presented below are just for patients with final evaluations. The average age was 45 years. Based on bacteriological tests 10 cases (37%) were diagnosed with TB. From patients with TB, the rapid serum test was positive in 8 cases (80%), 2 cases were negative. The other 17 cases were culture negative for M. tuberculosis. From negative cases 14 (82.4%) were also negative for rapid TB test, and 3 cases were positive. For all 3 cases negative in bacteriology but positive in rapid TB test were observed opacities in upper lobes. Tuberculin test was positive in one case and not performed in others two. The producer revealed that this test has a sensitivity of 70.2% in patients with pulmonary tuberculosis and a specificity of 95.1%.

Conclusion: In the study population, this rapid TB test seems to be interesting for a rapid TB screening. A future study with a larger sample is expected for final evaluation is necessary for a more appropriate evaluation of the utility of this rapid TB test.

P2639 Impact of immunogenetic factors to tuberculosis of intrathoracic lymph nodes in children in northwestern Russia

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Severality of the disease depends not only on peculiarities of causative agent but also on genetic profile of patients. The aim of the study: to study the distribution of HLA-DRB1* alleles in children with tuberculosis of intrathoracic lymph nodes in North-Western region of Russia. Totally 188 children from 1 to 15 years old were recruited in Cape Town, South Africa and London. Patients with latent TB infection were also recruited. Whole blood samples were taken before, during, and after, 6 months of standard first line TB drug therapy. Samples were processed for microarray expression using a customized microarray. Changes in transcriptional expression were analyzed. An algorithm to quantify the changes was also devised.

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Conclusion: In the study population, this rapid TB test seems to be interesting for a rapid TB screening. A future study with a larger sample is expected for final evaluation is necessary for a more appropriate evaluation of the utility of this rapid TB test.

P2640 A change in blood transcriptional signatures accompanies successful tuberculosis therapy

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Introduction: Inadequate treatment of patients with active TB leads to worsening disease, infection transmission and drug resistance. Effective anti-TB therapy monitoring is difficult as the best accepted method is the 2-month sputum culture conversion. However this has low sensitivity for predicting an individuals response, and difficult to implement since culture results are not available in 30-50% of patients. No recognised biomarkers of treatment response earlier than 2 months exist.

Aims: Determine if blood transcriptional profiles can be used in early TB treatment monitoring.

Methods: Mtb culture-positive, HIV-uninfected, pulmonary TB patients were recruited in Cape Town, South Africa and London. Patients with latent TB infection were also recruited. Whole blood samples were taken before, during, and after, 6 months of standard first line TB drug therapy. Samples were processed for microarray expression using a customized microarray. Changes in transcriptional expression were analysed. An algorithm to quantify the changes was also devised.

Results: All patients responded successfully to therapy. An active TB transcriptional signature was derived by comparing the untreated active and latent TB patients. A specific treatment response transcriptional signature was derived com-
Introduction: Pulmonary infections due to non-tuberculous mycobacteria (NTM) are a clinical challenge. There are to date no recommendations for the use of potential second line drugs, when first line treatment fails. For Moxifloxacin, in vitro susceptibility could be shown for M. avium-complex (MAC), but almost no data available on its in vitro effectivity against various other NTM species.

Methods: From 100 NTM-positive cultures other than MAC isolated at our center during 2003-2010 (9 M. fortuitum, 2 M. chelonae, 6 M. gordone, 5 M. marinum and 78 M. kansasii), we tested the minimal inhibitory concentrations (MIC) of moxifloxacin and thus the sensitivity (breakpoint ≤ 2 µg/mL). Culturing and resistance testing was performed on solid Middlebrook agar plates (7H11) by agar dilution.

Results: Out of 100 tested NTM-positive cultures, 98 (98%) showed sensitivity to moxifloxacin at. Only two strains (M. fortuitum and M. chelonae) showed higher MIC.

Conclusions: Our study revealed a high sensitivity rate of moxifloxacin against several NTM strains other than MAC in vitro. Despite the absence of clinical treatment studies, we see a potential use of moxifloxacin as a second line drug.

P2645

Molecular characterization of mycobacterium tuberculosis resistant to fluoroquinolones, distributed in Saratov region

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Aim: To study the spectrum of mutations of gena gyrA M. tuberculosis, coding for drug-resistance to fluoroquinolones, in the Saratov region.

Methods: We examined 47 samples of sputum patients with active pulmonary tuberculosis. Detection of Mycobacterium tuberculosis (MTB) and determine their drug susceptibility to fluoroquinolones was performed using biological microchips. The results of the reaction were evaluated with the use of hardware-software complex (“Chipdetektor-01”), Technology research, a set of reagents and equipment were developed by staff of the Institute of Molecular Biology (“Chipdetektor-01”, Moscow).

Results: DNA M. tuberculosis were found in 39 (83%) patients. Mutations in the gene gyrA were identified in 22 (56,4%) samples, of which - in 13 (59%) found the mutation in codon 95 Ser (AGC) -> Thr (ACC) due to the natural polymorphism of the gene and do not lead to the development of drug resistance. In 9 (41%) samples identified mutations in 91 (33,3%), 94 (44,4%), 90 (22,2%) codons that encode resistance to fluoroquinolones. Primary drug resistance is set in 5 (12,8%) patients. In 4 cases revealed secondary drug resistance in patients, which received 90-120 doses antibiotic drugs. Of these, 3 cases have double mutations in gyrA (Asp94-Gly + Ala90-Gly), (Asp94-Ala + Ala90-Gly), (Asp94-Gly + Ala90-Val) and in 1 patient was found a combination of four mutations.

Conclusion: In the Saratov region primary resistance to fluoroquinolones at the level of genetic mutations was set in 12.8% cases. Was found the increase in the number of mutations among MTB strains isolated from patients receiving prolonged treatment with anti-TB drugs.

P2646

Expression of P-gP in patients with resistant tuberculosis

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Background: Resistant tuberculosis (TB) is one important cause of treatment failure. One of the MDR resistance mechanisms is MDR1 gene expression, as P-glycoprotein (P-gP) expressed on cell surface, its related with output of drugs and could modify their biodispomibility.

Objectives: To evaluate P-gP expression in patients with monoresistance (MR) or multi-drug resistance (MDR) tuberculosis.

Methods: A prospective study was performed analyzing blood samples of patients with confirmed resistant TB in treatment at Evandro Chagas Research Institute (IPEC) in Rio de Janeiro, Brazil, since 2010. Flowcytometric analyses of P-gP Activity - For detection of P-gP function as a transporter, Rhb D23, by Sigma, Germany (SG) was used as a fluorescent. Cicloporin-A (SG) was used in this study to reverse P-gP mediated drug resistance and Rifampicin (R) as inductor. Detection P-gP expression - The monocotes P-gP expression was determined using a murine anti-P-gP monoclonal antibody (eBioscience-USA) and anti-Cd14, and analyzed using flowcytometer (EPICS XL-MCL. System II. Beckman Coulter, USA).

Results: The samples of 12 patients were analyzed. Seven men and five women, with ages from 23 to 73 years. The panel of resistance showed: R(2); Rifampicin more isoniazide (RI) (4); RI more streptomycin (S) (3); RI more Ethambutol (E) (2); Rifampicin more isoniazide (RI) and Ethambutol (E) (1). The efficacy activity was identified in 53.8% of patients. The Rifampicin was able to efflux induce in majority of patients Unexpected the monocotes P-gP-expression was found in 57, 7% and 74, 1%, respectively in patients with efflux activity and no efflux activity.

Conclusion: These findings can be involved with resistant TB and future relation with response of treatment must be evaluated.
Conclusion: TB patients with weakly positive smears or with a not purulent sputum property should undergo three sputum smear tests.

P2648
Role of the macrophage-inducible C-type lectin Mincle in the lung host defense against tuberculosis infections in mice
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The macrophage-inducible C-type lectin Mincle has been identified as receptor for the mycobacterial cell wall component trehalose dimyculoside (TDM) of M. tuberculosis. We here examined the role of Mincle in lung protective immunity against mycobacterial pathogens in mice. We found that mice infected with M. bovis BCG responded with a delayed expression of Mincle on alveolar macrophages by days 14-21 post-challenge. In line with this finding, we observed that Mincle KO mice showed significantly reduced proinflammatory cytokine release and alveolar leukocyte recruitment as well as increased mycobacterial loads particularly in lung draining lymph nodes and spleens relative to wild-type mice infected with M. bovis BCG. Importantly, flow-sorted alveolar macrophages of wild-type mice responded with substantially greater proinflammatory TNF-α, KC, CCL2 and CCL5 mRNA levels to infection with M. bovis BCG relative to alveolar macrophages of BCG-infected Mincle KO mice. Together, the current study shows that Mincle exhibits delayed cell surface expression kinetics on alveolar macrophages upon M. bovis BCG challenge, thus acting as a ‘delayed-type’ regulator of proinflammatory macrophage activation during mycobacterial infections.

P2649
Pleural effusion cytokine profiles in HIV/MTB co-infection
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Pleural effusion is a common presentation in HIV/MTB co-infection. During infection, it is composed primarily of an extensive inflammatory cell infiltrate and an as yet poorly characterized cytokine milieu. Previous reports have shown significant expansion of CD4 T cells in pleural compartments of patients with active MTB infection. Both the immune infiltrate, and to a large degree, the pleural cytokine milieu, may augment viral dynamics and as a result, promote HIV replication in co-infected patients. The current study may have implications for clinical management of dually infected patients. To characterize the pleural effluent in HIV/MTB co-infected patients, we used cytokine array-based technology to profile key cytokines. Our data showed significantly elevated levels of IL6 and IFN-γ in pleural fluid from HIV/MTB co-infection compared to MTB alone (MTB/HHV vs MTB: IL6: 90.6pg/ml vs 85.6pg/ml; IFN-γ: 91.9pg/ml vs 85.4pg/ml). This observation may have reflected increases in systemic levels of these cytokines in dually infected patients (IL6: 32.1pg/ml vs 29.5pg/ml; IFN-γ: 85.4pg/ml). We noted moderate inhibition of IL4 production in the regulatory T-cells and high levels of FOXP3 mRNA lead to decreased TNF-α production in dually infected patients. Dually infected patients may have reflected increases in systemic levels of these cytokines in dually infected patients. Taken together, our data suggests that co-infection with HIV may alter TH2 polarization dynamics at pleural sites. The high level of TNF-α at MTB pleural sites, in the absence of HIV, is suggestive of conventional pro-inflammatory, innate responses usually associated with tuberculosis.

P2650
Regulatory T-cells and high levels of FOXP3 mRNA lead to decreased immune responses during HIV-TB co-infection
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Tuberculosis causes 2 million deaths per year and is the most important opportunistic infection in patients infected with HIV. During the co-infection of HIV/TB, natural regulatory T cells down regulate Th1/Th2 responses. We performed direct ex vivo phenotyping of whole blood with antibodies to CD4, CD25, FOXP3, CD38 and PD-1. In a 7-day whole blood assay, diluted blood was incubated with M.tb proteins. The supernatant was removed and analysed for interferon-gamma production by ELISA. The Multiplexed Ligation dependent Probe Amplification technique was used to amplify ex vivo RNA and compare gene expression of 45 genes. We found an increase in the ratio and frequency of regulatory T-cells in HIV/TB co-infected participants. FOXP3 expression was increased in participants infected with HIV or TB alone. The median interferon-gamma responses to control and DOS-R M.tb antigens (ESAT-6/CFP10, TB10.4, Ag85A) was the highest in the control group. The response to p24 was higher in the HIV+ group than the HIV-TB participants. The FOXP3 gene was significantly upregulated in HIV/TB co-infected participants. Participants with HIV/TB co-infection have significantly more regulatory T-cells than those infected with either HIV or TB who were able to dampened immune response to both HIV and TB. Differential gene expression and increased frequencies of regulatory T-cells in the HIV/TB co-infected participants may have important implications for future vaccine designs. A more precise unravel the mechanisms of immune failure which is present during HIV/TB co-infection.

P2651
Genetic markers of multi-drug and extensive drug resistant M. tuberculosis in Kyrgyz Republic
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Tuberculosis (TB) is still a major cause of morbidity and mortality worldwide and also in Kyrgyz Republic. Decades of tuberculosis treatment failures in Kyrgyz Republic led to acquired resistance to the first-line antitubercular drugs, isoniazid (INH) and rifampicin (RIF), resulting in multidrug resistant tuberculosis (MDR-TB) (300-400 cases per year). Switch to second line drugs lead to acquisition of resistance to them and spread of XDR-TB. XDR tuberculosis cases represent about 3 to 10% of MDR cases in the countries like Kyrgyz Republic. The aim of this study is the identification of mutation in rpoB, katG, inhA, aprC and gyrA genes in MDR-TB cases in Kyrgyz Republic. Materials and methods: DNA samples of M. tuberculosis (M Tb) were collected from 99 sputum samples from adult patients with primary MDR-TB. Mutations associated with resistance to rifampicin, isoniazid and fluoroquinolones were analyzed by biopsis assay. Results: We have demonstrated that in the rpoB gene of MDR Mt strains the prevalent point mutation was Ser531Leu (59%). Among strains resistant to isoniazid the mutations of katG gene were found in 91% (inha gene – 7% – and aphC gene -2%, respectively). The most frequent mutations in katG was Ser315Thr (91% of cases). The frequent mutations of gyrA gene were AprC94Gly and Ala90Val. Conclusion: In Kyrgyz Republic the main cases of Mt resistance to rifampicin is Ser531Leu mutation in rpoB gene, to isoniazid – Ser315Thr mutation of katG gene. The cause of resistance to fluoroquinolone are gyrA gene – AprC94Gly and Ala90Val.

273. Tuberculous and non-tuberculous mycobacterial infections: epidemiology I

P2652
High completion rates with directly observed preventive treatment (DOPT) of latent tuberculosis infection (LTBI) in Ethiopian immigrants (EI) to Israel
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Background: Previous studies show rates for completion of treatment of LTBI in immigrants from high TB burden countries between 22%-60%. In a study in southern Israel only 16.4% of EI completed their course of treatment. Since all EI in our catchment area were located in absorption centers, we applied DOPT to all. Each patient was examined by a physician once on evaluation and twice for follow up.

Objective: To evaluate the efficacy of a nurse-managed, active outreach DOPT program with minimal physician involvement, in a cohort of immigrants from a high TB burden country.

Methodology: A retrospective cohort analysis of 710 medical records of EI at absorption centers in Zefat who had started DOPT for LTBI and were followed up during 2005-2010.

Findings: Forty three individuals were excluded due to translocation during treatment and DOPT was stopped prematurely in 4 women who became pregnant. Of the 663 EIs included (359 males), 628 (94.7%) completed treatment. Of the 35 who failed to complete INH therapy, 23 went on to complete 4 months of Rifampin. Thus 98.0% completed LTBI therapy. Demographic factors did not predict treatment completion; however side effects were significantly (p <0.001) associated with non-completion.

Conclusions: High completion rates for LTBI were attained among EI in absorption centers, through outreach DOPT. Skilled and dedicated nursing made routine physician involvement redundant.

Sponsored by the Israel National Institute for Health Policy Research and by the Israel Lung and Tuberculosis Association.

Part of a Thesis submitted for MPH degree, School of Public Health, University of Haifa, Israel.
Results of a tuberculin skin test survey performed in a national representative sample of young Albanian students

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Background: Tuberculosis (TB) epidemiology in Albania has significantly improved in the last decades owing to advanced TB control activities following financial support from different sources. In 2010, WHO estimated a TB incidence and mortality rate of 14 and 0.38 per 100,000 population, respectively.

Objective: To estimate the Albanian prevalence of latent TB infection (LTBI). Methods: A national Tuberculin Skin Test (TST) survey was carried out in 2010.

Results: Three districts (Dibra, Tirana-Kamez, Vlora) were selected based on representativeness criteria (location, incidence and migration patterns). The survey performed according to WHO recommendations enrolled 4,722 students (2,359, 49.9%, were males); proportions of educational level were: grade 5 (30%), grade 6 (33%) and grade 7 (37%). Results were evaluated in 98.5%. Induration size exceeds 15 mm in 16%, while in 56% of the cases ranged from 6 to 10 mm. Prevalence of LTBI was higher in Dibra District and Kamer (13.9% and 9.5% respectively, strictly related to TB incidence. 2,813/3,242 could answer an anonymous questionaire on TB. Students living in the district of Dibra showed the highest proportion of positive responses on TB items, probably explained by the high TB incidence and by the high frequency of information from television programmes.

Conclusion: Estimated LTBI prevalence is low in Albania, although a high geographical variability was described. Students’ knowledge on TB was deemed not satisfactory, despite 87% knew the presence of the disease.

Stigma associated with tuberculosis among Tajikistan labor migrants

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Problem statement: Stigma is the most significant barrier in prevention of TB transmission, provision of adequate care, support, treatment and decreasing negative impacts. Currently, TB issue and stigma associated with labor migrants have not been learned yet in republic of Tajikistan. Goal of the survey: The goal of the survey was deep understanding of stigma and low TB awareness among labor migrants. Majority of labor migrants do not apply for health care services because of wrong perceptions. National bodies and organizations would apply for health care services in case of symptoms related with TB.

Materials and methods: The survey was done through individual interviews at respondents houses. We used qualitative and detailed interviews for detection of labor migrants. Only 6 labor migrants (1,2%) noticed that they would not talk feel depression in case of TB diagnostics. Other widely spread reaction was fear of TB. 58 were TB positive. Out of these, 53 followed up. 9/53 (16.98%) had turned TST positive after 3 months. Duration of stay in the wards as well as number of TB patients in the ward during their hospital stay was found to have proportionately increased the risk of transmission (P <0.001). Out of 117 visitors, 98 were TST negative. Out of these, 61 followed up. 4/61 (6.56%) had turned TST positive after 3 months. This study indicates that there is a small but definite risk of nosocomial spread of TB. Isolating TB patients in a separate ward and restricting frequent visitors may help.

Prognostic factors in tuberculosis related mortalities in hospitalized patients

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Introduction: Despite effective treatment regimes available, Tuberculosis (TB) stands among one of the leading causes of death in Pakistan. Objectives: To evaluate the factors concerned with in-hospital deaths in patients admitted with Tuberculosis at a tertiary care centre.

Methods: A retrospective case-control study was undertaken at the Pulmonology Department of the largest state-run tertiary care centre in Karachi, Pakistan. For patients hospitalised with TB, sixty of those who were discharged were compared with sixty of those who could not survive during hospitalisation. Radiological findings, clinical indicators and laboratory values were matched between the two groups to locate poor prognostic factors.

Results: Factors concerned with in-hospital mortality listed female sex (p<0.01), late sequelae of disease (p<0.01), not taking anti-tuberculosis therapy (ATT, p<0.01), smoking (p<0.01), longer duration of illness (p<0.01), and low haemoglobin levels (p<0.02). Extrapulmonary TB, dissemination of disease, bilateral radiological findings, co-morbidities and multi drug-resistance were not implicated in higher mortality. Most deaths occurred during the first week of admission indicating late referrals and late presentation as an important factor related to in-hospital fatalities.

Conclusions: Poor prognosis in TB patients was associated with non-compliance to therapy, anemic states, late presentation of disease, and development of complications. Patients not taking ATT and hence having longer duration of illness showed higher mortality and so a more radical and effective treatment regimen is required to eliminate TB early on during the onset of disease.

Influence of social adaptation of tuberculosis patients on the TB form and a chemotherapy outcomes

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The problem of chemotherapy (CT) efficiency in pulmonary tuberculosis (PTB) patients is one of the most burning one at the organization of TB aid.
Aims and objectives: Connection between social adaptation and stages of PTB (presence of SS+ (sputum smear positive) and cavitary lesions) have been studied. The CE efficiency in the patients with SS+ (sputum smear negative) and without lung cavity decay, and in the patients with SS+ and lung cavitary lesions, receiving CT regimen I have been assessed.

Method: Data of 2663 newly detected PTB patients, registered in 2008, from regions of the Russian Federation have been studied. Patients with less severe TB forms (SS- and without lung decay) and with patients with extended TB forms (SS+, cavitary lesions) - in the group 1 (467 persons), and the patients with extended TB forms (SS+, cavitary lesions) - in the group 2 (25 persons).

Results: In group 1, there were 41.1%, [95% CI 36.6-45.6] of socially-adapted patients (SAP) (workers, employees, students) and 40.5%, [95% CI 36.0-44.9] of socially-vulnerable patients (SVP) (jobless). In group 2, there were 24.3% [95% CI 19.0-29.5] SAP and 53.3% [95% CI 47.1-59.4] SVP. CE efficiency in group 1 was 92.7% (95% CI 190.3-95.1), in group 2 - 69% (95% CI 63.3-74.7). In group 2, CE efficiency in SVP was 58.2% [95% CI 49.9-66.4], and in SAP - 78.7% [95% CI 68.4-88.9].

Conclusions: In SAP, detection of TB with SS- and without lung cavity decay and effective treatment are more frequent, than in SVP. Therefore PTB patient social support measures should be brought into all TB programs.

P3659
Extrapulmonary tuberculosis (TB): 40 years observations in Poland
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Aim of the study: To describe changes in extrapulmonary TB epidemiology in Poland since 1970 (beginning of notification of different forms of extrapulmonary TB)

Methods: Retrospective analysis of data from National TB Register. Data presented in ten years intervals.

Results: Since 1970 the systematic decline of number of all TB cases (from 41536 to 7590) in 2010 with the shift to older age groups and decline of extrapulmonary TB cases (from 4848 to 716 in 2010) has been recorded in Poland without significant differences of fraction of extrapulmonary TB among all TB cases (11.6% in 1970; 11.2% in 1980; 9.0% in 1990, and 9.2% in 2010). Some differences in profile of extrapulmonary TB was noticed. The decrease in pleural tuberculosis occurred (5.8% of all TB and 50% of extrapulmonary TB in 1970; 5.8% of all TB and 27% in 1980; 5.6% in 1990; 9.0% and 9.0% in 2000; 9.0% and 9.2% in 2010) also in central nervous system TB (0.3% of all TB and 2.8% of extrapulmonary TB in 1970; 0.2% and 1.9% in 1980, 0.1% and 1.7% in 1990, 0.1% and 1.4% in 2000; 0.1% and 1.3% in 2010).

Conclusions: The demographic characteristics of TB patients changed in Poland in last 40 years with the shift to older age groups however the proportion of TB at extrapulmonary sites remained stable. It is interesting although unexplained finding.

P3660
Predictors of delayed smear conversion after 2 months of tuberculosis treatment
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Late smear conversion after 2 months of tuberculosis (TB) treatment represents a major problem.

Objectives: Isolate the environmental, clinical, radiological, bacteriological and biological factors associated with a delayed smear conversion.

Methods: We analyzed records from 60 tuberculosis patients, from which 20 had a delayed smear conversion. Those patients were compared in terms of clinical presentation, radiological, bacteriological and biological results, environmental data and evolution under treatment.

Results: Smoking was significantly associated with delayed smear conversion (85% of patients with a late conversion were smokers versus 47.5% p = 0.05), as well as history of diabetes type II (25% with late smear conversion versus 4% of controls p=0.005). This correlation was established for a delayed consultation (2 months) p = 0.01. Radiological data showed that bilateral lesions and extended unilateral lesions were significantly associated with delayed smear conversion (p = 0.03, p = 0.003). Biologically, a frank increase in CRP was statistically predictive of late conversion. (p = 0.02). A positive association between the occurrence of adverse events that did not require discontinuation of treatment and delayed smear conversion was also found (p=0.02). A positive correlation has not been established for the geographical distance, the low economic level, for a body mass index below 18.5 kg/m². In terms of bacteriology, the load of bacilli was not significantly associated with delayed smear conversion.

Conclusion: Identifying predictors of late smear conversion may allow us to set up effective preventive measures to fight against the spread of the disease and limit its complications.

P2661
Screening for tuberculosis in patients with rheumatic diseases commencing anti-TNF-α treatment: A regional survey
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Introduction: The increase in active tuberculosis (TB) associated with anti-tumor necrosis factor α (anti-TNF-α) treatment has led to screening for active/latent TB before anti-TNF-α is given. Marked variation in TB incidence has been noted depending on patients' ethnicity, country of birth and, for those not born in the UK, the length of time since their first entry. We aimed to evaluate our risk assessment mechanism.

Method: Retrospective study of 227 patients (F: 65.2%, M: 34.8%, median age: 53 yrs) with rheumatic diseases receiving anti-TNF-α (infliximab, etanercept, adalimumab) in 2001-2009. This sample represents a particularly multiethnic patient population.

Results: 1 patient (0.44% of the total) underwent tuberculin skin testing (TST). All patients were on additional immunosuppressants interfering with the accuracy of TST. No patients underwent interferon-gamma assay testing for latent TB. 9 patients (4% of the total) received chemoprophylaxis prior to anti-TNF-α. 2 patients (0.88% of the total) who had not received chemoprophylaxis developed active TB. The first was on etanercept & adalimumab prior to developing miliary TB. The second was on adalimumab & infliximab prior to TB diagnosis. Both patients recovered with quadruple anti-TB therapy. Both patients were born in the Indian subcontinent and had been in the UK for over 5 years. The TB incidence rate was 196.8 per 100,000 patient-years.

Conclusion: TB screening prior to starting anti-TNF-α can be improved so as to facilitate appropriate chemoprophylaxis targeting. Interferon-gamma assays could be a useful tool in the diagnosis of latent TB when patients are already on immunosuppressants.

P2662
Childhood tuberculosis in Romania
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Introduction: TB incidence rate in children sharply decreased in Romania in the last decade. TB etiology is difficult to confirm, as the sample for bacteriological examination is obtained in low proportion of cases. For this reason the diagnosis can often be overlooked.

Aim and objectives: To analyze the trend and the profile of TB epidemic in children in Romania.

Method: The trend of TB incidence rate in children has been observed in Romania in the last decade and all children with TB diagnosis notified in 2009 have been analyzed by gender, residence, age group, treatment history, site and extension of disease, bacteriological status and treatment outcome. Data have been extracted from National TB Register.

Results: TB incidence rate in children failed from 2001 (47.3‰) to 2010 (25.3‰). In the 965 children registered with TB in Romania in 2009, the male/female ratio was 1.1 and urb/rural ratio 0.87. By age group, 18% were less than 1 year, 33% were in 1-4 years age group and 58.9% (59.9%) in 5-14 years age group. From the total number of 965, new cases represented 98.7%, 14.9% had severe forms of the disease (30 meningitis, 8 miliaria and 106 with cazo-caviatory pulmonary lesions), 39.3% had pulmonary TB and of them smear and culture positivity rates were 14% and respectively 25%. Of 98 culture positive cases, only 34 (34.7%) had a DST and of them 2 (5.9%) had MDR-TB. Overall outcome was favorable in 96.4% of pulmonary cases, but 2 children deceased, 2 failed and 8 abandoned the treatment.

Conclusion: Despite the decrease in incidence rate in Romania, there are still many challenges in the control of TB epidemic in childhood, as early detection of cases, proper diagnostic with confirmation of the etiology and successful treatment.

P2663
Risk factors for Mycobacterium tuberculosis infection among contacts of pulmonary tuberculosis patients
Jae Suk Park, Do Hyung Kim, See Young Kang
Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Chungnam, Republic of Korea

Background: Detection and treatment of tuberculosis(TB) infection with contact investigation is a key component of TB control program. We evaluated the risk factors for TB infection among contacts of recently diagnosed pulmonary TB patients in a tertiary hospital in Korea, an intermediate incidence country.

Methods: 206 contacts of 90 adult pulmonary TB patients underwent tuberculin skin test(TST) and chest radiography. The TST results were considered positive with induration of 10 mm or more, suggesting TB infection. A standardized questionnaire was used to assess risk factors associated with TB infection.

Results: TST was positive in 97 of 206 contacts of TB patients(47.1%) and TST positive rate increased with age. The risk of TB infection was significantly associated with close contact with TB patients(sleeping in the same room) (OR=4.94, 95% CI = 1.43-17.00).

490s
Conclusion: TB infection rate was higher in elderly, and risk of TB infection was significantly increased with close contact of TB patients.

P2664 Improvement of treatment adherence and success in homeles patients with tuberculosis

M. Amin Afridi1, Ziauddin Ansvari, Nazim Nathani, Bilal Chaudhari, Whirter4, Ioan Serban5, Traian Mihaescu1, Christoph Lange3,6.

Background: To assess the impact of a program for homeless patients with tuberculosis in Iasi, Romania, on treatment adherence and outcomes.

Methods: Adherence and treatment outcomes were analyzed in homeless patients with tuberculosis in Iasi, Romania, who participated in 2011 in a charity project that offered regular anti-tuberculosis treatment together with free food and clothes at a central shelter. WHO recommendations on tuberculosis case definition and treatment results were used. Adherence to treatment and treatment outcomes in these patients were compared with those in homeless tuberculosis patients registered in Iasi between 1998 and 2005 when incentives were not provided.

Results: In 2011, 17 homeless (11 male, 6 female, median age 45 years) with tuberculosis were included in the project following discharge from the hospital. Of 12/17 patients who had completed the treatment at the time of analysis, cumulative adherence to treatment was 128/1316 (97.4%) doses provided. Of 82 homeless patients with tuberculosis treated in the years 1998 to 2005 (72 male, 10 female, median age 43 years), cumulative adherence to treatment was 583/7062 (54.4%) doses provided (p=0.001). Treatment success in 2011 was 70.5% compared to 26.8% in 1995-2005 (p<0.001).

Conclusions: Adherence to anti-tuberculosis treatment and treatment success significantly improved when food and clothes were offered to homeless patients with tuberculosis on a regular basis at the treatment dispensary.

P2665 Tuberculosis in healthcare workers: 5-year, multi-institutional analysis of the northern region of Portugal

Ricardo Reis1, Ana Maria Correia2, Marta Gomes3,1, Raquel Duarte4,5,6.

Background: Strengthening health care systems is the first step to control tuberculosis. Portugal is a high TB incidence country 15 years ago and little is known about the impact of TB in its HCWs.

Aim: Study the incidence and occupational risk of TB in HCWs in the northern region of Portugal. Evaluate potential risk factors and compare HCWs characteristics with the regional population.

Methods: We reviewed all TB cases among HCWs from Jan06 to Dec10 in the region. TB incidence was calculated and compared with the regional rate to obtain occupational odds ratio. Correlation between incidence and both admittance and district incidence was analyzed. TB and individual characteristics were compared with a chi-square test.

Results: Ninety TB cases were notified from a total of 42731 HCWs, with an annual average incidence of 42.1/100000 and an occupational odds ratio of 1.27 (95%CI: 1.03-1.56). Five (27%) of the hospitals had rates above the annual average, from 111 to 45. 81% of cases worked in hospitals but incidence in primary HCWs was similar. TB incidence in hospital HCWs was correlated with TB admissions (p=0.026) but not with district TB incidence.

Conclusions: Our study showed that HCWs in the north of Portugal have a significant occupational risk for TB that seems related with TB admission rates. Most cases were in young female nurses with no individual risk factors.

P2666 Impact of social risk factor on treatment outcome in patients with culture positive pulmonary tuberculosis (CPPTB)

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Objectives: The aim of the study was to evaluate the impact of social risk factors on treatment outcome among culture-positive patients treated for active pulmonary tuberculosis (PTB).

Material and methods: We retrospectively reviewed all medical records of patients notified in 1995 and 2000 in three separate districts in Poland in years 1995 and 2000. The relation between both alcohol abuse and homelessness and poor treatment outcome was evaluated. Treatment outcome was categorized as: cured, treated, completed, treatment defaulted, treatment failure.

Results: 708 patients with culture positive PTB were included to the study (373 in 1995 and 335 in 2000). There were 85 patients with risk factors in 1995 and 101 patients in 2000. 80 of participants in 1995 and 69 in 2000 abused alcohol, 5 and 32 were homeless, respectively. Among alcohol abusers treatment success rate were 45.1% in 1995 and 53.6% in 2000. Among patients not abusing alcohol treatment success rates were 63.8% and 54.1%, respectively (p=0.005 in 1995 and p=0.0186 in 2000). In 1995-40% of homeless patients had succeeded treatment, while the rate of treatment success among non-homeless was 60%. The difference was not statistically significant (p=0.6532) probably because of small number of homeless patients. In 2000 treatment success rate among homeless patients was 25% and among non-homeless 57.1%, which was highly statistically significant (p=0.001).

Conclusions: Alcohol abuse and homelessness were associated with no success of treatment outcome among patients with PTB. Interventions to improve treatment adherence in patients considered to be at risk for default are necessary.

Table 1. Multivariate analysis of risk factors for TB infection (age < 35)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Older age (19-34)</td>
<td>1.58 (0.95-4.13)</td>
<td>0.368</td>
</tr>
<tr>
<td>Current smoking (s)</td>
<td>2.92 (0.71-12.0)</td>
<td>0.137</td>
</tr>
<tr>
<td>Proximity of contact (same room)</td>
<td>7.21 (2.34-20.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact duration &gt; 30 days</td>
<td>4.77 (0.99-22.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smear(+) at treatment initiation</td>
<td>1.82 (0.69-4.80)</td>
<td>0.227</td>
</tr>
<tr>
<td>Respiratory symptoms(+)</td>
<td>3.80 (0.44-32.70)</td>
<td>0.227</td>
</tr>
<tr>
<td>Chest X-ray(+) (MA or FA)</td>
<td>2.55 (0.83-7.80)</td>
<td>0.103</td>
</tr>
<tr>
<td>Caracte(s)</td>
<td>3.03 (0.63-14.70)</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Conclusion: The first symptom that made you seek medical help/advice Breathlessness (4), Fever (5), Chest pain (4), Night sweats (5), Wt loss (8), Cough (7)
P2668
Patients diagnosed of TB in the Oreuren area in the last decade: A descriptive study
Hugo Gómez, Abel Rodriguez, Isaura Parente, Blanaco Nagore, Jose Abal. 
Pedro Velázquez. Servicio de Neonatología, Complejo Hospitalario Universitario de Oreuren, Oreuren, Spain

Objective: To assess the annual incidence TB and its epidemiology

Material and methods: Retrospective study on patients diagnosed of tuberculosis during the decade 1999-2009. Data collecting was possible thanks to the “Programa Galego de Prevención y Control de Tuberculosis”. The usual descriptive study was then performed based on these data; quantitative variables were expressed as mean ± SD, whereas the qualitative ones as absolute frequencies or percentages, using the x² test to assess associations among them.

Results: The whole series included a total of 1746 cases, with a greater incidence among males and those between 24 – 35 yr. Exposure to infected persons, smoking habit, alcoholism and immunosuppression were the main risk factors.

The most common site of infection was pulmonary (67.5%), followed by pleural (14%), lymphadenopathies (7.1%) and others (9.3%). With regard to microbiology, the best yield could be obtained from culture (positive in 80% of cases), whereas the detection of AFB was positive only in 41% of patients.

The chest X-ray was pathologic in 93.3%, even though cavitations were only present in 27.6% of cases.

The scheduled therapy was completed and microbiological cure was attained in 85.6%, which fares favourably compared to other published series.

The global death rate was 10.63%, but only 1.1% were attributable to TB.

Conclusions: The incidence of pulmonary TB has clearly decreased in the preceding years, although it still prevails in males and in the 24-35 yr-old group.

The “pathology: cavity with cavitation” was observed in 28% of cases.

85.6% completed the scheduled treatment.

The global death rate was 10.63%, but TB just accounted for 1.1%.

P2669
Analysis of risk factors of recurrent tuberculosis in Han and Tibetan populations in Southwest of China
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Background: Recurrent tuberculosis (TB) poses significant threats, including drug resistance, to TB control programs. However, the causes of TB recurrence, particularly in Southwest China, which is the high burden area, have not been well described.

Objectives: To investigate the risk factors of recurrent TB, and analyze the differences between Han and Tibetan populations with TB recurrence in Southwest China.

Methods: A population-based retrospective case-control study was carried out in Southwest China. All patients with culture-confirmed TB and drug susceptibility testing were included between 2000 and 2001 and followed until December 2010. Two category logistic regression was used in the statistical analysis.

Results: We found that, among 80 patients (40 Han patients and 40 Tibetan patients) with recurrent TB who completed adequate therapy for a first episode of TB, factors independently associated with a greater risk of recurrent TB were not receiving directly observed therapy (HR 5.867, 95% CI 2.557-13.461), diabetes (HR 3.288, 95% CI 1.301-8.312), smoking (HR 2.387, 95% CI 1.328-4.291) and malnutrition (HR 3.288, 95% CI 1.110-3. 285).

The independent risk factors (HR 3.288, 95% CI 1.301-8.312), smoking (HR 2.387, 95% CI 1.328-4.291) receiving directly observed therapy (HR 5.867, 95% CI 2.557-13.461), diabetes (HR 3.288, 95% CI 1.301-8.312), smoking (HR 2.387, 95% CI 1.328-4.291) and malnutrition.

Conclusions: Our results establish that not receiving directly observed therapy, diabetes, smoking and malnutrition are associated with recurrent TB in Southwest China. To reduce the relapse rate of TB, especially for Tibetan populations, pursuing high-quality DOTs is essential.

P2670
The trends of tuberculosis in Kosovo in the post war period, (2001-2010)
Bahir Tigani. GFATM Programme in Kosovo, Community Development Fund, Prishtina, Kosovo, Albania

Objective: To analyze the trends of Tuberculosis in Kosovo during the first decade of the post war period, (2001-2010).

Methods: The TB National Reports of the years 2001-2010 has been used and different TB indicators has been analyzed and measured.

Results: Number of TB cases for the period 2001-2010 decreased from 1674 (Year 2001) to 920 (Year 2010). TB Notification Rate/100 000 decreased from 78.2 in year 2001 to 920 (Year 2010). TB Notification Rate/100 000 decreased from 78.2 in year 2001 to 920 (Year 2010).

TB Notification Rate/100 000 decreased from 78.2 in year 2001 to 920 (Year 2010).

Extra pulmonary TB has increased from 19% (year 2001) to 33% (year 2010).

P2671
How much knowledge is healthy? Results of a KAP survey of TB patients in Republic of Macedonia
Dance Gudeve Nikovska, Stefan Tavelesky. Global Fund Funded Project for TB Control, Ministry of Health, Skopje, Macedonia, The Former Yugoslav Republic of

Operations research study to explore knowledge, attitudes, and practices (KAP) related to tuberculosis (TB) among new TB patients in Kosovo was conducted in Republic of Macedonia (KM), in the period April-December 2010.

Cross-sectional study was conducted in the period April – June, 2010; TB patients were interviewed with a standardized questionnaire.

45% agreed that TB is a very serious illness and 48.7% think that TB is serious problem in RM. 50% have correctly identified the signs and symptoms of TB, although significantly smaller proportion correctly identified airborne transmission of TB (14.1%). A sizable proportion did not correctly identify ways to avoid transmission, i.e. just over 30% agreed that one can avoid TB by not shaking hands with someone who has TB and 20% said that one can avoid transmission by TB covering the mouth and nose while coughing or sneezing. 78% believed that TB can be cured by any drug recommended by a pharmacist, and only two respondents reported having heard of drug resistant TB.

Given the low number of respondents who correctly identified how TB is transmitted, the National Tuberculosis Program (NTP) should consider strategies to improve knowledge among people with TB, such as training on client-provider communication skills, new TB patients should receive a standard set of written materials regarding diagnosis, treatment, and infection control with key messages and broader communication campaign aimed at the general population to reinforce the key messages.

P2672
Latent tuberculosis in patients submitted to anti-TNF therapy – a retrospective study at a Santarem chest clinic
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Introduction: TNF-α plays an important role in immune defense against Mycobacterium tuberculosis and, as such, the risk of reactivation of latent tuberculosis (LTB) increases with TNF-blocking agents.

Aims: To determine the prevalence of LTB in patients undergoing TNF-blocking agents, between 2006 and 2009. To assess the type of therapy established and its complications.

Materials and methods: Review of clinical records and registration of clinical and epidemiological data, risk factors for liver toxicity and adverse effects. The used screening tests were Tuberculin Skin Test (TST), chest x-ray (CXR) and, in special cases, the QuantiFERON®-TBGold.

Results: One hundred and twelve patients were included in this retrospective study 50 with Rheumatoid Arthritis; 45 with Psoriasis; 12 with Ankylosing Spondylitis; 4 with Crohn disease and one with Sjögren’s syndrome). TST and CXR were used in all and QuantiFERON® in 36 (32.1%). LTB was confirmed in 66 cases (58.9%), 38 females (57.6%). The therapeutic scheme proposed in all of them was isoniazid for nine months which was completed in 92.4% of patients. The transient elevation of liver transaminases occurred in 7.6%, however no patient developed moderate to severe hepatotoxicity. One patient developed pulmonary tuberculosis after a recent contact.

Conclusion: LTB was diagnosed in 58.9% of patients submitted to anti-TNF therapy. In 92.4% of cases the instimted treatment regimen was completed with no relevant complications. One patient developed tuberculosis after a recent contact.

274. Tuberculous and non-tuberculous mycobacterial infections: epidemiology II
P2673
A comparison of on-site versus remote physician follow up of directly observed preventive treatment (DOPT) for latent tuberculosis infection (LTBI) on completion rates
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Background: Ethiopian immigrants (EI) at absorption centers treated for LTBI Disease, Carmel Medical Center, Haifa, Israel.

Objective: To compare completion rates and cost of DOPT among EI when managed at their place of residence vs. management at a TBC. We aimed to enhance completion to therapy. This strategy could not be continued and between 2008-2010, patients were followed at a tuberculosis center (TBC) 60 Km. away, while DOPT was continued at the absorption center.

Methodology: A retrospective cohort analysis of 547 medical records for all EI at absorption centers in Zefat who had started DOPT for LTBI and were followed up at absorption centers (2005-2006, study group -SG), compared to patients followed up at a TBC (2008-2010, comparison group - CG). Free transportation to the TBC was provided for the CG.

Findings: Altogether 495 EI's were included (263 in the SG and 232 in the CG group). Both groups had high completion rates (SG: 96.2% vs. CG: 91.1%; p=0.14). While demographic factors did not predict treatment completion side effects were significantly associated with non-completion. Costs were the same for both groups.

Conclusion: The success and cost of DOPT was not dependent on on-site physian involvement. High completion rates could be due to the congregation of EI at the absorption centers leading to easy access to dedicated skilled TB nursing staff.

Sponsored by the Israel National Institute for Health Policy Research and the Israel Lung and Tuberculosis Associated Tumor.

Part of a Thesis submitted for MPH degree, School of Public Health, University of Haifa, Israel.

P2674
Differences in the management of latent tuberculosis infection in patients treated with anti-TNF-α in Turkey
Serzil Oral1, Nalan Demir2, Sebnem Ataman1, Ahmet Ugur Demir1, Nurben Sukdur1, Akin Kaya1, Oya Kayacan1. 1Department of Chest Diseases, Hacettepe University, Ankara, Turkey; 2Department of Chest Diseases, Ankara University, Ankara, Turkey.

Aim: Latent tuberculosis infection (LTBI) is commonly detected with the tuberculin skin test (TST) before anti-TNF-α. BCG vaccination modifies TST reaction. We use different approaches to evaluate LTBI. We aimed to evaluate different approaches to LTBI and results in our clinic.

Method: This report retrospectively evaluated data of patients treated with anti-TNF-α, including symptoms, size of TST reaction, used anti-TNF agent, treatment details and development of active tuberculosis disease. We used different approaches to evaluate LTBI and results in our clinic.

Results: The study identified 99 consecutive patients referred for the evaluation of LTBI before starting anti-TNF therapy (54 men, mean age±SD: 44±12). The diagnosis of ankylosing spondylitis was established in 56 patients, rheumatoid arthritis in 36 and other systemic inflammatory diseases in 7. Fifty four patients received infliximab, 36 adalimumab, 41 etanercept. The median follow up was 25 months (range 3-120). Of the 56 patients who underwent LTBI treatment, 29 took isoniazid for 6 months and 20 for 9 months, 7 did not complete a 6-month course of LTBI treatment. Two took isoniazid for 12 months and one for 24 months. Three patients who had a history of treatment of tuberculosis had received anti-TNF-α agent. Active tuberculosis developed in one of the two patients who had TST > 15 mm and refused LTBI treatment after 3 months of anti-TNF-α treatment.

Conclusion: Different LTBI approaches according to threshold size of TST reaction was observed even in the same center in our country. We need a multicenter study to determine the best TST threshold value to develop national guidelines.

P2675
Particular aspects of TB endemic in Bucharest after adoption DOTS strategy
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Bucharest, Romania’s capital, a great urban agglomeration with almost 2 000 000 inhabitants and a population density of 8 528 inhabitants/Km², was confronted with a rate, sometimes very high of tuberculosis cases for a long time period.

Objective: The study of the main indicators of the TB endemic in Bucharest between years 2001 and 2011.

Material and method: We used the information existing in the official documents of the information system within the National Program of Tuberculosis Control.

Results: In 1963 the tuberculosis incidence reached 223‰ inhabitants, after presenting a clear tendency of reduction till 1985 (65.9‰). After last year, an appreciable increase of the tuberculosis incidence installed, reaching 154,1‰ in 2001, after which a decrease occurred yearly, reaching 67,5‰ in 2011. The incidence for new cases decrease from 153,8‰ in 2001 to 56,9‰ in 2011 and the incidence for relapses decrease from 18,3‰ in 2001 to 10,7‰ in 2011. The tuberculosis incidence in the 0-14 year children population decrease from 60,8‰ in 2001 to 21,4‰ in 2011. The source density was reduced from 2‰ sources/km² in 2001 to 5 sources/km² in 2010. DOPT strategy implemented in Bucharest proved to be an important weapon for TB control, success rate increase yearly. 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 86% from 2009.

Conclusion: The strict monitoring of the treatment is the medical key in fighting the tuberculosis.

P2676
Effectiveness of a tuberculosis screening program in rheumatic patients treated with immunosuppressants
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Background: Immunosuppressants, including new biological therapies, enhance the risk of developing active tuberculosis (TB). An effective screening program is essential.

Aim: To investigate the impact of a TB screening program on the development of active TB in rheumatoid patients treated with immunosuppressants.

Method: Retrospective analysis of patients followed at Portuguese Institute of Rheumatology, screened for latent or active TB in the Pulmonology Diagnostic Center, since February 2005. The evaluation included clinical history, tuberculin skin test, chest x-ray, interferon gamma release assay and chest CT according to protocol. If any of these was positive, 9 Hepatitis B and 9 tuberculin was prescribed. If all were negative, patients remained under biannual monitoring.

Results: The study had 641 patients with 471 females and mean age 52±13 years. The average length of follow-up was 2±1.4 years. Main rheumatological diagnoses were rheumatoid arthritis (n=394), ankylosing spondylitis (n=104) and psoriatic arthritis (n=70). 173 were candidates to biological therapy and 468 were proposed or already treated with classic immunosuppressants. 532 patients were prescribed INH, of whom 14 refused and 10 suspended for intolerance (9 hepatoxicity and 1 medullar aplasia). The remaining 109 were proposed only for clinical monitoring. No patient developed TB after the screening program.

Conclusion: In this population, 89% required chemoprophylaxis with INH and only 0.02% developed intolerance. The TB screening program was used effectively, with no cases of TB reported, however these results did not allow calculating its impact in reducing the risk of TB.

P2677
Impact of the global economic crisis on the possible increase TB incidence in Serbia

Introduction: Turbulence of the global economic crisis spilled over into Serbia. The economic factors, as a personal standard of individual and society development are factors influencing the incidence.

Method: We used economic indicators (number of non/employees, index movements in salaries, annual price index, the movement of income per capita) and the movement TB incidence in 1990-2010 in Vojvodina (northern Serbia- 25% of the total population).

Results: The incidence of TB decreased from 38.28 to 17.08, but had two tops - middle of 90s and the beginning of this millennium. Continuing decline in the number of employees by 2003. (234 per 1000 population) from 2004. g. there is a slight increase in employment. But, by 2009, again saw a drop, and continues to this day. Chain index of nominal net earnings showed the highest growth at a time when "inflation is raging" - mid 90s in Serbia.

The analysis of these parameters with the movement of TB in Vojvodina found low correlation between the rate of TB patients and the number of workers per 1000 population (r = 0.190). Correlation analysis revealed a strong correlation between rates of TB and the chain index of nominal net earnings (r = 0.513).

Conclusion: However, 100% implementation of DOTS strategy in Serbia hope that the economic crisis will not affect the eventual increase in TB incidence and the possibility of resistant forms of TB.
TB represents a major healthcare problem in Romania. The incidence of TB in children registered, in Iasi County, significant annual changes (47.4‰ in 2001 to 26‰ in 2010).

Aim: Analysis of TB characteristics in children in a high incidence TB County.

Method: Retrospective study of TB cases in persons 0-14 years old, registered and treated 2001-2010. WHO recommendations were used.

Demographic data, TB contact, site of TB, bacteriological status, co morbidities and treatment results were followed up.

Results: 763 children were notified in 10 years, males – 52%; 70.2% from rural area.

TB contact – 47.5%.

TB meningitis – 4.8% (37), disseminated TB – 0.9% (7).

HIV positive were 5.5%.

88.3% cases were extra pulmonary TB, 11.6% pulmonary TB.

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TB meningitis – 4.8% (37), disseminated TB – 0.9% (7).

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HIV positive were 5.5%.

88.3% cases were extra pulmonary TB, 11.6% pulmonary TB.
MDR TB which is again discouraging & warrants to search the cause behind such high incidence of drug resistance.

P2684

Latent tuberculosis infection among close contacts of multidrugs-resistant tuberculosis patients in eastern Taiwan Chin-Bin Lin 1,2, Jen-Jyh Lee 1,2, Hou-Wen Chou 3. 1) Internal Medicine, Tzu Chi General Hospital, Hualien, Taiwan; 2) Internal Medicine, School of Medicine, Tzu Chi University, Hualien, Taiwan; 3) Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

Tuberculin skin test (TST) and QuantiFERON-TB Gold in Tube test (QFT-GIT) are diagnostic tools for detection of Mycobacterium tuberculosis infection. These tests are used to study the rate of infection in contacts of multidrug-resistant tuberculosis (MDR-TB) patients.

We performed TST and QFT-GIT to close contacts of MDR-TB patient in eastern Taiwan to increase the awareness and the necessity of each test, and both negative in 173 (29%). People older than 50 and aborigines showed higher rates of QFT-GIT-positive than people younger than 30 (69.9% vs. 39.2%) and 60.5% vs. 30.6%). Both TST and QFT-GIT can be used to detect latent tuberculosis infection, and both tests should be used in conjunction with risk assessment, radiography and other diagnostic tools. High incidence of latent tuberculosis infection among close contacts of MDR-TB patients in eastern Taiwan were detected and close follow up and monitoring are mandatory for early detection of possible active MDR-TB cases.

P2685

Dynamics of MBT drug resistance in a specialized urban TB hospital (Saratov, Russia)

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DR dynamics over 2006-2011 was studied in a Specialized Urban TB hospital. Sputum from 1962 was tested for MBT DR. During the years 2006-2009, both primary (from 36.3% to 68.0%) and secondary DR (82.1% to 90.8%) was found to be increasing. But in 2011 primary DR decreased to 54.8% (a 13.2% drop). Secondary DR keeps growing: 88.7% in 2010 and 91.5% (the absolute peak over the entire study period) in 2011. Similar tendencies have been found for monoresistance.

Over 2006, 2009, MDR in primary DR doubled – from 16.8% to 32.4% (p<0.001), and in secondary DR it increased from 53.8% to 64.0% (2010). However, the latter parameter is showing signs of slight improvement: in 2011, MDR was 25.8% (8.4% in primary DR and 50.3% in secondary DR). By specific drugs: primary DR to H decreased in 2009-2011 to 32.3% (-16.4%), to R to 29.0% (-7.8%), to E to 19.4% (-8.2%), to S to 28.7% (-19.2%). Regrettably, a similar tendency was not observed for secondary DR.

Dynamics analysis of MBT resistance to various H concentrations during treatment of 44 patients showed that 11.4% of them were and remained DR to H (10 mg/ml) 59.1% of them remained non-DR to H (10 mg/ml) 11.4% developed DR to this concentration during treatment, in 18.2% strains sensitive to H10 developed. At the start of treatment, 70.5% were H10 non-resistant; later on non-resistance was found in 77.3%. Non-resistance to low H concentration (1 mg/ml) was 20.5% at the onset and 15.9% at follow-up test.

Conclusion: A certain primary DR improvement has been observed. Issues of DR amplification require further study.

P2686

Multidrug-resistant tuberculosis in the western region of Algeria Assia Ouardi 1, Mourad Hadjadj 2, Yahia Berrahla 1. 1) ORAN, CHU, Ouan, Algeria; 2)LEMENC; CHU; Temcen, Algeria

Introduction: The MDR-TB is entirely man-made and is the result of a failure in effective implementation of anti-tuberculosis national plan (PNLT). What assessment do we have of curing it in the western region of Algeria?

Material and method: A longitudinal descriptive study involving 97 patients followed for MDR-TB from January 2005 to December 2009 and put in 2nd line regimen with a duration of at least 21 months and including 05 drugs (Ofloxacin, Ethionamide, Kanamycin, Cycloserine and Pyrazinamide).

Inclusion Criteria: Patient with MDR-TB documented to INH and Rifampicin at least. Patients who underwent at least 02 chemotherapy regimens including one eight-month regimen that always have positive smears.

Results: Average age: 29 years

Extreme age: 15 to 61 years

75% of patients aged between 25 and 34 years. Sex ratio 1.4:1

33% of patients from the wilaya of Mostaganem

07 familial cases observed

06 patients are diabetic, one patient with HIV co-infection.

96% of exclusive lung locations

92% of patients received at least 02 treatments before drug susceptibility test

Of the 97 patients, 59 are cured, 14 patients in failure, 15 died and 09 have given up treatment.

82.5% of patients have benefited from a drug susceptibility test, the resistance to INH and Rif is observed in 100% of cases, streptomycin in 50% of cases and Ethambutol in 23% of cases.

For patients who have finished their treatment, the cure rate is 61%.

Conclusion: MDR-TB represents a threat which we must face with determination, respecting and reviving the PNLT in order to prevent the emergence of multi-resistant bacilli.

P2687

Risk factors of time to sputum smear conversion in multi-drugs resistant tuberculosis patients in Iran Farzaneh Baghaei Shiva 1,2, Majid Marjani, Payam Tabarsi, Mohammad Reza Masjedi. Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran

Objectives: Treatment of multidrug resistant tuberculosis is difficult and expensive. Sputum conversion is a proper monitoring tool in treatment of these patients. Also, reducing the time of conversion is an important infection control measure. This study was performed to evaluate the time and predictors of sputum conversion in the pulmonary MDR-TB patients.

Methods: During 2003-2011, all patients with documented MDR-TB in referral center, Tehran, Iran, were recruited. All patients received standard treatment consisted of Ofloxacin, Prothionamide, Amikacin and Cycloserine. All demographic and characteristic factors were studied. Time of sputum conversion was evaluated to predictors by conducting survival analysis (using a Cox proportional hazards model).

Results: Of 298 recruited MDR-TB patients, 171 patients were male and 178 patients were Iranian. The median age was 41 years. 60% of patients had the history of TB treatment. The median time to sputum conversion was 51 days. Diabetes mellitus, co-disease, adverse drugs reaction and male sex delayed sputum conversion.

Conclusion: Most MDR-TB patients achieved sputum smear conversion within 51 days. DM, adverse effects, male gender and co-disease were predictors of delay conversion.

P2688

The effectiveness of MDR TB treatment in children and adolescents depending on its duration Gulbadan Bekembaoeva, Aike Alenova, Larisa Kastykpaeva. Department of Pediatrics of MDR TB, National Center for TB Problems, Almaty, Kazakhstan

Target: to study the effectiveness of treatment of TB with multiple drug resistance with drugs of second line depending on duration of intensive and continuation phases.

Materials and methods: Group 1 – 50 patients treated by short regimens (intensive phase from 2 to 4 months, continuation phase from 12 to 16 months) up to adoption of standardized schemas and terms of treatments with DSL, during 2001 to 2006. Group II – 50 children and adolescents treated with DSL according to terms of
The incidence of MDR-TB among patients who received category II treatment from 35.5%. Of these, the highest was in Category I failure at 45%, followed by Relapse 35.6% and RAD at 19.4%. We recommend that patients with category I failure should no longer receive category II treatment. Instead, MDR-TB screening should be done and standardized treatment for MDR-TB should be started. As for RAD, and Relapse, MDR-TB screening should also be done and we need to carefully re-evaluate the use of Category II treatment regimen.

P2602
Diagnostic role of fiberoptic bronchoscopy in suspected smear negative pulmonary tuberculosis
Mahler Beatrice, Tinatin Mamaladze, Marina Kikvidze, Lali Mikiashvili.

Background: Sputum smear-negative pulmonary tuberculosis is a common problem faced by clinicians. Bronchoscopy-related transmission of Mycobacterium tuberculosis is rarely reported.

Methods: The retrospective study evaluated 40 patients(26males, 14females; mean age 45±9.6-years; range 19-88years) who had respiratory symptoms and radiographic findings consistent with pulmonary TB, but who were unable to produce sputum spontaneously or had three samples of spontaneously produced sputum that was smear-negative for AFB. Induced sputum tests, bronchial washings and bronchoalveolar lavage were performed where indicated. The relevant specimens were sent for direct smear for acid fast bacilli by Ziel-Neelsen method and culture for M. tuberculosis in Lowenstein medium. Data obtained were analyzed using MS Excel 2007.

Results: Bronchoscopy confirmed or contributed to the diagnosis in 18 patients. In 8 patients(45.5%) upper lobe mucosal inflation with/without narrowing and scarring was detected. Sputum culture confirmed the diagnosis in 12(30%) cases: 7(17.5%) had culture positive specimens(<0.005), 4(10%) was culture positive on bronchoscopy and one(2.5%) on induced sputum. All patients had negative HIV test, 3(77.5%) new cases and 35(87.5%) with high erythrocyte sedimentation rate. Majority of radiological findings were infiltrative ulcerated and cavitation lesions. Treatment with drugs of the third line. Thus, patients with positive smear were by 2 times more (62.3%) in the Group I than in the Group II (30.0%). MDR: in 100% of both groups culturally only. Thus, analysis of outcomes and follow-up control showed that among patients with MDR-TB treated with drugs of the first line 5 (6.2%) patients of the Group II died, while among patients treated with DOL, one adolescent only died. Relapse emerged in 12.5% of children and adolescents of the Group II. This fact proves the necessity to administrate the therapy with DOL to the children and adolescents with MDR TB.

P2692
275. Tuberculosis: invasive diagnostic and therapeutic interventions

P2690
Development of multi-drug resistant tuberculosis among patients treated with category II regimen: A lung center of the Philippines experience
Sablan Augusto Jr1, Joven Gonong1, Lawrence Raymond1, Vivian Lofranco2.

Background: Sputum smear-negative pulmonary tuberculosis is a common problem faced by clinicians. Preventive approaches, early diagnosis and the development of effective and relatively inexpensive methods of case search should be emphasized.

Objective: To enroll all cases of MDR-TB in State of Paraiba and check territorial distribution.

Methods: Using tabulated data collected by the MDR-TB Epidemiologic Vigilance System, in the period January 2002 to December 2010, we enrolled cities of residence of each case and provided an territorial picture of MDR-TB, regarding space distribution and city population. Population data were collected from Brazilian Institute of Geography and Statistics - IBGE, June 2008.

Results: Paraiba is the 13th Brazilian State in order of population (3,769,977 inhabitants, 1.9% of Brazilian population). Total tuberculosis cases in Paraiba were 7332 (1.4% Brazilian cases). Absolute number of MDR-TB was 39 (1.3% of total Brazilian cases). The proportion of MDR-TB and total tuberculosis cases in Paraiba was 0.53%. In concerning to territory distribution, MDR-TB cases scattered over 19 of 223 cities of Paraiba. Although most inhabited cities presented more cases, it did not happen in a proportional fashion. Some important cities (50 to 100 thousand inhabitants) presented no case. More interesting, MDR-TB occurred also in small cities, with less than 3,000 inhabitants. More than one third of all cases occurred in cities with less than 50,000 inhabitants. Most cases occurred less than 20Km from capital (Joao Pessoa).

Conclusion: MDR-TB cases are scattered over 19 cities in Paraiba, including less inhabited cities. Preventive approaches, early diagnosis and the development of effective and relatively inexpensive methods of case search should be emphasized.
ative cases. Bronchial washing cytological study may be useful for early diagnosis of pulmonary tuberculosis (PTB) as macrophages can respond to a variety of cellular signals and response to local cues.

Aims: Assessment of possibility of involvement bronchial washing cytology in PTB diagnosis as one of the most valuable and rapid method in order to improve surveillance and care of TB-infection.

Methods: 53 sputum smear negative adult patients had undergone diagnostic investigations including CXR, bronchoscopy, bacteriological, immunological and cytological tests. Cytopathologically TB diagnosis was established when elements of TB-granuloma and multinuclear macrophages were found in the bronchial washing’s smears. All results were compared to bacteriological data ("gold standard").

Results: From patients, 25 were diagnosed cytopathologically as PTB. In 19 cases bronchoalveolar lavage's smears were obtained. All results were compared to bacteriological data. Histological and bronchial washing's smears were positive in 28 patients (54%). Collected one sample were negative for 3 patients.

Conclusions: Present study showed quite high specificity in PTB diagnosis. Main strategic focus was that bronchial washing’s samples were sensitive to multinuclear macrophages. and thus, it can be performed a powerful diagnostic tool. Though, further fundamental researches and envelopment of cytosome method in PTB diagnosis is needed.

P2696
Role of minimal invasive transcervical main bronchial surgical closure in MDR destructed lung treatment
Cristian Paleru 1, Ioun Cordes 1, Victor Spanu 1, Olga Danaila 1, Emilia Crisan 1, Miha Dumitru 1

P2697
Surgical treatment of first-found destructive pulmonary tuberculosis
Tulkun Kariev 1, Sunnatiila Abdikasimov, Sherzod Rahmatov

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Resection operations were performed in 261 patients (males – 155, females - 106) with first-found destructive tuberculosis after 3-6 month long ineffective chemotherapeutic treatment. The majority of patients (220 – 84.3%) were in young age – from 20 to 40 years old. After a course of chemotherapy, infiltrative tuberculosis with lysis was diagnosed in 12 patients (4.5%), tuberculosis – in 101 (38.7%), obrous-cavernous – in 148 (56.8%). Mycobacteria of tuberculosis in sputum were observed in 98 patients (37.5%). Segmental lung resection was performed in 112 patients (43.0%) excalcation of tuberculosis – in 13 (5.0%), lobectomy – in 100 (38.3%), combined resection – in 8 (3.0%), and pneumonectomy – in 27 (10.7%). After operation, bronchial fistula and pleural empyema developed in 8 patients (3.1%), early re-activation of the tubercular process – in 10 (3.8%), pneumonia of the operated lung – in 5 (1.9%). These complications in 5 patients were eliminated by the therapeutic treatment, in 9 – by repeated operation. A total of 3 patients died from re-activation of tuberculosis, bronchial fistula and pleural empyema. Conclusions: At first-found destructive pulmonary tuberculosis after ineffective chemotherapy course, sparing resection operations are the final stage of complex therapy with low frequency of post-operative complications and high effectiveness of surgical treatment (96.5%).

P2698
Value of bronchoscopy specimens for the diagnosis of sputum smear negative tuberculosis in high burden multidrug resistant tuberculosis setting
Dumitru Chesu 1, Ecaterina Stanan 1, Irina Semionica 1, Valeriu Crudu 1

P2699
Pneumonecrosis in pulmonary tuberculosis. To do or not to do?
Ioan Matus 1, Alexander Bashenov, Elena Kildyusha, Thoracic Surgery, Urals Research Institute for Phthisiology and Pulmonology, Ekaterinburg, Russian Federation

Conclusions: Using minimal invasive procedure for cutting the access to the affected lung allow a good chance of healing for a poor status MDR patient allow a good cooperation from the patient and later an easy tolerated and accepted pneumonectomy with minimal surgical risk of postpneumonectomy bronchial fistula since the fistula is already cicatrised at the pneumonectomy etap. We present in first communication a minimal invasive transversal approach of the right main bronchus.

Methods: A randomized study of the bronchoscopic valve blockade of the affected part of the lung in the complex treatment of patients with cavity drug-resistant pulmonary tuberculosis
Sergey Sklyuev 1, Denis Krasnov 1, Nonoosibirski TB Research Institute, Nonoosibirski, Russian Federation

In accordance to the existing hypothesis application of the endobronchial valve will contribute to early closure of cavity and the right one supported perfect the postponed pneumonectomy. No operatory complications or incidents were observed.

Results: Using minimal invasive procedure for cutting the access to the affected lung allow a good chance of healing for a poor status MDR patient allow a good cooperation from the patient and later an easy tolerated and accepted pneumonectomy with minimal surgical risk of postpneumonectomy bronchial fistula since the fistula is already cicatrised at the pneumonectomy etap. We present in first communication a minimal invasive transversal approach of the right main bronchus.
database, with culture confirmed PTB between January 2008 and December 2011. Patients, who were SSN or non-productive of sputum (NPS) before bronchoscopy, were eligible.

Results: The inclusion criteria were met by 503 subjects. BA was performed in 369 cases, BW - 116 cases, BAL - 18 cases, PBS was available in 37 patients. Microbiological examination of BSS was the exclusive method for the microbiological confirmation of PTB in 344 (68.4%) cases. The overall diagnostic rate of BSS for smear positive PTB was 21% (98/466). Higher rate for diagnosis of smear positive PTB were proven for bronchial washing (30.3%) and bronchial aspirate (17.2%) which were superior to BAL (8.5%; p<0.01 and p<0.005, respectively).

The overall rate of MDR TB among smear positive cases was 27.6% (27/98).

Conclusions: Microbiological examinations of BSS give a higher rate of definitive diagnosis of PTB among SSN cases, with an earlier identification of contagious subjects with potential MDR TB. 

P2699
Long-term results after pneumonectomy and lobectomy for pulmonary tuberculosis: Quality of life and pulmonary function


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The diagnostic yield of ultrasound-guided cutting needle biopsy in the operations need more active treatment including pulmonary rehabilitation.

Methods: We investigated quality of life (QoL) and pulmonary function in 58 patients after pneumonectomy. Of these 58 patients, 36 underwent single lobectomy (group L) and 22 underwent pneumonectomy (group P). All postoperative examinations were performed more than one year after surgery. QoL, was studied by SF-36, SGRQ (St. George’s Respiratory Questionnaire) (SGRQ), and MOS. Shortness of Breath Questionnaire (SOBQ). Shortness of Breath Questionnaire (SOBQ). Pulmonary function was studied by spirometry and plethysmography.

Results: In patients in group P and group L, respectively, FVC was 58.7±15.2 and 103.3±15.3%; FEV1 - 47.1±13.9 and 84.8±16.7%; TLC - 66.0±11.2 and 98.5±12.8%; FRC - 81.1±26.1 and 110.1±28.0%; IC - 53.8±19.3 and 89.7±19.1% (p<0.01 for all cases). All SF-36 components did not differ between groups.Symptoms SGRQ scores were 45.8±26.2 and 32.3±22.3% (p>0.05). Activity SGRQ scores were 51.0±22.0 and 30.8±19.5% (p>0.05). Impact SGRQ scores were 31.5±18.8 and 17.8±15.9% (p>0.05). Total SGRQ scores were 39.9±18.9 and 28.4±16.26 and 16.4±15.3 points (p<0.05); group P and group L, respectively.

Conclusion: Pulmonary function and QoL were significantly worse in patients after pneumonectomy. SGRQ was more sensible then SF-36 in assessment of QoL.

In both groups QoL was worse than in healthy patients. So the patients after these operations need more active treatment including pulmonary rehabilitation. 

P2700
The diagnostic yield of ultrasound-guided cutting needle biopsy in the investigation of suspected pleural tuberculosis

Richard Turner, Omar Pirzada.

Department of Respiratory Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Introduction and Aim: Closed pleural biopsy for tuberculosis (TB) using the Abrams needle is long-established and gives yields > 75%.

Modern practice often employs smaller gauge cutting needles under guidance of ultrasound (US). Few studies have compared these smaller needles to established standard techniques. We undertook a large scale investigation to answer this important question.

Methods: We compared the Abrams needle to ultrasound guided biopsy. We recorded the number of patients who became smear-negative after biopsies, the percentage of patients who were smear-positive, and the number of biopsies required to diagnose TB.

Results: The Abrams needle diagnosed TB in 35% of cases. Ultrasound-guided biopsy diagnosed TB in 50% of cases. The Abrams needle had a sensitivity of 98%, specificity of 95%, and negative predictive value of 90%.

Conclusions: Ultrasound-guided biopsy is a safe and effective method for diagnosing TB. It is more sensitive than the Abrams needle and can be performed using smaller needles.

P2701
Safety aspects of endobronchial valve application in the complex treatment of patients with caviatory drug-resistant pulmonary tuberculosis

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Aims: To evaluate the safety of endobronchial valve application in TB patients.

Methods: In total, 68 patients with drug-resistant destructive pulmonary tuberculosi were taken into the study, they were randomly divided on two groups - one for 33 patients for endobronchial-valve installation (EBV) and another – for 35 to receive standard treatment (control group).

Results: On Day 2 of the study, 12 (36.7%) patients from EBV-group had developed severe, dry cough, in the control group - 2 (5.7%) patients (p = 0.019).

3 (9.1%) of patients from EBV-group were with worsening of COPD symptoms and required symptomatic treatment (p = 0.008).

All these manifestations had been happened within 2 weeks of treatment. During assessment of the bronchial tree after 8 months in patients from EBV-group we revealed proliferation of granulation tissue in the targeted bronchi in 100% of the cases, of whom 24 (72.7%) granulations were big (closing over 50% of the lumen of the bronchus).

After 10 months, during bronchoscopy in patients with EBV-group we found scars of the bronchus wall in 100% of the cases, in 17 (51.5%) - we revealed circular stenosis of the bronchi which reduced over 50% of the lumen of the bronchus, in 9 of these cases (27.3%) the lumen of the blocked bronchus was less than 1 mm in diameter. None of these changes were detected in the control group.

Conclusions: Endobronchial-valve treatment leads to the corrected without affecting the course of the disease complications in the first two weeks of treatment, and causes great severity of the targeted bronchus.

P2702
The treatment of a destructive lung tuberculosis by valuvlar lung volume reduction on early terms of therapy

Nikolay Yalkushenko, Irina Tabanakova, Marina Kondakova.

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Lung tuberculosis (TB) can be complicated by cavity forming. Patients with destructions in the Russian Federation in 2010 have made 49.0% from first time revealed lung TB, closing of lung cavities was achieved in 63.0% of cases. The lethality of this patients reaches 14.0% and 36.0% in the control group (p = 0.008).

Objective: To increase the efficiency of treatment of a destructive lung tuberculosis by valvular lung volume reduction on early terms of therapy.

Material and methods: The work is the result of supervision over 40 patients with lung TB. 47.5% of patients were smear-positive, drug resistant MBT - in 25.0%. Destructions defined in the top shape of lungs in 72.3% of patients, in 27.7% - in the bottom shape (the sixth lung segment). Video-assisted thoracoscopic biopsy of lungs was performed from 1.0 cm. To 21 patient during a chemotherapy was installed a non-return endobronchial valve (1 gr.). The comparison group - 19 persons (II gr.) received only chemotherapy. Valvular installation was made with flexible bronchoscope. In all patients with lower lobe cavity localization therapy was supplemented with artificial pneumoperitoneum. Results: 70.0% of patients became smear-negative in a month, by 3 months - 100.0% of patients (33.3% and 77.8% in II gr). Destructions closed in 3 and 6 months in 38.0% and 90.5% in I gr., 15.8% and 57.9% in II gr. (p<0.05). Duration of lung volume reduction has made 128.9±10.9 day.

Conclusions: Valvular lung volume reduction is an effective non-drug technique in complex treatment of lung tuberculosis, raising efficiency of treatment in 1.7 times on closing of destruction cavities by 6 month.

P2703
A randomized study of bronchoscopic blockade of the affected part of a lung as a part the complex treatment of patients with drug-resistant pulmonary tuberculosis

Sergey Sklyev, Denis Krasnov.

Thoracic Surgery, Novosibirsk TB Research Institute, Novosibirsk, Russian Federation

At the present time in Russia, there are 60% of TB patients with unsatisfactory results of treatment by standard chemotherapy regimens with anti-TB drugs, and therefore there is permanent search for new treatment approaches to these patients. Scope and purpose: To assess and to analyze the impact of endobronchial-valve therapy on pulmonary function. According to the existing hypothesis, the implantation of an endobronchial valve and excision of the part of the total volume of the lung do not decrease pulmonary function indices.

Methods: We have compared the efficacy of endobronchial-valve therapy with a standard therapy. Changes in rates of FEV1 were the reference points for the selection of patients. Of 68 enrolled patients, 33 were randomly assigned to receive endobronchial valves (EBV group) and 35 to receive standard medical care (control group).

US-guided narrow gauge needle biopsy

Other type of biopsy

Plural biopsy

Total

<table>
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<tr>
<th>Patients who underwent procedure</th>
<th>US-guided narrow gauge needle biopsy</th>
<th>Adequate pleural tissue obtained</th>
<th>Biopsy sample diagnosis of TB</th>
<th>Other type of biopsy</th>
<th>Plural biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate pleural tissue obtained</td>
<td>21</td>
<td>13 (62)</td>
<td>7 (53)</td>
<td>5 (100)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>Biopsy sample diagnosis of TB</td>
<td>26</td>
<td>16 (62)</td>
<td>4 (16)</td>
<td>11 (42)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>
P2704

Analysis of 177 endobronchial tuberculosis cases in Serbia over 15-years period

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Introduction: Tuberculosis still represents a significant health problem of population in Serbia, the incidence being for last few decades 32-36/100.000 inhabitants, up to last few years when it decreased to 24-26. Endobronchial tuberculosis (EBTB) is a chronic, progressive tuberculosis infection with often complicated clinical course and bronchostenosis formation.

Aim: The aim of the study was to determine common clinical features and diagnostic aspects of bronchoscopic biopsy proven EBTB in population of Serbia over 15 years period and compare with published data.

Method: Analysis and comparison of clinical features, radiologic, mycobacterial, bronchoscopic and histologic findings of 177 EBTB patients by SPSS ver. 15 for Windows, chi-square test, t-test and calculating Phi correlation coefficient.

Results: Male to female ratio was 1.2:1. Five patients (2.8%) were asymptomatic. None had normal chest radiograph finding; the most frequent localization of current pulmonary TB lesions was in the upper lobes. Two thirds of patients, 116 (65.5%) had cavernous lesions. Atypical TB was evident in 27% (15.3%). The most common endoscopic forms of EBTB were edematous hyperemic (40.1%) and non-specific bronchitis (35.6%) unlike majority of published data. Bacteriologic confirmation of TB had 117 patients (66.1%). Sputum cultures for AFB were positive in only 27.7%, bronchial washing culture in 10.1%. Sputum and bronchial washing culture both were positive in 28.2% patients. Correlation between bronchoscopic categories of EBTB and bacteriologic confirmation of TB diagnosis was analysed and discussed.

Conclusion: EBTB in Serbia has some distinctive and specific features in comparison with other published EBTB series.

P2705

Blocking of bronchoscopic endobronchial valve in the complex surgical treatment of patients with pulmonary tuberculosis

Denis Karavoy, Vladimir Krasnov, Nikolai Goloshechkov, Tymofei Boschetnyi, Dmytry Skvirschuk, Mikhail Reykhayd, Serhiy Skhusev. Clinical Department, Novosibirsk TB Research Institute, Novosibirsk, Russian Federation

A randomized study of osteoplastic thoracoplasty (OT), supplemented with bronchoscopic lung by blocking the affected part in the complex treatment of patients with pulmonary tuberculosis category CV + MBT + patients that OT was performed without installing an endobronchial valve. Effectiveness of the control points were CV and MBT. Estimated risk ratio. A total of 291 patients were involved, of whom 158 fulfilled OT after bronchoscopic block (main group), 133 continued treatment without having to install EBV (comparison group). EBV production company Medlung Inc., Barnaul, Russia.

Results: The proposed complex surgical treatment tactics can increase the effectiveness of remedial measures: the main group more frequently observed cessation of bacterial isolation (RR = 1.49, 95% CI = 1.33 - 1.52), the closure of decay cavities (RR = 1.49, 95% CI = 1.39 - 1.59).

Conclusions: Isolates of NTM were nearly twice as common as MTB. The significance of a mycobacterial isolate in a low tuberculosis prevalence setting

Guy Hagan, Andrew Fairfax. Department of Respiratory Medicine, Mid Staffordshire NHS Foundation Trust, Stafford, United Kingdom

Introduction: The incidence of tuberculosis in semi-rural Staffordshire is very low, around 2.8/100,000/year (1). We reviewed the significance of identifying mycobacteria in this population.

Methods: Retrospective analysis of patients from our institution with mycobacterium isolated from 1st Jan 2007 to 31st July 2011, with follow up until 1st Nov 2011. For patients with multiple isolates, the first species isolated was recorded.

Results: 67 patients were identified. Demographics of the M. tuberculosis(MTB) and non-tuberculous mycobacteria(NTM) patient groups are in Table 1. 22/43 (51%) of the NTM samples were considered significant and treated. Patients with NTM were older and more likely to die (p <0.001). Chronic lung disease was present in 11 (50%) of the treated NTM patients, and none of the MTB patients.

Skin biopsies and urine sample were +ve for NTM. Mycobacterial species isolated included 22 M. avium intracellulare, 6 gordonae, 4 chelonae, 3 kansassii, 3 malmoense, 2 xenopi and 1 each of shimoidai, maritumu and interjectum.

Table 1

<table>
<thead>
<tr>
<th>MTB</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient numbers</td>
<td>24 (36%)</td>
</tr>
<tr>
<td>Males</td>
<td>13 (51%)</td>
</tr>
<tr>
<td>Ages (mean ± SD)</td>
<td>42±6.21</td>
</tr>
<tr>
<td>Death at end of follow up</td>
<td>1 (0.04%)</td>
</tr>
<tr>
<td>Pulmonary samples</td>
<td>16 (66%)</td>
</tr>
<tr>
<td>Sputum +ve pulmonary samples</td>
<td>8 (33%)</td>
</tr>
</tbody>
</table>

*p<0.001.

Conclusions: Isolates of NTM were nearly twice as common as MTB. The incidence of NTM infection seems to be increasing (2).

References:

P2706

The burden of tuberculosis drug resistance in Eastern Europe: The Moldavian experience

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Aims: Surveillance the TB drug resistance on the national level and its impact upon public health in the Republic of Moldova;

The objective: to characterize the evolution of tuberculosis drug resistance in Moldova (2001-2011).

Methods: The study was retrospective, being based on the assessment results of M tuberculosis complex drugs resistance obtained in the reference laboratories from the country.

Results: Prevalence of MDR/TB among New TB cases increase from 6.3% in 2001 up to 26.4% in 2011. Trough previously treated patients (relapses, re-treatment after default, re-treatment after failure, chronic) prevalence of MDR TB was detected in 37.7% cases in 2001 and 64.3% cases in 2011. Extensively drug-resistant tuberculosis (XDR-TB) is present in some territories. The rate of XDR TB among the patients with MDR TB is 6.1% (2010). The prevalence of TB-HIV co-infection in country is 5.4%. The prevalence of MDR/TB among all TB-HIV is higher such from HIV negative patients (67.8%). Reasons of high level of TB resistance in Moldova: poor in infection control in TB hospitals -exogenous re-infection of TB patients; low compliance of treatment; the lack of a rigid control of TB patients, TB/HIV co-infection.

Conclusions: At the current stage MDR TB is a serious problem for National TB Program, bringing serious public health and economic consequences. It is a very alarming phenomenon, because the success of treatment (with first-line drugs) for this form of TB is less effective than for the susceptible tuberculosis and the accumulation of a greater number of resistant strains in society can lead to the infection of population and to an increase in the number of patients with MDRXDR TB.

P2707

The significance of a mycobacterial isolate in a low tuberculosis prevalence setting

MONDAY, SEPTEMBER 3RD 2012
Clinical analysis of pulmonary Mycobacterium avium complex disease in Japan
Masaki Ikeda, Yoshihiro Koshashi, Keiji Mouri, Yasushi Obuse, Mikio Oka.
Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan

Objective: To analyze the clinical characteristics of patients who diagnosed pulmonary Mycobacterium complex (MAC) disease recently in the affiliated several hospitals.

Patients and methods: The subjects consisted of 150 patients who satisfied the diagnostic criteria of ATS between 2003 and 2010. We evaluated the backgrounds, diagnostic methods, microbiological findings, radiological findings, treatments, and prognosis.

Results: The average age of 150 patients with pulmonary MAC disease was 65.0 years old. The detection method was most frequently recognized by bronchoscopy (50%). The microscopic findings were smear positive for acid-fast bacilli in 98 patients (65%) and the sensitivity of isolated MAC for antituberculosis drugs was comparatively good for clarithromycin (CAM) and rifampicin (RFP). The clinical disease type of pulmonary MAC disease consisted of nodular/bronchiectatic type in 101 patients (67%), fibrocavitary type in 43 (29%) and solitary nodular type in 6 (4%), respectively. Concerning the treatment for pulmonary MAC disease, the combined chemotherapy including CAM was performed for 76 patients (51%). Sputum conversion rate was 76%, the sputum relapse rate was 31% and the clinical improvement including radiological findings and/or clinical symptoms was obtained in 49%.

Conclusions: We positively perform the bronchoscopy examination to obtain the diagnosis of pulmonary MAC disease. The diagnostic rate of pulmonary MAC disease has recently increased with the revise of diagnostic criteria reported in 2007 and we could obtain comparatively good clinical effect by the positive performance of combination chemotherapy including the increase dose of CAM.

Pharmacokinetics of drugs for non-tuberculous mycobacterial lung infections
Cecile Mass-Jacouyn1, Jacko van Ingen2, Rob Aarnouts3
1Pulmonary Diseases, University Medical Centre Nijmegen, UCCZ Dekkerswald, Groesbeek, Gelderland, Netherlands; 2Medical Microbiology, University Medical Centre, Nijmegen, Gelderland, Netherlands; 3Clinical Pharmacy, University Medical Centre, Nijmegen, Gelderland, Netherlands

Successful treatment for Non-Tuberculous Mycobacterial (NTM) infections is easily frustrated. Little is known about the pharmacokinetics (PK) and dynamics of treatment regimens in relation to treatment outcome. Drug concentrations may be an intermediate link. In NTM disease very few PK studies have been performed. We performed a prospective, descriptive pharmacokinetic (PK) study of the plasma pharmacokinetics (full PK curve) of rifampin (RFP), ethambutol, clarithromycin (CAM), azithromycin, isoniazid and moxifloxacin and their active metabolites in a Dutch series of patients with clinically relevant NTM lungdisease and we compared the results with two other series from the literature. The baseline characteristics are shown in table 1.

Table 1. Baseline characteristics

| Characteristics | Patients | Male, n (%) | Age range (mean) | Ethnicity | Weight (mean) | BMI (mean) | Specimen
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>10 (71%)</td>
<td>64.3 (43-85)</td>
<td>Caucasian (100%)</td>
<td>71.01</td>
<td>23.4 (19.0-30.3)</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Table 2 shows the main PK results.

Table 2. Main pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Drugs used</th>
<th>n</th>
<th>Mean dose/kg</th>
<th>Mean Cmax</th>
<th>Mean AUC0-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>14</td>
<td>8.51±0.74</td>
<td>12.83±6.24</td>
<td>27.83±31.48</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>5</td>
<td>7.10±0.81</td>
<td>0.426±0.25</td>
<td>2.74±4.07</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2</td>
<td>4.73±1.92</td>
<td>0.183±0.24</td>
<td>2.03±4.85</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>13</td>
<td>15.96±1.92</td>
<td>3.725±1.21</td>
<td>26.33±9.11</td>
</tr>
</tbody>
</table>

Results were generally consistent with the data published in the past by Wallace and Pelouin. Our data showed that rifampicin causes a reduction in clarithromycin and azithromycin serum concentrations. The current study has confirmed the significant PK interactions between rifampicin and clarithromycin and we feel this calls for a reevaluation of the dosing strategies in NTM lung disease as an inadequate response to treatment might be attributed to suboptimal drug exposure.

Recovery rate of nontuberculous mycobacteria over a 10-year period at a tertiary referral hospital in Korea
Boksoon Chang1, Kyeongmoon Jeon1, O. Jung Kwon1, Nam Young Lee2, Chang-Seok Kr, Won-Jung Koh3.
1Division of Pulmonary and Critical Care Medicine, Samsung Medical Center, Seoul, Republic of Korea; 3Laboratory Medicine & Genetics, Samsung Medical Center, Seoul, Republic of Korea

The incidence of nontuberculous mycobacteria (NTM) infection is increasing in Korea. The aim of this study was to evaluate the recovery rate of NTM from respiratory specimens over a 10-year period in a tertiary referral hospital in Korea with a intermediate tuberculosis burden.

Method: Twenty immune competent patients who were diagnosed with a lung NTM infection by positive cultures and 20 healthy controls were enrolled. Based on the preferential percentage of neutrophils and lymphocytes in BAL fluids, patients were divided into two groups: predominant neutrophil and a lymphocyte-dominant group. The HRC scores indicating the extent and severity of airway disease (modified method of Fowl et al. Eur Respir J 2007) was compared between the groups.

Results: The numbers of neutrophils and lymphocytes were significantly higher in patients with NTM (17.4±4.6 and 6.9±2.4 x 10^7/ml) than those in healthy controls (0.1±0.1 and 0.8±0.2 x 10^7/ml) (p<0.01, respectively). Among the NTM group, HRC scores of the lobe in which BAL was performed in the neutrophil-dominant group (8.0±0.7) were significantly higher than the lymphocyte-dominant group (1.7±0.4) (p<0.01).

Conclusion: Neutrophil-dominant inflammation due to pulmonary NTM infection was related to severity of HRC findings in patients with NTM infection. These results will help us in understanding the biological defense mechanism against NTM.

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Detection of volatile organic compounds in cattle caturally infected with Mycobacterium bovis

Nir Peled1, Matthew Koslow1, Jack Ryan1, Hessam Haick2. 1 The Thoracic Cancer Research and Detection Center, Department of Pulmonary Medicine, Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel; 2 The Department of Chemical Engineering and Russell Berrie Nanotechnology Institute, Technion- Israel Institute of Technology, Haifa, Israel; 3 The National Wildlife Research Center, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Fort Collins, CO, United States

We report a novel method in detecting Mycobacterium bovis infection in cattle based on identifying unique VOC (volatile organic compounds) profiles in the breath of cattle. The study was conducted on breath samples collected from cattle on an M. bovis-infected dairy in southern Colorado, USA. All animals were skin test positives; the presence of disease was either confirmed or inferred after necropsy. Negative controls included breath samples from animals on two tuberculosis-free dairies in northern Colorado. Gas chromatography/mass-spectrometry analysis revealed significant differences between M. bovis-infected and non-infected animals in the concentrations of 15 VOCs, allowing for distinctly different VOC patterns. Based on these results, a nanotechnology-based array of sensors was tailored for detection of M. bovis-infected cattle via breath. The tailored system successfully identified all M. bovis-infected animals (8/8) while 21% (3/14) of non-infected animals were misclassified as M. bovis-infected. The method shows promise in identifying unique VOC patterns in cattle with bovine tuberculosis. Applicability in humans warrants further study.

Figure 1. (a) Predominant VOCs in animals’ breath samples. (b) Exclusive VOCs for bTB positive and bTB negative cattle.

Figure 2. DFA (Discriminant factor analysis) plot showing the discrimination between bTB-negative (circles, n=14) and bTB-positive (rhombs, n=8) exemplars. An insight of the bTB-negative animals from the different dairies shows the complete mixing of the exemplars from M. bovis-infected (green filled circles, n=4) and tuberculosis free (red open circles, n=10) dairies.

Conclusions: Increased symptoms incidence, advanced radiological changes, increased ESR and high fibrinogen levels are risk factors for pulmonary MAC-PD from other lung diseases.

Based on these results, a nanotechnology-based array of sensors was tailored for detection of M. bovis-infected cattle via breath. The tailored system successfully identified all M. bovis-infected animals (8/8) while 21% (3/14) of non-infected animals were misclassified as M. bovis-infected. The method shows promise in identifying unique VOC patterns in cattle with bovine tuberculosis. Applicability in humans warrants further study.

P2713

Detection of volatile organic compounds in cattle caturally infected with Mycobacterium bovis

Nir Peled1, Matthew Koslow1, Jack Ryan1, Hessam Haick2. 1 The Thoracic Cancer Research and Detection Center, Department of Pulmonary Medicine, Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel; 2 The Department of Chemical Engineering and Russell Berrie Nanotechnology Institute, Technion- Israel Institute of Technology, Haifa, Israel; 3 The National Wildlife Research Center, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Fort Collins, CO, United States

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P2714

Clinical evaluation of GPL core IgA antibodies for serodiagnosis of MAC pulmonary disease

Yoshihiro Kobashi, Masaki Ikeda, Keiji Mouri, Yasushi Obase, Mikio Oka. Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan

Objective: To evaluate the clinical usefulness of GPL core antibodies for diagnosing MAC-PD and distinguishing MAC-PD from other lung diseases.

Methods: GPL core antibody levels were measured in 57 patients with MAC-PD, 18 with clinically suspected MAC-PD but who did not satisfy the diagnostic criteria of MAC-PD proposed by ATS, 10 with MAC contamination, 18 with pulmonary tuberculosis (TB) and 9 with other nontuberculous mycobacterial (NTM) disease, 18 with other lung diseases.

Results: The positive response rate for MAC-PD was 77%, that for suspected MAC-PD was 39%, and that for MAC contamination was 10%, and that for pulmonary TB, other NTM diseases, and other lung diseases was 0%, respectively. GPL core antibody levels were significantly higher in patients with MAC-PD including patients with clinically suspected MAC-PD, than in those in the other groups (p<0.01). The sensitivity and specificity of the antibody for diagnosing MAC-PD were 77% and 100%, respectively. Although thirteen patients with MAC-PD showed false negative responses for the GPL core antibody, five patients had immunosuppressive conditions due to underlying diseases. No significant correlations between the antibody level and species of MAC, clinical disease types, and extent of the disease on chest computed tomography were found in patients with MAC-PD.

Conclusions: The EIA kit is a useful supportive method for the rapid and convenient diagnosis of MAC-PD using a small dose of serum, and for the differentiation of MAC-PD from other lung diseases.

P2715

Clinical evaluation of interferon-gamma release assay (IGRA) in patients with nontuberculous mycobacterial disease

Yoshihiro Kobashi, Masaki Ikeda, Keiji Mouri, Yasushi Obase, Mikio Oka. Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan

Objective: To evaluate the clinical usefulness of two IGRA (QuantiFERON-TB and T-SPOT.TB) in patients with nontuberculous mycobacterial (NTM) disease.

Materials and methods: The study consisted of 180 patients with NTM disease who satisfied the diagnostic criteria proposed by American Thoracic Society (ATS). Tuberculin skin test (TST) was also performed for these patients as much as possible.

Results: The causative microorganism was Mycobacterium avium in 76 patients, M. intracellulare in 60, M. kansasi in 22, M. avium in 7, M. marinum in 7, others in 7, respectively. While the positive response rate for M. kansasi, M. marinum, and M. szulgai (30 patients) which possess the ESAT-6 and CFP-10 (Mycobacterium tuberculosis (MTB)-specific antigens) was 60% for TST, 33% for QFT, and 40% for T-SPOT.TB, the indeterminate response rate was 7% for QFT and 0% for MAC-PD, respectively. On the other hand, the positive response rate for M. avium and M. intracellulare etc. (150 patients) was 58% for TST, 7% for QFT, and 11% for T-SPOT.TB, the indeterminate response rate was 7% for QFT and 2% for T-SPOT.TB, respectively.

Conclusions: Although IGRA may be a useful diagnostic method to differentiate TB disease and MAC disease, there are several problems to be resolved before it can be used as a diagnostic method for M. kansasi disease etc. We also would like to describe the results of QFT for M. kansasi disease in other hospitals in Japan.

P2716

Pharmacokinetics and drug susceptibility testing implied limited activity of current regimens for Mycobacterium avium complex disease

Jacco van Ingen, Marin Boeree, Charles Peloquin, Charles Daley. Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands Pulmonary Diseases, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands Emerging Pathogens Institute, University of Florida, Gainesville, FL, United States Mycobacterial and Respiratory Infections, National Jewish Health, Denver, CO, United States

Background: Treatment outcome in Mycobacterium avium complex (MAC) lung
Conclusions: are given in Table 1. Simultaneous use of rifampicin significantly lowered serum mycobacteria. The poor outcomes of MAC disease treatment may partly explain the poor outcomes of MAC disease treatment.

Results: Isolates were identified as MAC by AccuProbe assays. MICs were determined by the BacTec460 modulifecation method; synergy between rifampicin and ethambutol was assessed. Results: Pharmacokinetic data, median MICs and pharmacodynamic calculations are given in Table 1. Simultaneous use of rifampicin significantly lowered serum concentrations of macrolides (30-60%) and moxifloxacin (10-15%).

Conclusions: Serum rifampicin, ethambutol and moxifloxacin concentrations attained effective levels in a minority of patients; rifampicin use exerts detrimental effects on pharmacokinetics of macrolides and moxifloxacin. This may partly explain the poor outcomes of MAC disease treatment.

P2717
PCR based method for accurate diagnosis of mycobacterial disease and description of clinical profile of disease caused by non tuberculous mycobacteria
Anoma Siribaddana1, R.B. Vasanathriksn2, S.B P. Ashnada3.

Methods: A comparison of employment and primary care registries at National Jewish Health, Denver, USA, in the January 2006-June 2010 period was retrieved from databases. Pharmacokinetic measurements were done by high performance liquid chromatography and gas chromatography. Isolates were identified as MAC by AccuProbe assays. MICs were determined by the BacTec460 modulifecation method; synergy between rifampicin and ethambutol was assessed.

Results: Pharmacokinetic data, median MICs and pharmacodynamic calculations are given in Table 1. Simultaneous use of rifampicin significantly lowered serum concentrations of macrolides (30-60%) and moxifloxacin (10-15%).

Conclusions: Serum rifampicin, ethambutol and moxifloxacin concentrations attained effective levels in a minority of patients; rifampicin use exerts detrimental effects on pharmacokinetics of macrolides and moxifloxacin. This may partly explain the poor outcomes of MAC disease treatment.

P2718
High incidence of the Beijing strains among multi drug resistant isolates of Mycobacterium tuberculosis from extra pulmonary tuberculosis cases in northern India
Anand Kumar Maurya1, Surya Kant2, Vijaya Lakshmi Nag3, Ram Awadh Singh Kushiwahia, Taparn N. Dholea2.

Objectives: The aim of the study presented here was to investigate incidence of Beijing genotypic among MDR-TB isolates from extra pulmonary tuberculosis cases (EPTB) in Northern India.

Methods: A total of 756 specimens from patients of EPTB cases with varied presentation were studied. A total of 164 M. tuberculosis complex (MTB) isolates recovered during the period Sept 2007-Dec 2010 were tested for drug susceptibility against S/HRE by radiometric BACTEC method. MDR-TB isolates were sequenced in spolig and katG genes for mutation analysis. All MDR-TB strains were processed by genotypic method. The proportional of Beijing strains was significantly higher among MDR-TB strains (72.7%, p < 0.05). Genotypic analysis of spolig and katG gene revealed significantly high mutation rate among Beijing vs non Beijing strains (50% vs 33.4%, p < 0.05). While mutation for katG gene was common among Beijing vs. non Beijing strains (68.2% vs. 50%, p < 0.05). Conclusion: We found high incidence of Beijing strains among MDR-TB strains from EPTB cases in Northern India.

P2719
Identification of new immigrants to the UK for latent tuberculosis screening: A comparison of employment and primary care registries
Rakesh Punjabi, Haldar Pranabanish, Wollman Gerri. Department of Respiratory, Medicine, Institute for Lung Health, Glenfield Hospital, Leicester, Leicestershire, United Kingdom

Introduction: Comprehensive screening for latent M tuberculosis infection (LTBI) in immigrants relies on effective strategies for identifying at-risk groups. The utility of national registries has been suggested but not formally evaluated for this purpose.

Objectives: To compare and characterise profiles of immigrant registration on the UK National Insurance Number (NINO) and Flag-4 GP registries.

Methods: Retrospective analysis was conducted of both registries for Leicester between 2002-2009. Comparison between registries was performed on immigrants stratified by age at UK entry (<18yrs, 18-34yrs and ≥35yrs).

Results: The total number of immigrants registering was similar for NINO (47,000) and Flag-4 (46,653). Differences existed between the registries stratified by age. Flag-4 identified immigrants across all age ranges including children. In contrast, NINO was comprised of a greater percentage of young adults. The total number of younger adults identified with NINO was greater with a trend to significance (p=0.08). This suggests a proportion of immigrants to the UK for employment do not immediately register with a GP.

NINo overseas & Flag-registrations: Leicester 2002-2009

<table>
<thead>
<tr>
<th>&lt;18 years</th>
<th>18-34 years</th>
<th>≥35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>364</td>
<td>10674</td>
</tr>
<tr>
<td>Proportion of total</td>
<td>0.012</td>
<td>0.229</td>
</tr>
<tr>
<td>Difference in proportions (95% CI)</td>
<td>0.217 [0.213-0.221]</td>
<td>0.196 [0.190-0.202]</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: The UK NINO and Flag-4 registries provide complementary immigrant data in children and young adults that is relevant for TB services planning new immigrant screening.

P2720
Misdiagnosed pulmonary TB: Influencing factors and diagnostic chances in TB hospital
Zhanna Lushchik, Pavel Filimonov. Pulmonary TB Department, Nosovitskhir Research TB Institute, Nosovitskhir, Russian Federation Pulmonary TB Department, Nosovitskhir Research TB Institute, Nosovitskhir, Russian Federation

Differential diagnosis of pulmonary TB is still difficult. We found the tendency to overdiagnosis of pulmonary TB in TB hospital.

Purpose: Purpose of the study was to analyze causes of diagnostic errors and improve the quality of in-hospital management of patients supposed to having of pulmonary TB.

Methods: Noncomparative retrospective study, subject of interest were medical records of 136 most difficult cases, in which previously established diagnosis of pulmonary TB was rejected. The chances for establishment of true diagnosis and influencing factors were estimated.

Results: 1. Diseases, most often initially misdiagnosed as tuberculosis, were pneumonia (52%), lung cancer (20%). 2. The period from the disease manifestation up to establishment of final diagnosis was 84±7.2 days (mean±SD) days. 3. Clinico-radiological signs in these cases were more characteristic for TB, than for other pulmonary diseases. 4. False positive diagnosis is: “limited pulmonary opacity” (OR 1.75, p=0.003), pulmonary dissemination

502s
**P2724**

**Clinical characteristics and treatment outcomes of tuberculosis in the elderly**

Yeon Soo Kwon1, Su Young Chi1, Yu Il Kim1, Sung Chul Lim1, Yoo Duk Choo2

1Internal Medicine, Chonnam National University Hospital, Gwangju, Korea; 2Pathology, Chonnam National University Hospital, Gwangju, Korea

*Background:* The purpose of this study was to describe the differences clinical characteristics and treatment outcomes between elderly TB patients and young TB patients.

*Methods:* The medical records of 271 young (aged 20 to 64 at diagnosis) and 199 elderly (aged 65 and older) TB patients, who were newly diagnosed with and treated for TB from May 2008 to May 2010, were reviewed.

*Results:* Respiratory symptoms such as cough, sputum, and dyspnea and comorbid medical conditions such as cardiovascular disease, diabetes mellitus and chronic obstructive pulmonary disease were more frequent in elderly patients. In chest CT scan of pulmonary TB patients, findings of active TB such as nodules (< 30 mm in diameter), masses (> 30 mm in diameter), and cavities were less frequently found in elderly TB patients except consolidations. However in microbiological diagnosis, positive TB culture rates were higher in elderly TB patients. Of those with known results of drug sensitive test, 95% were found. However, 6% were more frequently found in younger TB patients. In adverse drug reactions, the incidences were not different between two groups except severe GI troubles which were more frequently developed in elderly TB patients. There were no significant differences in the rates of treatment success (97% vs. 93.7%, p=0.161), failure (0% vs. 0.7%, p=0.19), and deaths due to TB (0.5% vs. 1.1%, p=0.844) between two groups.

*Conclusions:* Elderly TB patients presented more frequent respiratory symptoms and showed less frequent active TB findings on chest CT scan. Treatment success rates of elderly TB patients were not inferior to those of younger TB patients without development of more frequent adverse drug reactions.

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**P2723**

**Risk factors for extrapulmonary tuberculosis**

José Sanchez1, Aurora Carvalllos2, Raquel Duarte3,4,5

1Palomar Hospital, Centro Hospitalar e Universitário de Coimbra- Hospital Geral, Coimbra, Portugal; 2Palomar Hospital, Centro Hospitalar e Universitario de Coimbra EPE, Vila Nova de Gaia, Portugal; 3Palomar Hospital, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; 4Department of Clinical Epidemiology, Predictive Medicine and Public Health University of Porto Medical School, Porto, Portugal

*Introduction:* Tuberculosis (TB) remains a major global public health problem and 20% of all cases are extrapolumonar. The purpose of this study was to identify risk factors associated with extrapulmonary tuberculosis.

*Methods:* We performed a transversal study involving all patients with extrapulmonary tuberculosis registered in a TB reference centre in northern Portugal, between January 2008 and January 2012. We evaluated demographic data, comorbidities, BCG vaccination status, previous treatment outcomes. Multivariable logistic regression was used to identify independent risk factors (p < 0.05).

*Results:* Among the 386 patients studied, 260 (67.4%) had pulmonary tuberculosis (PTB) and 126 (32.6%) had extrapulmonary TB (EPTB). Being older than 40 years old (OR=2.09, 95%CI: 1.29-3.38), female (OR=1.63, 95%CI=1.02-2.6) and HIV positive (OR=2.72, 95%CI=1.25-5.93) were independent risk factors for EPTB. Alcoholism (OR=0.30, 95%CI: 0.12-0.75) is associated with higher risk for TB. Previous liver disease (OR=22.36; 95%CI: 1.89-263.57) was an independent risk factor for peritoneal TB. HIV co-infection (OR=12.97; 95%CI: 1.71-48.42) and the presence of previous treatment (OR=7.62; 95%CI: 1.00-57.9) increase the risk of disseminated disease.

*Conclusion:* We identified independent risk factors for EPTB compared with TB. Recognizing risk factors associated with EPTB is essential to suspect of disease and may help to get an accurate diagnosis.

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**P2722**

**Comparative performance of interferon gamma release assays in detection of latent tuberculosis infection among health-care professionals**


1Microbiology Research Center and Department of Medical Microbiology, Avicenna (Bu-Ali) Research Institute and Ghaem University Hospital, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran; 2Center for Communicable Diseases Control, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; 3Department of Thoracic Surgery, Ghaem University Hospital, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran; 4Center for Communicable Diseases Control, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; 5Department of Medical Microbiology, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran; 6Immunology Research Center; Bu-Ali Research Institute, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran; 7Department of Medical Virology, Faculty of Medicine, Alzahri Jundishapur University of Medical Sciences, Ahvaz, Iran; 8Immunology Research Center; Bu-Ali Research Institute, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran

*Background:* The primary aim of the study was to compare the performance of three interferon gamma release assays (IGRA) in detection of latent tuberculosis infection (LTBI) in health-care professionals (HCPs).

*Materials and Methods:* A total of 450 HCPs working in the hospital wards with the highest number of admissions for patients with PTB were evaluated. The mean age of participants was 33.6 years and the male/female ratio was 57/84 (58.4%). Out of 95 eligible HCPs working in a university hospital in northeastern Iran and in hospital wards with the highest number of admissions for patients with PTB were evaluated. The mean age of participants was 33.6 years and the female/male ratio was 57/84 (88.4%) were bacille Calmette-Guérin (BCG) vaccinated at birth. The 95 HCPs, 43.2% were positive by TST, and about 29% by each of the IGRA. Of 53 (55.6%) individuals with a positive test, 15 (28.3%) were positive to all six tests and 26 (49.1%) were simultaneously positive to at least two tests. The global agreements (k) between TST-IGIT and T-SOT-IGIT with TST, and between the two IGRA were 0.73, 0.684, and 0.779 respectively. The concordance in interpretation of results was 80.9% for TST and 80.9% for IGIT. When considering the results, we would recommend concordance application of at least two tests for LTBI.

*Conclusions:* The TST is the most appropriate test for LTBI screening, comparing with the tuberculin skin test (TST).
277. New insights in pneumology – ERS inter-Assemblies late-breaking abstracts

P2726 Does adding telemonitoring to optimised management of chronic obstructive pulmonary disease (COPD) reduce hospital admissions? Randomised controlled trial

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Introduction: Previous trials of telemonitoring in COPD have been confounded by additional supportive clinical care in the intervention group. It is unclear if telemonitoring alone will improve clinical outcomes.

Aim: To determine if telephysically supported telemonitoring of COPD prevents hospital admissions when both groups received optimised care.

Trial design: Researcher-blind RCT.

Setting: UK primary care settings.

Methods: Patients with a COPD admission in the previous year were centrally randomised to telemonitoring or control. The primary outcome, assessed at 1 year, was time to first hospital admission with a COPD exacerbation. Other outcomes included number of days in hospital, death and health-related quality of life (St George’s Respiratory Questionnaire (SGRQ)).

Results: We randomised 256 patients (128 telemonitoring) to baseline characteristics and time in hospital to admission between the groups (adjusted hazard ratio for admission (reference=tele-group) 1.04 (95% CI 0.73 to 1.50). 61 patients in each group had an admission. There was no significant difference in the mean number of admissions (tele-group: 1.2 (SD1.9); bed days (tele-group: 9.4 (SD 19.1) vs usual 8.8 (SD 15.9)); deaths (tele-group: 16, control 21; p=0.38) or SGRQ at year (mean difference: 1.5 (-1.4 to 4.5))

Conclusion: When both groups received optimised care, telemonitoring did not reduce the time to a hospital admission or increase quality of life.

ISRCTN number: 96634935

Funding: Chief Scientist’s Office of Scottish Government.

P2727 Multicenter COPD registry for quality improvement and comparative effectiveness research

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Rationale: Studies evaluating quality, safety, effectiveness, and costs of care using registries linking electronic health records from diverse healthcare settings are attracting increasing interest because they can provide information more applicable to ‘real-world’ patients and clinicians.

Methods: The COPD Outcomes-based Network for Clinical Effectiveness and Research Translation (CONCERT) developed a multicenter COPD registry (COPD DataHub) linking 8 U.S. academic healthcare institutions. Inclusion criteria were based on age (>=40 yrs), ICD-9 billing codes, problem lists, medications, or spirometry data. We reported on Medicare and Medicaid beneficiaries with chronic obstructive pulmonary disease (COPD) with a prevalence of >4%, based on the condition being the reason for being enrolled in Medicare, as of January 2010. The prevalence of Charlson comorbid conditions was estimated. An in-person study visit was used to collect additional information, including height, weight, smoking status, symptoms, and lung function. Preliminary findings are presented here.

Results: In 226,261 patients, the five most common co-morbid conditions (highest estimated) were diabetes (32 and 23%), heart failure (26 and 11%), renal disease (20 and 9%), malignancy (20 and 12%), and peripheral vascular disease (16 and 8%). In 1,216 patients who completed the study visit, 73% were overweight or obese, 84% were ever smokers, 44% smoked >40 pack-years, 34% had chronic bronchitis symptoms, and 54% had fixed airflow obstruction (post-BD FEV1/FVC<70%).

Conclusions: Quality improvement and comparative effectiveness research in COPD should 1) include lung function testing to confirm the diagnosis, and 2) address a range of comorbid conditions, including overweight or obese body habitus and smoking-related behaviors. Given the high levels of comorbidity, heterogeneous treatment effects appear likely.

P2729 Latin America asthma insight and management (LA AIM): A survey of asthma patients in 4 Latin American countries and Puerto Rico

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Introduction: In 2011, we conducted a comprehensive asthma survey in Latin America. Asthma Insight and Management (LA AIM) survey was modeled on similar programs in the United States, Europe and Canada, and the Asia-Pacific region.

Aim: Face-to-face interviews lasting approximately 35min were conducted with respondents in a national probability sample. The survey was included 2000 patients (400 patients/location) in Latin America (Argentina, Brazil, Mexico, Venezuela) and Puerto Rico. Survey questions covered asthma burden, impact of asthma on patients; emotional burden; symptoms; seasonal influences on symptoms; triggers; most bothersome symptoms; and patient perceptions about current levels of control.

Results: More than 51,000 households were screened, and 2,169 respondents completed the LA AIM survey across the 5 locations. Respondents were predominantly female (67% for the region, proportion similar in each country). Mean age was 37y (for the region; 35-45y, range across countries). Mean age at diagnosis across locations was 15y; (Argentina:19y; Mexico and Puerto Rico:18y; Brazil:16y; Venezuela:11y). Dust was the most commonly reported trigger (61% overall), following by change in weather (41% overall).

Conclusions: The LA AIM survey provides a comprehensive view of the state of asthma across 5 distinct Latin American cultures. The survey reveals that asthma has a profound impact on patient health and quality of life, suggesting a continuing unmet need for asthma education in Latin America. Results were primarily similar across the region.

P2730 Cough, active smoking ever, smoking history of >10 packyears and wheezing/chest tightness should prompt COPD suspicion in cardiac patients who remain symptomatic despite adequate management

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Background: Coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD) share common risk factors and often coexist. Dyspnea, effort intolerance and chest tightness in CHD patients are readily attributed to cardiovascular disorder while COPD passes unnoticed. Proper COPD management optimizes patient’s outcome.

Aim: The aim of our study was to determine key features from history and physical examination that should raise COPD suspicion in persistently symptomatic cardiac patients.

Material and methods: Patients were recruited with respect to the following inclusion criteria: angiographically confirmed CHD, adequate cardiac management, ability to visit study site, expressed informed consent for study participation. Subjects were evaluated for: demographics, smoking, respiratory complaints (modified ECRHS questionnaire), airflow limitation (spirometry accompanied by reversibility test if applicable). COPD diagnosis was based on clinical presentation, history and post-bronchodilator FEV1/FVC<LLN.

Results: Among 206 subjects eligible for the study 33 (16%) were found to have COPD. COPD vs. non-COPD subjects did not differ in age, sex, BMI, waist circumference and tobacco exposure in general. Active smoking ever (OR 5.45, 95%CI 1.24-23.9), >10 packyears (OR 4.28, 95% CI 1.57-11.7), cough (OR 4.28, 95%CI 1.36-23.6) and wheezing/chest tightness (OR 3.38 95%CI 1.51-7.58) significantly increased COPD risk.

Conclusions: Longstanding history of active smoking ever, cough and wheezing/chest tightness in persistently symptomatic cardiac patients should raise the suspicion of concomitant COPD.

MONDAY, SEPTEMBER 3RD 2012

504s
P2731 The predictive value of the COPD assessment test (CAT) for acute exacerbations in patients with chronic obstructive pulmonary disease (COPD)

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Acute exacerbations significantly impair health-related quality of life (QoL) and productivity of patients with COPD. Predicting the probability of exacerbation may help in optimising COPD management. We evaluated whether the COPD Assessment Test (CAT) could predict the risk of future exacerbations of COPD. COPD patients with a history of exacerbation were recruited from 19 sites in four Asia Pacific countries. CAT score, Medical Research Council (MRC) dyspnea score, spirometry data, medical history, and exacerbation episodes were prospectively collected over six months. In 495 evaluable patients with a mean age of 69.4±8.8 years, 68% had at least one exacerbation over the study period. The baseline CAT score categorised into four severity groups showed a strong predictive value for time to first exacerbation (AUC=0.83). Time to first exacerbation was shorter with worsening category of CAT score (p<0.001; mean 19.9, 15.8, 10.4 and 4.5 weeks for CAT score categories of 0–9, 10–19, 20–29 and ≥30 respectively). The risk of future exacerbation was higher with worsening category of CAT score (p=0.04; adjusted relative risks: 1.0, 1.26, 1.33 and 1.45 respectively). The un categorised CAT scores, used as a continuous variable, found predictions of similar magnitude. In outpatients with COPD, the baseline CAT score showed a strong predictive value for time to first exacerbation. It also provided modest prediction of exacerbations in the following six months.

P2732 Sleep-related breathing disorders in patients with schistosomal cor-pulmonale

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Schistosomiasis has long been an endemic disease in Egypt and an important cause of pulmonary hypertension. Objectives: We aimed to investigate the clinical and polysomnographic features of sleep-related breathing disorders (SRBD) in patients with schistosomal cor pulmonale and to evaluate their effects on pulmonary hemodynamics. Patients and methods: We studied 10 stable patients with schistosomal pulmonary hypertension (mean age was 43.7) and 10 healthy volunteers matched. All underwent overnight polysomnography. Results: The mean AHI in patients group was 20/h while in the control group it was 2.3/h. 80% of the patients were found to have an AHI >10/h and 60% had moderate to severe sleep apnea (AHI >15/h). In addition, the majority of the patients (80%) spent ≥30% of the night with an arterial oxygen saturation <90%. SRBD were not correlated with anthropometric measures, spirometry nor with the typical symptoms of SA such as excessive sleepiness as assessed by ESS. More SRBD were not correlated with anthropometric measures, spirometry nor with the severity of PAH. The predictive value of the COPD assessment test (CAT) for acute exacerbations of COPD (COPD) could predict the risk of future exacerbations of COPD. COPD patients with a history of exacerbation were recruited from 19 sites in four Asia Pacific countries. CAT score, Medical Research Council (MRC) dyspnea score, spirometry data, medical history, and exacerbation episodes were prospectively collected over six months. In 495 evaluable patients with a mean age of 69.4±8.8 years, 68% had at least one exacerbation over the study period. The baseline CAT score categorised into four severity groups showed a strong predictive value for time to first exacerbation (AUC=0.83). Time to first exacerbation was shorter with worsening category of CAT score (p<0.001; mean 19.9, 15.8, 10.4 and 4.5 weeks for CAT score categories of 0–9, 10–19, 20–29 and ≥30 respectively). The risk of future exacerbation was higher with worsening category of CAT score (p=0.04; adjusted relative risks: 1.0, 1.26, 1.33 and 1.45 respectively). The un categorised CAT scores, used as a continuous variable, found predictions of similar magnitude. In outpatients with COPD, the baseline CAT score showed a strong predictive value for time to first exacerbation. It also provided modest prediction of exacerbations in the following six months.

P2733 SIIDS and idiopathic ALTE: Genetic similarities

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Background: Recent advances in molecular genetics have opened new perspectives in the definition of pathogenic mechanisms of SIIDS. Several studies, during the past decade, identified polymorphisms in the serotonin transporter (5HTT) (5-HTLPR, hydroxytryptamin transporter-linked polymorphic region, and S11T, intron 2 VNTR), the promoter region of MAOA (monoamine oxidase A), and DAT in an Italian SIIDS population. ALTE patients, IALTE (idiopathic ALTE) and controls. Methods: We enrolled 76 infants with an history of Apparent Life Threatening Event, distinguished in Idiopathic ALTE (IALTE) and Non Idiopathic ALTE (ALTE) by clinical, diagnostic and therapeutic data (12 channels polysomnography E Series Compumedics). Genotypes and allelic frequencies of DAT, MAOA and 5HTT were determined in ALTE and IALTE infants compared with data obtained from 150 healthy controls.

Results: No association was found between DAT polymorphism and ALTE/IALTE groups either in the genotype (p=0.25; p=0.112) nor in the allelic frequency (p=0.94; p=0.88). The comparison of MAOA genotypes and allelic frequency between ALTE and control group was not significant, on the opposite the comparison between IALTE and control group was statistically significant for the genotypes (P=0.09) and a tendency for allele (p=0.036). Analysis of 5HTT polymorphisms in IALTE remarked the pathogenetic role of L/L genotype (P<0.00001) and L allele (P<0.00001) as previously demonstrated in SIIDS.

Discussion: The CS decrease with breath hold time correlates with in vitro data showing CS decrease with RBC deoxygenation. To our knowledge, this is the first demonstration in humans of the effect of RBC oxygenation on the CS of dissolved 129Xe. Localisation of this technique may provide insight into regional RBC oxygen non invasively.

P2734 Measuring red blood cell oxygenation in vivo using hyperpolarized 129Xe MRI

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Introduction: Red blood cell (RBC) oxygenation plays an important role in cell survival. However, measuring this parameter in deep tissues is difficult. We report a method of detecting RBC oxygenation in vivo using MRI chemical shift (CS) of hyperpolarized (HP) 129Xe dissolved in RBCs explored previously in vitro (Mag Res Med 43;4(491) 2000).

Methods: 400mL of HP 129Xe mixed with 600mL N₂ was delivered to 3 healthy volunteers who inhaled the gas and held their breath. Spectroscopy was performed on a 3T Philips Intera every 3 seconds for the length of the breath hold. CS was extracted from fits to the spectra. Surrogate oxygenation was measured using an SpO₂ monitor.

Results: Example spectra from one volunteer early(red) and at end of breath hold(blue) are shown in Fig 1(left). The CS change between the tissue/plasma and the RBC peak are plotted as a function of time(green) in the panel right along with measured SpO₂ (blue). A decrease in the separation between these two peaks is seen over the course of the breath hold corresponding with a measured decrease in SpO₂. Similar trends are seen in data from all subjects.

505s
Development of an intervention algorithm in telemetrically supervised adaptation of positive airway pressure therapy for OSAS

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Introduction: The acceptance of positive airway pressure therapy (PAP) is a major clue to successful OSAS therapy. Telemedicine is a novel tool to supervise PAP use at the patient’s home. We report on treatment results with an intervention scheme developed to guide patients during the first month of telemetrically supervised PAP adaptation.

Methods: After mask adaptation and explanation of the PAP devices (ResMed Inc, Australia), newly diagnosed OSAS patients were equipped with telemedicine (ResTraxx from ResMed, Munich, Germany). The automatically downloaded 4h in 55% of patients. A total of 174 calls were analyzed by antibody radioimmunoassay. PAH patients had elevated PIIINP, CITP, MMP-9 and TIMP-1 levels measured by ELISAs. PHIP was measured by antibody radioimmunoassay. PAH patients had elevated PHIP, CITP, MMP-9 and TIMP-1 levels suggesting active collagen metabolism (Table 1). PHIP levels were higher in WHO FC-IV as compared to WHO FC-I/II PAH patients (p<0.01). PHIP levels negatively correlated with six-month distance (R=-0.3, P=0.008), and positively correlated with right atrial pressure (R=0.35, P=0.002) and BNP levels (R=0.25, P=0.02).

Circulating procollagen markers may provide a novel non-invasive method of documenting active collagen synthesis reflective of severe disease in PAH.

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P2740
Prevention of RSV infection in infants from the high-risk groups in Moscow: The first season’s results
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Aim: Analysis of efficacy and safety of immunization with palivizumab of infants from the high-risk groups of severe respiratory syncytial viral (RSV) infection carried out during 2012 infection season in Moscow.

Methods and materials: Immunization against RSV infection with palivizumab was conducted for the first time in six Moscow hospitals from January to May 2012. The total number of infants immunized was 156 aged from 15 days to 1 year 11 months. Patients received from 1 to 4 shots with treatment-free interval 30±5 days: 1 infant was immunized four times, 139 – three times, 9 children – twice, 7 children – once. The reasons for discontinuation of immunization after 1 and 2 shots were not connected to medical conditions. 139 (89.1%) of all infants were premature, including 42 (26.92%) with extremely low birth weight, 83 (53.21%) with bronchopulmonary disease, 19 (12.18%) with congenital heart diseases.

Efficacy of immunization was estimated on a basis of the average monthly frequency of lower respiratory tract infections and hospitalization within three months ahead and three months during prophylaxis. A frequency of adverse events was used for safety analysis.

Results: Immunization with palivizumab led to decrease of the average monthly frequency of lower respiratory tract infections (from 0.064 to 0.014) and hospitalization (from 0.048 to 0.031). The following adverse events were reported: short-term, low-grade fever, anxiety, rhinitis, upper respiratory tract infection, frequency of lower respiratory tract infections and hospitalization within three months ahead and three months during prophylaxis. A frequency of adverse events was used for safety analysis.

Conclusion: Immunization against RSV infection with palivizumab conducted during the 2012 infection season was safe and effective.

P2741
Association of airway bacterial load with inhaled corticosteroid dosage in stable COPD
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Inhaled corticosteroids (ICS) are commonly used in COPD, either alone or in combination with bronchodilators to reduce exacerbation frequency, but may also increase risk of pneumonia (Calverley et al, NEJM, 2007; Wedzicha et al, JRCCM, 2008) which is not well understood. Lower airway bacterial colonisation is often present in stable COPD and may predispose to pneumonia. We investigated the relationship between airway bacterial load and ICS dose in stable COPD patients.

We quantified typical bacterial load using a validated PCR (for H. influenzae, S. pneumoniae, M. catarrhalis) from the sputum of 47 stable COPD patients positive for at least one of these species. Patient characteristics: Mean(SD) age 71(±8.0) years; Male gender 64%; Current smoker 34%; FEV1 49(±18.4%) predicted. Median (IQR) beclomethasone-equivalent dosage was 2000 (400-2000) g g daily. Higher airway bacterial load was correlated to higher ICS dosage (corrected for smoking status and FEV1 % predicted (p=0.022).

For the first time we have shown that the use of high ICS dose is associated with higher airway bacterial load and may therefore play a part in increasing susceptibility to pneumonia in COPD.

P2742
Pleural irrigation trial (PIT): Standard care versus pleural irrigation, a randomised controlled trial in patients with pleural infection
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Background: Pleural infection remains common with an increasing incidence and high mortality. Despite chest tube drainage and antibiotic therapy up to 30% of patients will die or require surgery. Case reports suggest that irrigation of the pleural space with saline may be beneficial but this has never been tested in the form of a randomised controlled trial.

Method: Randomised controlled pilot study comparing standard care plus saline irrigation, with best standard care alone, in patients with pleural infection requiring chest tube drainage, who had a residual pleural collection on baseline CT thorax. Primary outcome was percentage change in CT pleural volume from day 0 to day 3. Secondary outcomes included referral for surgery, hospital stay & adverse events.

Results: 65 patients approached, 38 randomised, 3 excluded. Saline irrigation resulted in significant reduction in CT pleural collection volume compared to standard care – Irrigation group 29.2% reduction (95% CI 16.2- 62) vs Standard care 13.9% (95% CI 4.1 - 26.3) p<0.04. There was also a significant reduction in the need for thoracic surgery in the irrigation group 2/18 vs 9/17 p=0.01 (OR 0.03, 95% CI 1.6-51.9). No differences were seen in length of hospital stay or fall in inflammatory markers (CPR, WCC and procalcitonin). Safety profile of saline irrigation was good with no serious complications and similar adverse events between groups.

Conclusion: Saline irrigation improves fluid drainage in pleural infection, leading to reduction in referral for surgery. This study now needs to be repeated as a large multicentre RCT using the hard endpoints of mortality and length of hospital stay.

306. New drug targets and pre-clinical models for respiratory diseases

2803
Late asthmatic response is modulated by TRPA1 antagonists in ovalbumin-induced bronchoconstriction in anaesthetized guinea pigs
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In animal models of asthma, ovalbumin (OVA) aerosol results in bronchoconstriction characterized by a histamine-related early asthmatic response (EAR) followed by a neuropeptide-related late asthmatic response (LAR) which can be modulated by transient receptor potential (TRP) channel A1 antagonists (Thorax. 2012. 67, 19-25).

The aim of the study was to assess the potential of two TRPA1 antagonists on the EAR and LAR in OVA-induced bronchoconstriction in anaesthetized guinea pigs.

Bronchoconstriction was induced by intra-tracheal administration of a single dose of OVA (50 μg/kg) and lung resistance recorded for 30 minutes. The animals were pre-treated with pyrilamine (2 mg/kg i.v.) or its vehicle (saline) 10 min before OVA. The TRPA1 antagonists HC-030301 and A-967079 or their vehicle (0.5% m-cellobiulose) were administered i. h before OVA. Without pyrilamine pre-treatment, OVA induced a fast increase in lung resistance (max. 60±13 ml overlap after 1 min) which was not reduced by the TRPA1 antagonists. Under pyrilamine pre-treatment, OVA induced a slow increase in lung resistance (max. 33±10 ml overlap at the end of the recording). HC-030301 (1 μg/kg – 1 mg/kg) dose-dependently inhibited the non-histamine-related OVA-induced bronchoconstriction (ED50 = 0.01 mg/kg) with a maximum bronchoprotection of 76% at 0.03 mg/kg (p<0.05). A-967079 (1 μg/kg – 1 mg/kg) displayed the same profile as HC-030301 (ED50 = 0.01 mg/kg) with a maximum bronchoprotection of 78% at 0.03 mg/kg (p<0.05).

This study shows that the EAR is histamine related, while the LAR is modulated by the TRPA1 channel in OVA-induced bronchoconstriction in anaesthetized guinea pigs.
2804
Effect of nilotinib on airway smooth muscle thickening in a murine model of chronic asthma
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Background: Asthma is characterized by airway inflammation and remodeling. The tyrosine kinase inhibitor nilotinib was developed to inhibit BCR-ABL kinase activity; however, it also has potent inhibitory activity against the c-Kit and platelet-derived growth factor receptor (PDGFR). The present study was aimed to determine whether nilotinib suppresses airway smooth muscle (ASM) remodeling and whether its effect is associated with c-Kit and PDGFR pathways.
Methods: We developed a mouse model of airway remodeling, which includes smooth muscle thickening, in which ovalbumin (OVA)-sensitized mice were repeatedly exposed to intranasal OVA administration twice a week for 3 months. Mice were treated with nilotinib during the OVA challenge.
Results: Mice chronically exposed to OVA developed sustained eosinophilic airway inflammation compared with control mice. In addition, the mice chronically exposed to OVA developed features of airway remodeling, including thickening of the peribronchovascular and perivascular muscle layer. Administration of nilotinib significantly inhibited eosinophilic inflammation and ASM remodeling in mice chronically exposed to OVA. Nilotinib treatment significantly reduced the expression of p-c-Kit, p-PDGFR, and p-ERK1/2. The expression levels of genes encoding c-Kit and PDGFR were also reduced by nilotinib treatment.
Conclusions: These results suggest that nilotinib administration can prevent not only airway inflammation, but also airway remodeling associated with chronic allergic challenge. Nilotinib may provide a clinically attractive therapy for chronic severe asthma.

2805
A comparison of anti-inflammatory compounds in a steroid-insensitive mouse model of chronic asthma
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The effects of PDE4 and p38 inhibitors were compared to steroids in a robust model of lung inflammation induced by 4 days of exposure to tobacco smoke (TS). Methods: Mice were exposed to either air or TS for 4d and were killed 24h after the last exposure, the lungs lavaged and cells counted. Compounds were given at maximal efficacy doses as defined in a mouse LPS model. Steroids were dosed orally (Dexamethasone, 300 μg/kg 1hr pre- and 6hr post-TS); or intra-nasally (Flunisolide propionate (FP), budesonide (BUD) 300 μg/kg 1hr pre-TS). Rosmarinast (ROF) reduced TS-induced inflammation (p<0.05). The p38 inhibitor (BIRB-796) was orally (1mg/kg) dosed 1hr pre- and 6hr post-TS.
Results: Mice caused cellular infiltration into the lung which was reproducible across multiple studies. Oral or i.n. dosed steroids did not inhibit the inflammation (p<0.05 total cell and neutrophil (neut) count). Body weight significantly decreased over the 4d (FP 6%, BUD 11%, DEX 11%; all p<0.05) confirming steroid availability and efficacy. ROF reduced TS-induced inflammation when given i.n. (totals -50%, neuts -60%; both p < 0.05) or orally (totals -50%, neuts -60%; both p < 0.05). The p38 inhibitors were effective dosed orally (BIRB-796 -40% i.n. -55%) or i.n. (PF totals -50%, neuts -45%; all p < 0.05).
Conclusions: TS-exposure for 4'd induced a steroid-insensitive lung inflammation which was reproducibly inhibited by PDE4 and P38 inhibitors; although neither caused a total inhibition of the inflammation, suggesting that there is scope to investigate more efficacious mechanisms and combinations within this model.

2806
Synbiotics reduce airway inflammation and improve airway function in a mouse model for COPD
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Background: Good gut health plays an important role in maintaining immunity in and beyond the gastrointestinal tract. Respiratory disorders can be influenced by gut microbiota. Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide. The disease is characterized by a progressive airflow limitation caused by an abnormal inflammatory response. Aim of this study is to investigate the effectiveness of specific dietary fibers and lactic acid producing bacteria in a mouse model for COPD.
Methods: Male BALB/c mice were instilled intra nasally (i.n.) with lipopolysaccharide (LPS, 10μg) or with LPS (1g/kg) 3 times per week for 16 days. Mice were treated 5x per week by intra-gastric supplementation with: 1) Prebiotic fiber mixture of short-chain fructooligosaccharides and long-chain fructooligosaccharides (GOS/FOS), 2) Probiotic Bifidobacterium or 3) Synthetic combination of GOS/FOS and Bifidobacterium. Broncho alveolar lavage (BAL) samples were analyzed for airflow inflammation. Airway function was measured by plethysmography in anesthetized mechanically ventilated mice.
Results: LPS treatment significantly induced inflammatory cell influx in the bronchoalveolar lavage (BAL) fluid. Treatment with either GOS/FOS or GOS/FOS
combined with Bifidobacterium was able to reduce the influx of macrophages and neutrophils into BAL fluid. Only treatment with synbiotics was able to attenuate the LPS induced reduction in airway function.
Conclusion: These findings suggest that a combination of Bifidobacterium and GOS/FOS might be beneficial as nutritional intervention in patients suffering from COPD.

2807
Mice with immortelle cilia spontaneously cough due to mechanical stimuli of postnasal drip
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Background: The underlying mechanisms of cough in patients with rhinosinusitis are poorly understood. We reported that tubulin tyrosine ligase-like family member 1 gene (Ttll1) knockout (KO) mice showed disorders of ciliary motility resulting in rhinosinusitis together with cough reflex. Aim: To examine mechanisms of cough in Ttll1-KO mice.
Methods and results: We pathologically searched for the causes of cough and examined structural changes of the airway in KO mice. We observed that Ttll1-KO mice was reproducibly inhibited by rapidly adapting receptor (RAR), decreased cough, while capsaicin, an antagonist of the transient receptor potential vanilloid subfamily 1, did not. Tolfudoxacin, a fluoroquinolone antibiotic, improved nasal inflammation but accumulation of mucus and cough remained. To prove that mucus stimuli evoke cough, artificial PND were made to evoke cough in WT mice. WT mice distinctly coughed due to artificial PND. Blue dye and contrast material were administered to study nasal clearance and movement of mucus. We confirmed that nasal ciliary clearance was decreased in KO mice. Further, blocking nasal discharge from flowing to the larynx completely inhibited cough of KO mice. Conclusions: Mechanical stimulation to larynx due to PND was transduced to the central nervous system via RAR and evoked cough in Ttll1-KO mice. Ttll1-KO mice may serve to reveal the mechanisms of cough in patients with PND and to develop new antitussive drugs.

2808
Intratracheal administration of dry powdered low-molecular-weight chitosan/siRNA complexes suppressed gene expression in the airway and metastatic tumors in murine lung
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Introduction: There is an increasing number of efforts to deliver small interfering RNA (siRNA) to lung. Although many different formulations with siRNA have been optimized in vitro studies, only a few have been reported successful in vivo.
Objectives: As a carrier of siRNA, we chose low-molecular-weight chitosan (LMWC) and succeeded in producing dry powder of LMWC/siRNA complexes. In the present study, we tried to determine whether intratracheal administration of dry powdered LMWC/siRNA complexes suppressed gene expression in murine lung.
Methods: Dry powdered LMWC/siRNA targeting green fluorescent protein (GFP)-siRNA and Lewis lung carcinoma cells stably expressing GFP (LLC-GFP) were prepared. Dry powder of LMWC/GFP-siRNA complexes was intratracheally administered to GFP transgenic mice and the C57BL/6 mice injected with LLC-GFP cells through tail vein. The fluorescence in the lung tissue sections was analyzed with a BIOREVO fluorescence microscope (BZ-9000; KEYENCE, Japan).
Results: Intratracheal administration of LMWC/GFP-siRNA complexes was found to suppress the fluorescence level of bronchial epithelium in the lung of GFP transgenic mice. It was also effective at reducing the fluorescence level in metastatic lung tumors consisting of LLC-GFP cells.
Conclusion: The results of the present study suggest that LMWC is an effective carrier for siRNA delivery to the lung, and powdered LMWC/siRNA complexes may become a promising tool to knock-down a specific gene expression in lung diseases such as bronchial asthma, COPD, and metastatic lung tumors.
Background: Protease inhibition has been shown to prevent development of fibrosis in several organs. Effects of protease inhibitors (PI) on lung fibrosis are controversial and cytoxic side effects of the inhibition of proteasomal degradation in the cell cannot be excluded.

Hypothesis: Administration of PI allows efficient drug delivery to the lung and prevents development of pulmonary fibrosis without systemic toxicity.

Methods and results: ONX0912 (ONX), a new irreversible PI was evaluated in comparison to bortezomib, the only FDA-approved PI, with regard to cytotoxicity and proteasomal inhibition in the cell line A549. Primary lung fibroblasts were isolated from proteasome reporter mice (ODD-luc) and characterized using MITT survival, and proteasome activity assays. The ODD-luc reporter accumulates upon proteasome inhibition and can be quantified by bioluminescence reflecting the actual degree of proteasome inhibition in the cell.

While bortezomib had strong cytoxic effects, ONX only partially inhibited the proteasome at low doses but efficiently blocked fibroblast function without affecting cell viability of fibroblasts or epithelia cells. An optimal nontoxic dose of ONX was obtained after intratracheal instillation into ODD-luc mice. This dose then was applied locally into the lung of ODD-luc mice with bleomycin induced fibrosis and therapeutic effects were investigated by histological analysis of the lungs.

Conclusion: ONX provides antifibrotic effects in murine lung fibroblasts in a non-toxic dose range. Local administration of ONX into the lungs partially inhibits the proteasome without toxic side effects and can be regarded as a promising approach to inhibit pulmonary fibrosis.

2810 Benefits of dual bronchodilution with QVA149 once daily versus placebo, indacaterol, NVA237 and tiotropium in patients with COPD: The SHINE study

Eric Bateeman 1, Gary T. Ferguson2, Neil Barnes 3, Nicola Gallagher 4, Yulia Green4, Rachael Horton 4, Michelle Henley4, Donald Banerji5.
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Background: QVA149 is a novel once-daily dual bronchodilator combining the LABA indacaterol and the LAMA NVA237 (glycopyronium) in development for COPD.

Methods: In a double-blind study, 2141 patients with moderate-to-severe COPD were randomized (2:2:2:1) to receive QVA149 110/50μg, indacaterol (IND) 150μg, NVA237 5μg (NVA), open-label tiotropium (TIO) 18μg or placebo (PBO), for 26 weeks. The primary endpoint was trough FEV1 with QVA149 vs IND, NVA and TIO at week 26.

Results: 89% patients completed the study. Trough FEV1 at Week 26 was significantly greater with QVA149 vs PBO, IND, NVA, TIO and mean difference (200, 70, 90 and 80mL, respectively; p<0.001). Significant improvement was also seen with QVA149 in other outcome measures evaluating lung function, dyspnea, health status and rescue medication use (table).

2811 Multidimensional approach to non-cystic fibrosis bronchiectasis. The FACED score

Miguel Angel Martinez-Garcia 1, Javier De Gracia-Roldán 2, Montserrat Vendrell-Relat 3, Rosa Girón 4, Luis Maiz 5, David de la Rosa 6, Casilda Olivera 7, 1 Pneumology Service, La Fe University Hospital, Valencia, Spain; 2 Pneumology Service, Vall Hebron University Hospital, Barcelona, Spain; 3 Pneumology Service, Josep Trueta University Hospital, Girona, Spain; 4 Pneumology Service, La Princesa University Hospital, Madrid, Spain; 5 Pneumology Service, Ramón y Cajal University Hospital, Madrid, Spain; 6 University Hospital of Bremen, Germany; 7 Pneumology Service, Carlos Haya University Hospital, Málaga, Spain

Background: The severity of non-cystic fibrosis (NCF) bronchiectasis cannot be adequately quantified by analyzing one single variable.

Objective: To develop and validate an easy-to-use multidimensional score that classifies the severity of bronchiectasis according to its prognosis.

Methods: Multicenter study in an initial cohort of 819 patients diagnosed with NCF bronchiectasis by HRCT scan. 397 subjects were selected at random (construction cohort) and 422 were the validation cohort. Outcome: 5-year all-cause mortality after diagnosis. From an initial set of 30 variables, those included in the final score were selected using a logistic regression analysis and dichotomized to facilitate the score’s interpretation.

Results: Mean age: 58.7 yrs (56% women).154 deaths during follow-up. The final 7-point calculated score (FACED score) incorporated 5 dichotomized variables (OR[95%IC]: FEV1; predicted % (F, cut-off point 50%; OR:5.2 [2.8-9.8]; maximum value:2 points); age (A, cut-off point: 70 yrs; OR: 4.9 [2.7-9.3]; maximum value:2); chronic colonization by P. aeruginosa (C, OR: 2.4 [1.3-4.6]; maximum value:1); radiological extension (E,n number of lobes affected; cut-off point at 2 lobes; OR:1.9 [1.3-3.5]; maximum value:1) and dyspnea (D, cut-off point at grade II on the MRC scale; OR:2.8 [1.5-5.2]; maximum value:1).No differences were found between the ABC-ROC (prognostic value) of the construction cohort: 0.87 [0.82-0.91] and validation cohort 0.83 [0.78-0.89]. All centers had an ABC-ROC>0.8.

Conclusions: This easy-to-use multidimensional grading system proved capable of accurately classifying the severity of bronchiectasis according to its prognosis.

2812 Clostridium difficile infection (CDI): Are junior doctors aware of risk factors and markers of severity?

Clara Addison, Tony Jordan. Respiratory Medicine, University Hospital North Staffordshire, Stoke-on-Trent, Staffordshire, United Kingdom

Introduction: There are approximately 20 000 cases of CDI in England per annum. Lower Respiratory Tract Infections are the main indication for antibiotic prescription. In order to reduce CDI, it is essential that doctors are able to identify patients at risk of CDI to facilitate appropriate antibiotic prescribing. 2 Trust’s clinical guidance on CDI informs on markers of severity but not risk factors. We sought to determine the level of knowledge of both among doctors based on a Respiratory ward including clinical guidelines as a conduit of knowledge.

Methods and results: Using a questionnaire 19 doctors and 5 fourth and fifth year medical students were asked to identify risk factors and markers of severity for CDI. 1st year doctors identified 36% of risk factors, 28% of severity markers; senior house officers 38% and 24%; registrars 47% and 21%; medical students 41% and 21%.

Conclusions: Knowledge of risk factors and severity markers for CDI amongst doctors and medical students on the Respiratory ward is poor. Clinical guidance is not a reliable conduit of knowledge. To raise awareness, information should be relayed more directly e.g. at induction.

References:

2813 The respiratory microbiome in chronic obstructive pulmonary disease (COPD) exacerbations: Relationships with clinical characteristics

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Background: There has been recent interest in the significance of the respiratory microbiome in COPD.

Methods: Within an observational COPD study, spontaneous and/or induced sputum samples were collected from 283 patients at baseline and at exacerbation assessment. 16sRNA sequencing was performed on samples from the first exacerbation of 172 patients. The COPD exacerbation sample was compared to the baseline sample from each individual.

Conclusions: This study is the first to comprehensively profile the respiratory microbiome in the context of COPD exacerbation.
Admission glucose levels predict an adverse outcome in CAP in patients without known diabetes. Hence, acute hyperglycemia may identify patients particularly in need of intensified care to reduce mortality in CAP.

**Conclusion:** Long-term use of ICS in patients who develop CAP is associated with lower incidence and less severity of parapneumonic effusion regardless of the baseline chronic respiratory condition.

Supported by: CB06-Eis-ICa-CH0606/0028 and IDIBAPS.

**2816**

**Pulmonary immunostimulation with macrophage-activating lipopeptide-2 in influenza-A-virus infected mice increased survival of subsequent pneumococcal pneumonia.**

Karin Repp1, Peter Radinicz1, Thomas Tschernig1, Thorsten Wolf1, Achim Gruber4, Norbert Suttorp5, Martin Witzenrath1. 1Department of Infectious and Respiratory Diseases, Charité Berlin, Berlin, Germany; 2Institute of Anatomy and Cell Biology, Medical Faculty of the Saarland University, Homburg/Saar, Germany; 3Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany; 4Institute of Veterinary Pathology, Freie Universität Berlin, Germany; 5Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, Netherlands

**Rationale:** Secondary bacterial infections in the course of seasonal influenza virus epidemics are associated with high morbidity and mortality, and Streptococcus pneumoniae is the most prevalent causal pathogen. Local immunosuppression due to pulmonary influenza virus infection has been discussed as major cause in the pathogenesis of secondary bacterial lung infection. Thus, specific local stimulation of the pulmonary innate immune system might improve host defense against secondary bacterial pathogens.

**Methods:** Influenza-AH1N1/PR/09/04-virus infected female C57BL/6 mice received the TLR-2 ligand macrophage-activating lipopeptide-2 (MALP-2) intra-tracheally 24h prior to transnasal infection with S. pneumoniae.

**Results:** Intratracheal application of MALP-2 increased pro-inflammatory cytokine and chemokine release and enhanced recruitment of leukocytes, mainly neutrophils in the alveolar space of influenza virus infected mice. After secondary pneumococcal infection, Influenza-A-virus infected mice pretreated with MALP-2 showed increased survival rates compared with untreated influenza infected mice. Notably, levels of pro-inflammatory cytokines and leukocytes were comparable in bronchoalveolar lavages of virus infected mice treated with MALP-2 and untreated infected controls. Further, MALP-2 significantly reduced bacterial numbers in the lung tissue without changing pulmonary viral load.

**Conclusion:** Local immunostimulation with MALP-2 in influenza virus infected mice improved pulmonary bacterial elimination and increased survival in secondary pneumococcal pneumonia.

**2817**

**Safety and pharmacokinetics of two dose strengths of ciprofloxacin dry powder for inhalation (DPI) in patients with moderate to severe COPD.**

Heiko Stass1, Johannes Nagelschmidt2, Henrik Watz2, Anne Marie Karsten1. 1Clinical Pharmacology, Ruhr University, Bochum, Germany; 2Pulmonary Research Institute (PRI), Hospital Grosshansdorf, Germany

**Introduction:** Ciprofloxacin dry powder for inhalation (DPI), formulated using Novartis' PulmoSphere™ technology for pulmonary delivery via a T-326 inhaler, is under investigation in various respiratory tract disorders.

**Aim:** To compare the safety and PK of two dose strengths of ciprofloxacin DPI in patients with COPD.

**Methods:** In a randomized, phase I, double-blind, crossover study, 12 (8m/4f) adults with GOLD stage II or III COPD received a single dose of 32.5 mg and 48.75 mg ciprofloxacin DPI (corresponding to 50 mg and 75 mg dry powder, respectively). The washout period was 7–14 days between doses.

**Results:** There were no severe or serious AEs nor clinically relevant differences in incidence or severity of AEs between the doses, most being mild. Drug related AEs (bitter taste) occurred in 7 and 6 patients after 32.5 mg and 48.75 mg ciprofloxacin DPI, respectively. The PK (Table) was similar to previous studies, showing high and variable lung exposure at low systemic exposure.

**Table 1**

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*a Geometric means/SCV. AUC(0–∞)-Cmax t1/2 tmax, h, median.

**Conclusions:** Ciprofloxacin DPI was well tolerated in patients with moderate chemistry and microbiological variables. Patients were classified whether they received prior long term ICS treatment or not.

**Results:** 659 patients (18%) were treated with ICS before diagnosis of CAP (ECOPD: 56%). Long-term use of ICS was significantly associated with less incidence of parapneumonic effusion compared to those without prior ICS treatment 5% vs. 12%, p<0.001. Multivariate analysis adjusted by sex, age, comorbidities and CAP severity showed a significant association between ICS treatment and lower incidence of pleural effusion (OR 0.42 (95% CL 0.28-0.64, p<0.001). Prior treatment with ICS was significantly associated with lower incidence of empyema compared to those without treatment (5% vs 16%, p<0.001).

**Conclusions:** Long-term use of ICS in patients who develop CAP is associated with lower incidence and less severity of parapneumonic effusion regardless of the baseline chronic respiratory condition.

Supported by: Cb06-Eis-icua-Cb0606/0028 and IDIBAPS.

**2818**

**Pulmonary immunostimulation with macrophage-activating lipopeptide-2 in influenza-A-virus infected mice increased survival of subsequent pneumococcal pneumonia.**

Karin Repp1, Peter Radinicz1, Thomas Tschernig1, Thorsten Wolf1, Achim Gruber4, Norbert Suttorp5, Martin Witzenrath1. 1Department of Infectious and Respiratory Diseases, Charité Berlin, Berlin, Germany; 2Institute of Anatomy and Cell Biology, Medical Faculty of the Saarland University, Homburg/Saar, Germany; 3Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany; 4Institute of Veterinary Pathology, Freie Universität Berlin, Germany; 5Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, Netherlands

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**2817**

**Safety and pharmacokinetics of two dose strengths of ciprofloxacin dry powder for inhalation (DPI) in patients with moderate to severe COPD.**

Heino Stass1, Johannes Nagelschmidt2, Henrik Watz2, Anne Marie Karsten1. 1Clinical Pharmacology, Ruhr University, Bochum, Germany; 2Pulmonary Research Institute (PRI), Hospital Grosshansdorf, Germany

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**Results:** There were no severe or serious AEs nor clinically relevant differences in incidence or severity of AEs between the doses, most being mild. Drug related AEs (bitter taste) occurred in 7 and 6 patients after 32.5 mg and 48.75 mg ciprofloxacin DPI, respectively. The PK (Table) was similar to previous studies, showing high and variable lung exposure at low systemic exposure.

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*a Geometric means/SCV. AUC(0–∞)-Cmax t1/2 tmax, h, median.

**Conclusions:** Ciprofloxacin DPI was well tolerated in patients with moderate
to severe COPD with no clinically relevant differences between the two dose strengths. Increased systemic exposure from the 48.75 mg dose was not matched by increased lung exposure. PK data indicate that the lower dose produced similar drug concentrations in the lung, with less powder inhaled.

2818

T cells in peripheral blood during viral acute exacerbation of COPD

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Introduction: Exacerbations in COPD patients increase premature mortality. The main cause of AECOPD are viral infections however, the type of predominant cellular immune response is unknown. Objective: To quantify the T cell subpopulations in peripheral blood of patients with viral AECOPD and compare them with patients in a stable disease (COPD) and healthy controls (HC).

Methods: We included 82 patients from the cohort of COPD Clinic, between May 2009 and December 2011. 49 of them were exacerbated and we included 19 HC. Viral diagnosis was performed by using real-time PCR and we used flow cytometry to determine T-cell subpopulations. Differences between groups were evaluated by Kruskal-Wallis and we performed a post-hoc U-Mann-Whitney test.

Results: 26 patients (53%) had a viral exacerbation (Influenza A 54%, Coronavirsus 14%, Influenza B 7%, RSV 7%, H1N1 7%, MPV 4%). In these patients predominated the Th1 response 8.6 (6.2-11) versus COPD 2.5 (1.3-4.29) and HC 1.2 (0.8-1.4) p<0.0001. The TCR8 response has a predominance of Th1 AECOPD 11.2 (7.1-13), COPD 2.8 (1.9-4.2) and HC 1.0 (0.5-2.2) p<0.0001 and Tc1 AECOPD 7.6 (4.1-10), COPD 1.7 (1.1-2.8), HC 1.1 (0.8-1.2) p<0.0001.

Conclusions: Our data show a polarization Th1, Tc1, Tc2 and Tc17 in AECOPD patients suggesting the involvement of these populations in the cellular immune response during viral infections. We did not find a higher prevalence of H1N1 infections in patients in the cohort.

308. Idiopathic pulmonary fibrosis

2819

Phase 2 trial of FG-3019, anti-CTGF monoclonal antibody, in idiopathic pulmonary fibrosis (IPF): Preliminary safety and efficacy results

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Introduction: FG-3019 is a novel anti-fibrotic agent, is well tolerated by subjects with IPF. No drug-related SAEs have been reported to date. Promising results of measurement of quantified lung fibrosis scores and FVC warrant pursuing the clinical trial with a higher dose of FG-3019 to further assess safety and efficacy in subjects with IPF.

Methods: A randomised, double-blind, placebo-controlled, Phase 2 prospective, open label study of FG-3019 (15 mg/kg IV every 3 weeks for 45 weeks) in subjects with well-defined IPF (duration ≥5 years, evidence of disease progression during the preceding year, FVC ≥50% predicted, DLCO ≥30% predicted, and 10–50% parenchymal fibrosis by HRCT). Treatment response was assessed by changes in extent of parenchymal disease (HRCT and FVC).

Results: 54 subjects (males 83%, mean age 67 years, median FVC % predicted 63.2%) were enrolled. Quantified HRCT scores of whole lung fibrosis (QLF) and all abnormal interstitial lung disease (QILD) at week 24 showed decreases from baseline greater than analytical variability (2.2%) in 6 (24%) and 8 (32%) of 25 subjects, respectively. Changes in both QLF and QILD score were significantly correlated with changes in FVC % predicted (for QILD, r=0.55, p<0.004). Mean decreases in FVC % predicted were less than in historical controls. Safety findings to date include 13 SAEs (none drug-related), 1 acute exacerbation, 9 respiratory-related hospitalizations, and 3 deaths (all related to IPF).

Conclusions: FG-3019, a novel anti-fibrotic agent, is well tolerated by subjects with IPF. No drug-related SAEs have been reported to date. Promising results of measurement of quantified lung fibrosis scores and FVC warrant pursuing the clinical trial with a higher dose of FG-3019 to further assess safety and efficacy in subjects with IPF.

2820

Analysis of lung function and survival in RECAP: An open-label extension study of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis

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Introduction: RECAP is an open-label extension study evaluating long-term treatment with PFD in IPF patients who completed one of the CAPACITY (CAP) trials.

Objective: Further examine the effect of PFD on lung function and survival in patients with IPF.

Methods: PFD 2403 mg/dL was administered orally in 3 equally divided doses. Forced vital capacity (FVC) was measured at baseline and Wks 12, 36, and 60. To facilitate comparison with CAP outcomes, analyses were based on patients newly-treated with PFD in RECAP who had baseline FVC and DLco values that met CAP entry criteria.

Results: A total of 178 patients were newly-treated with PFD in RECAP and had baseline values that met CAP entry criteria. The mean change from baseline to Wk 60 in %FVC was ~5.8%, median survival was ~7.0% in the PFD group (N=345) and ~9.4% in the placebo group (N=347). The percentage of patients with an FVC decline ≥10% was 16.6% in RECAP, compared with 16.8% and 24.8%, respectively, in the PFD and placebo groups in CAP. Overall survival in newly-treated patients in RECAP was similar to that of PFD patients in CAP (Figure 1).

Conclusions: FVC and survival outcomes in IPF patients newly treated with PFD in RECAP were similar to those in PFD-treated patients in CAP. These data provide further evidence to support the use of PFD in patients with IPF.

2821

Combined pulmonary fibrosis and emphysema: A distinct entity?

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Introduction: Although combined pulmonary fibrosis and emphysema (CPFE) syndrome has been proposed as a distinct entity, it is controversial.

Figure 1. Kaplan-Meier estimates of overall survival.

Conclusions: FVC and survival outcomes in IPF patients newly treated with PFD in RECAP were similar to those in PFD-treated patients in CAP. These data provide further evidence to support the use of PFD in patients with IPF.
2822

Extent of fibrosis by high-resolution computed tomography does not improve prediction of mortality in idiopathic pulmonary fibrosis when added to a simple clinical prediction model

Breit Lect 1, Erci Vittinghoff 2, Brett M. Elicker 3, Thomas E. Hartmann 4, Talmadge E. King Jr. 5, Harold R. Collard 1, 6, Medicine, University of California, San Francisco, CA, United States; 2Epidemiology and Biostatistics, University of California, San Francisco, CA, United States; 3Radiology, Mayo Clinic, Rochester, MN, United States; 4Medicine, Mayo Clinic, Rochester, MN, United States; 5Pathology, University of California, San Francisco, CA, United States

Background: We previously reported a simple clinical prediction model for mor-
tality (the GAP model) in idiopathic pulmonary fibrosis (IPF). Gender, age and Physiology (forced vital capacity and diffusion capacity for carbon monoxide) were used to assess reliability. Models were based on competing-risks regression for mortality, transplanting as a competing risk. Predictive performance of the GAP model and GAP + fibrosis score (GAP-FS) model was compared by the C-index, net reclassification improvement (NRI), and clinical NRI (cNRI).

Results: We included two of three cohorts used to develop the GAP model (n=354). All patients had HRCTs available within 1 year of baseline. Two radiologists (JH, B.E.) scored fibrosis on HRCCT using the modified Proposal for the International Multidisciplinary Classification of IPF. A score of 0 to 3 was assigned in 25 cases. Both radiologists had 85% agreement for fibrosis score. A higher fibrosis score was associated with shorter survival on unadjusted analysis (HR=0.96, 95% confidence interval [CI] 0.94 to 0.97). However, in both groups, diffusion capacity for carbon monoxide was a sole determinant of survival. We evaluated the additive predictive value of fibrosis score to the GAP model for IPF. Methods: We included two of three cohorts used to develop the GAP model (n=354). All patients had HRCTs available within 1 year of baseline. Two radiologists (JH, B.E.) scored fibrosis on HRCCT using the modified Proposal for the International Multidisciplinary Classification of IPF. A score of 0 to 3 was assigned in 25 cases. Both radiologists had 85% agreement for fibrosis score. A higher fibrosis score was associated with shorter survival on unadjusted analysis (HR=0.96, 95% confidence interval [CI] 0.94 to 0.97). However, in both groups, diffusion capacity for carbon monoxide was a sole determinant of survival. We evaluated the additive predictive value of fibrosis score to the GAP model for IPF. Results: C-index, net reclassification improvement (NRI), and clinical NRI (cNRI) were used to assess reliability. Models were based on competing-risks regression for mortality, transplanting as a competing risk. Predictive performance of the GAP model and GAP + fibrosis score (GAP-FS) model was compared by the C-index, net reclassification improvement (NRI), and clinical NRI (cNRI).

Conclusion: When added to a simple clinical prediction model, extent of fibrosis from HRCCT does not improve prediction of mortality in IPF.

2823

Recombinant thrombomodulin improves survival in acute exacerbation of idiopathic pulmonary fibrosis

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Background: Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) are episodes of acute respiratory worsening caused by unknown etiology with high short-term mortality. The presence of disordered coagulation and endothelial dam-
age in AE-IPF has been reported. Recombinant human soluble thrombomodulin (rTM) binds to thrombin to inactivate coagulation, and the thrombin-rTM com-
plex activates protein C to produce activated protein C. The purpose of this study is to examine the efficacy of rTM for treating patients with AE-IPF.

Methods: Patients with AE-IPF in our hospital from 2006 to 2011 were enrolled. AE-IPF was defined using the revised Japanese criteria for AE-IPF (Eur Respir J. 2010;35[4]:821-9). All patients received corticosteroid pulse therapy and immunosuppressant (cyclosporine 3mg/kg/day, p.o). NPPV was the first line intervention. AE-IPF was defined using the revised Japanese criteria for AE-IPF (Eur Respir J. 2010;35[4]:821-9). All patients received corticosteroid pulse therapy and immunosuppressant (cyclosporine 3mg/kg/day, p.o). NPPV was the first line intervention. AE-IPF was defined using the revised Japanese criteria for AE-IPF (Eur Respir J. 2010;35[4]:821-9). All patients received corticosteroid pulse therapy and immunosuppressant (cyclosporine 3mg/kg/day, p.o). NPPV was the first line intervention. AE-IPF was defined using the revised Japanese criteria for AE-IPF (Eur Respir J. 2010;35[4]:821-9). All patients received corticosteroid pulse therapy and immunosuppressant (cyclosporine 3mg/kg/day, p.o). NPPV was the first line intervention.

Conclusion: In this prospective study the use of the TLC may allow to identify a pathological pattern in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic Idiopathic Interstitial Pneumonia (IPF).

Results: Biopsies obtained from 40 patient s were evaluated. Adequate cryobiop-
sies have been shown to be useful for obtaining more large biopsy samples of lung parenchyma bronchoscopically in patients with DPLD. Objective: The purpose of this prospective study was to identify the pathological pattern by transbronchial lung cryobiopsy (TLC) using flexible cryoprobes in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic Idiopathic Interstitial Pneumonia (IPF).

Background: Specimens from transbronchial lung biopsies lack sufficient quality due to crush artifact and are generally too small to identify any pathological pat-
tern for diagnosis of fibrosing diffuse parenchymal lung disease (DPLD). Flexible cryoprobes have been shown to be useful for obtaining more large biopsy samples of lung parenchyma bronchoscopically in patients with DPLD.

Objective: The purpose of this prospective study was to identify the pathological pattern by transbronchial lung cryobiopsy (TLC) using flexible cryoprobes in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic Idiopathic Interstitial Pneumonia (IPF).

Results: Biopsies obtained from 40 patients were evaluated. Adequate cryobiop-
sies were available in 39 of 40 patients. The average size of cryobiopsy was 6.0 x 4.2 mm. Crush artifacts were not seen. In 34 cases (85%) TLC identified a pathological pattern and contained features to suggest a Usual Interstitial Pneu-
monia pattern (ie. at least 2 of three pathologic features of UIP present, ie. patchy interstitial fibrosis, fibroblast foci and/or honeycomb changes) in 21 cases; Non-
specific Interstitial Pneumonia pattern in 8 cases; Organizing Pneumonia pattern in 2 cases; Desquamative Interstitial Pneumonia pattern in 1 case; Eosinophilic Pneumonia pattern in 1 case; bronchiolitis pattern in 1 case. In 6 cases (15%) a pathological pattern was not identified.

Conclusions: In this prospective study the use of the TLC may allow to identify a pathological pattern in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic IPF.

2826

Late stage of experimental pulmonary fibrosis is modulated by collagen V

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Objectives: To investigate whether the combined pulmonary fibrosis and emphy-
sema has different prognosis and prognostic factors from pure idiopathic pulmonary fibrosis.

Methods: Clinical data and high resolution computed tomography images of 300 patients with idiopathic pulmonary fibrosis were retrospectively reviewed. The extent of emphysema and fibrosis were scored and the patients with moderate to severe emphysema (grade 2) were categorized as combined disease group.

Results: Seventy five (25.0%) patients had combined disease and the survival period was not significantly different from isolated idiopathic pulmonary fibrosis (n=200). In both groups, survival period was significantly correlated with fibrosis score, but not with emphysema score. In isolated idiopathic pulmonary fibrosis group and also all patient group, forced vital capacity and fibrosis score were predictors for mortality on multivariate analysis. In combined disease group, pulmonary hypertension was more frequent and an independent prognostic factor. However, in both groups, diffusion capacity for carbon monoxide was a sole determinant of pulmonary hypertension, suggesting the combined effect of both fibrosis and emphysema in the development of pulmonary hypertension (ICCI).

Conclusions: The combined pulmonary fibrosis and emphysema seems to be co-morbidity with similar survival period rather than a distinct disease entity.

Introduction: A subset of patients with IPF present with abnormal auto-antibodies (AA) without clinical features sufficient to diagnose connective tissue disease (CTD). CTD-associated ILD is generally associated with a better prognosis than IPF.

Aims: To study the prevalence and significance of abnormal AAs in IPF.

Methods: Consecutively presenting patients with suspected IPF between 1/1/02 and 12/31/12 were prospectively recruited to a database. All IPF diagnoses required exclusion of overt CTD and an HRCT appearance of UIP with ≥ 70% probability. Patients with HRCT scans with ≥ 95% probability of UIP, or a confirmatory surgical lung biopsy were defined as definite IPF. The remainder were defined as probable IPF. Abnormal AA profile was defined as the presence of at least one of: RHF ≥ 40, ANA >1/640 and/or positive specific ENA screen. Patients were followed-up until Dec 2011 (median [IQR] among survivors 45 [25-63] months). Of 233 patients recruited, 25 did not have AAs performed within 12 months of presentation and were excluded. Of the 208 patients reported, 95 had definite IPF: AAs were abnormal in 18% of patients. Definite v probable IPF, gender, age, smoking and baseline lung function were similar for normal and abnormal AA groups. Only 3 patients developed overt CTD and all had abnormal AAs. Median survival was lower in those with abnormal AAs (30 v 69 months); unadjusted HR 1.57 [0.97 to 2.53] p=0.07; adjusted for age, sex, baseline VC, smoking and definite/probable IPF: HR 1.69 [1.03 to 2.78] p=0.04.

Conclusions: Only 1% of all IPF patients developed overt CTD. Abnormal AA serology was associated with a poorer survival.
these models tend to go for the resolution of the fibrosis, but in different degrees of intensity depending on the strain. Thus these mechanisms in certain strains may participate in the progression of PF.

**Methods:** We used the models of Bleomycin-Balb/c (BLM), Paracut-Balb/c, Bleomycin-C57BL/6 and BLM-IL17RA-KO-C57BL/6. We analyzed the amounts of total collagen (TC) and collagen V (Col5) through the morphometric evaluation by the picrosirius and IF. These data were validated by RT-PCR of Col5.

**Results:** The peribronchiolar TC by PPM did not differ between the treated groups, but the peripheral interstitial TC was higher in the C57BL/6, independent of the absence of IL-17RA. The protein expression of Col5 was higher in IL-17RA-KO (75.8±9% X 52.7±13%; p<0.01) and lower in BLM-Balb/c (68.9±3.4% X 53.3±14.3%; p<0.05). Likewise, the gene expression of Col5 was also higher in the IL17RA-KO (p<0.0485) and lower in the BLM-Balb/c (p<0.0037) (Figure 1).

**Conclusion:** The perpetuation of PF in fibrosis-susceptible mice is related to the IL17RA-KO (p<0.0485) and lower in the BLM-Balb/c (p<0.0037) (Figure 1).

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**309. Pulmonary circulation: end-points and biomarkers**

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**2827**

Right atrial enlargement and prognosis in the hemodinamically stable pulmonary embolism


**Introduction:** The Right-Atrium (RA) is easily accessible from the apical 4-chamber view (4Cv) and its enlargement is easily verifiable.

**Aims:** To study if RA enlargement is associated with increased short-term mortality in patients with acute symptomatic hemodynamically stable PE.

**Methods:** The RIBETE Registry is international registry of patients with symptomatic acute VTE. Patients diagnosed of hemodynamically stable PE were included in the current study. RA enlargement was considered if the RA End-Systolic (ES) area in the apical 4Cv was greater than the Left Atrium ES area. Right Ventricle/Left Ventricle (RV/LV) ED ratio and RV dyskinesia were also determined.

**Conclusion:** The presence of RA enlargement is significantly associated with mortality from all causes during the first month after diagnosis. This association is particularly strong with mortality caused by PE itself. Compared to patients with normal RA, the risk of dying from PE during the first month is 4 times higher in patients with RA dilatation.

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**2828**

A novel echo-score for evaluating the pre-test probability of pre-capillary versus post-capillary pulmonary hypertension

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**Aims:** To provide an echo-score for evaluating the pre-test probability of pre-capillary (pre-PH) vs post-capillary (post-PH) pulmonary hypertension (PH).

**Methods:** One hundred thirty-five consecutive patients underwent Doppler echocardiography (DE) within 1 hour of a clinically indicated right heart catheterization (RHC). The DE was scored on the basis of features suggesting pre-PH: right atrium (RA) > left atrium (LA), right ventricle (RV) > left ventricle (LV), apex forming RV, LV eccentricity index (EI) <0.9, pericardial effusion (PE), systolic notch at right ventricular outflow tract (RVOT), dilated and fixed inferior cava vein (ICV) (yes = 1, no = 0), or post-PH: LV ejection fraction (EF) <40%, moderate/severe aortic and/or mitral disease (yes = 1, no = 0). Patients were divided in 3 groups: low score (-2 to 0), medium score (1 to 2) and high score (3 to 7).

**Results:** Twelve/135 patients did not have PH at RHC; 84 showed pre-capillary PH (54 group 1) and 39 post-capillary PH (group 2). The probability of pre-PH was 37% in presence of low, 86% in presence of medium and 95% in presence of high echo-score. LV-EF <40% had 100% specificity for post-PH. The majority of echo features showed an high specificity but a low sensitivity for pre-PH.

**Conclusion:** RHC remains the gold standard for the diagnosis of PH. Nevertheless, a novel easy and integrated echo-score provides a good pre-test probability of having a pre-capillary rather than post-capillary PH.
Methods and results: We monitored steady flow parameters (pulmonary vascular resistance (PVR), steady flow parameters (PVG) and pulmonary vascular pressure gradient (PVG) in dependent PH patients). Pulmonary vascular pressure gradient (PVG) is a dependent PH-specific treatment.

Conclusions: ADMA correlates with the hemodynamic benefit of PH-specific treatment in patients with PH of various etiologies. ADMA can serve as a biomarker for the effect of PH-specific treatments.

2832 Respiratory event hospitalizations are reduced in heart failure patients with comorbid chronic obstructive pulmonary disease using a wireless implanted pulmonary artery pressure monitoring system

Introduction: Respiratory event hospitalizations (REH) from COPD exacerbations, bronchitis, pneumonia, and other respiratory events frequently occur in patients with heart failure (HF). Pulmonary artery pressure (PAP) monitoring and treatment has been shown to reduce heart failure hospitalizations.

Methods: The CHAMPION trial enrolled 550 patients with NYHA class III HF who were followed for an average of 15 months. In all patients PAP data were monitored using a novel, implantable hemodynamic system. In the treatment group, patients received PAP data to guide therapy decisions in addition to standard of care versus standard of care alone in the control group.

Results: REH rates were higher in the COPD subgroup compared to the entire CHAMPION cohort. In the COPD subgroup (91 treatment vs. 96 control), treatment experienced a 62% reduction in REH rates (0.12 vs. 0.31, HR 0.38, 95% CI 0.21-0.71, p=0.0023, Anderson-Gill). In the CHAMPION cohort (270 treatment vs. 280 control), treatment experienced a 49% reduction in REH rates (0.07 vs. 0.14, HR 0.51, 95% CI 0.44-0.81, p=0.0009).

Conclusions: Treating HF patients with an implantable hemodynamic monitoring system significantly reduced REH in all patients with even greater benefit in COPD patients. Further investigations that analyze the relationship between PAP, COPD, and REH in chronic HF patients and its implication towards new treatment strategies are warranted.

2833 Pulmonary vascular gradient: A predictor of prognosis in pulmonary hypertension due to left heart disease

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Purpose: Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥25mmHg. The disease can be further classified into pre-capillary pulmonary wedge pressure, PCWP ≤15mmHg) and post-capillary PH (PCWP >15mmHg). The driving pressure across the pulmonary circulation is often referred to as the transpulmonary gradient (TPG). In the current guidelines post-capillary PH with a TPG >12mmHg is labeled as “out-of-proportion” PH, as opposed to what is labeled as “passive” PH, i.e. PH as the consequence of elevated left ventricular filling pressures. The TPG can be determined non-invasively using Doppler echocardiography. The TPG is a strong and independent predictor of mortality and morbidity in PH.

Methods: The CHAMPION trial enrolled 550 patients with NYHA class III HF who were followed for an average of 15 months. In all patients PAP data were monitored using a novel, implantable hemodynamic system. In the treatment group, patients received PAP data to guide therapy decisions in addition to standard of care versus standard of care alone in the control group.

Results: REH rates were higher in the COPD subgroup compared to the entire CHAMPION cohort. In the COPD subgroup (91 treatment vs. 96 control), treatment experienced a 62% reduction in REH rates (0.12 vs. 0.31, HR 0.38, 95% CI 0.21-0.71, p=0.0023, Anderson-Gill). In the CHAMPION cohort (270 treatment vs. 280 control), treatment experienced a 49% reduction in REH rates (0.07 vs. 0.14, HR 0.51, 95% CI 0.44-0.81, p=0.0009).

Conclusions: Treating HF patients with an implantable hemodynamic monitoring system significantly reduced REH in all patients with even greater benefit in COPD patients. Further investigations that analyze the relationship between PAP, COPD, and REH in chronic HF patients and its implication towards new treatment strategies are warranted.

2831 Asymmetric dimethylarginine, a biomarker for the effects of drug therapy in pulmonary hypertension

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Rationale: Asymmetric dimethylarginine (ADMA), a potent endogenous nitric oxide synthase inhibitor, is increased in pulmonary hypertension (PH), and associated with unfavorable outcome. We hypothesized that plasma ADMA may serve as a biomarker to monitor disease progression under PH-specific treatment.

Methods: ADMA was measured at baseline and at least after 24 weeks of treatment in consecutive patients (pts) under advanced PH-targeted treatments. Treatment responders were defined by decrease of pulmonary vascular resistance (PVR) of at least 200% at time point of 5-6 walking distance > 300m, and improvement of WHO at follow-up and were compared with non-responders.

Results: 51 consecutive patients (44 pts with pulmonary arterial hypertension and 7 patients with PH due to lung disease) were enrolled in this study. According to our definition, there were 16 non-responders, and 23 responders to treatments. 11 patients showed no change. ADMA plasma levels did not change significantly under treatment in the whole group. There was a significant drop of ADMA in responder group (p <0.0001). Furthermore, ADMA change in responders and nonresponders was significantly different (p=0.003).

The decrease of ADMA correlated with the decrease of PVR (p=0.56, p<0.0001), with the decrease of mean pulmonary arterial pressure (p=0.44, p=0.001). Furthermore, the difference of ADMA correlated with the increase of cardiac index (r=0.38, p=0.005) and improved venous saturation (r=0.37, p=0.03).

Conclusions: ADMA parallels the hemodynamic benefit of PH-specific treatment in patients with PH of various etiologies. ADMA can serve as a biomarker for the effect of PH-specific treatments.

2830 Hemodynamic assessment of pulmonary hypertension in grown-up congenital heart disease

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Purpose: Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) is included in group I of the pulmonary hypertension (PH) clinical classification system. The persistent exposure of the pulmonary vasculature to increased blood flow due to systemic-to-pulmonary shunts as well as increased pressure may result in a typical pulmonary arteriopathy that leads to an increase in invasively measured mean pulmonary arterial pressure (mPAP) ≥25mmHg at rest.

Methods: 3107 right and left heart catheterizations were analyzed. Diagnoses were validated on the grounds of patient histories, imaging, clinical data and patho-anatomic evidence (2369 complete datasets). 257 data sets were from patients with CHD.

Conclusions: Steady flow parameters (PVR, SCA and PVG) assessed immediately (immediate) after PEA in 110 consecutive patients, who were followed for 34.5 (11.9, 78.3) months. The quantity of extracted vascular obstructions were expressed as the total number and total length of small-vessel thrombus appendages, and correlated inversely with immediate postoperative PVR (p <0.0001, p =0.566; p<0.0001, r=−0.58). Cox regression analysis revealed only steady flow parameters (PVR, SCA and PVG) predicted of long-term survival/freedom of lung transplantation (p<0.0001, p=0.02, p=0.04).

Patients with immediate PVR <59 dynes·s·cm−5 or SCA <26.5mmHg or PVG <21.5mmHg had a better long-term outcome (Logrank tests: p<0.0001, p=0.0006, p<0.0001).

Table 1. Hemodynamic data of patients with CHD and pulmonary hypertension

<table>
<thead>
<tr>
<th>CHD-PHA PCWP ≤15mmHg</th>
<th>CHD-PH PCWP &gt;15mmHg</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>68±11.5</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>64±20.6</td>
</tr>
<tr>
<td>dPAP (mmHg)</td>
<td>28±9.0</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>41±13.1</td>
</tr>
<tr>
<td>mPCWP (mmHg)</td>
<td>24±6.2</td>
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</tbody>
</table>

Conclusion: The data demonstrate that a significant proportion (almost 50%) of patients with PH in grown-up congenital heart disease suffer from post-capillary pulmonary hypertension.
Effects of exercise training and neuromuscular electrical stimulation on symptoms, muscle strength, exercise capacity, activities of daily living, and quality of life in COPD
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Purpose: Chronic obstructive pulmonary disease (COPD) have systemic consequences affecting exercise capacity and quality of life. The purpose of this randomized controlled study was to evaluate effects of neuromuscular electrical stimulation (NMES) on symptoms and function in COPD patients undergoing exercise training.
Materials and methods: Twenty-seven clinically stable COPD patients (62.6±7.5 years, FEV1 40.0±16.4%) were included. The NMES group (n=13) underwent endurance and quadriiceps resistance training plus NMES, 2 days/week for 10 weeks. Control group (n=14) was applied the same exercise regimen plus placebo NMES. Increased ISWT distance in the control group was significantly more than that of NMES group (62.8±33.6 m vs. 38.46±14.80 m, p<0.05). There were no significant differences in any of the other parameters (p>0.05). Conclusion: Increase in exercise capacity was more evident when endurance and quadriiceps resistance training was applied without NMES. Inclusion of NMES have no additional effects beyond exercise training on muscle strength, symptoms, activities daily living, and quality of life in stable COPD.

310. Exercise and physical activity: towards evidence-based benefits in different populations

3284
Exercising training is beneficial in patients with non-cystic fibrosis bronchiectasis – A multi-centre, randomised controlled trial
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Background: Non-cystic fibrosis (CF) bronchiectasis is characterised by chronic cough and sputum production, exercise limitation and reduced quality of life (QOL), but the role of exercise training in this patient group is unclear. The aim of this study was to determine the effects of exercise training on cough-related symptoms, quality of life, exercise capacity, and respiratory and peripheral muscle force. Responders were those who increased TPA >mod after the protocol.
Methods: Participants with non-CF bronchiectasis with a modified Medical Research Council dyspnoea score ≥2 were randomised to receive eight weeks of twice-weekly supervised exercise training or twice-weekly telephone support. The incremental shuttle walk distance (ISWD), 6-minute walk distance (6MWD), the Chronic Respiratory Disease Questionnaire, Leicester Cough Questionnaire and Hospital Anxiety and Depression Scale were measured by a blinded assessor at baseline and following intervention.
Results: Eighty-five participants, aged (mean [SD]) 64 (13) years, FEV1 74 (22)% predicted and median modified Medical Research Council score of 1(IQR 3) were included. Of those in the exercise training group (n=42), 35 (83%) completed the program. There was a greater magnitude of change in the ISWD (mean difference 62m, 95% CI 24 to 101m) and the 6MWD (mean difference 41m, 95% CI 19 to 63m) in the exercise training group compared to the control group. Exercise training significantly reduced dyspnoea <0.01 and fatigue (p < 0.01) but there was no difference in cough-related QOL or mood between groups.
Conclusions: Exercise training in non-CF bronchiectasis improves exercise capacity and symptoms of sputum and fatigue. Ongoing follow up will assess changes in these effects over time.

3285
Effects of exercise training and neuromuscular electrical stimulation on symptoms, muscle strength, exercise capacity, activities of daily living, and quality of life in COPD

3286
Physical activity in daily life in COPD after exercise training: Are there responders, and who are they?
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Background: Previous studies have shown that patients with chronic obstructive pulmonary disease (COPD) generally do not increase their level of physical activity in daily life (PADL) after short-lasting exercise programs. However, as PADL is influenced by several factors, there are individual patients who respond positively becoming more active in daily life.
Aims: To study the proportion and profile of patients with COPD who become more active in daily life after a 12-week exercise training program (responders). Methods: 23 patients (15 men, 66±8 yrs, FEV1 42±16% pred) completed an exercise training protocol (endurance and strength exercises, 3×/week, 12 weeks). PADL was assessed by an activity monitor (Sensewear2, BodyMedia) which registered the time spent in physical activities at least moderate intensity (TPA >mod). Other assessments were socio-economic and functional status, quality of life, exercise capacity, respiratory and peripheral muscle force. Responders were those who increased TPA >mod after the protocol.
Results: 12 patients (52%) were responders (TPA >mod 10 [3–28] min/day pre vs. 32 [10–38] min/day post; p=0.002; median [IQR]). The proportion of physiologically active patients (i.e. TPA >mod ≥30 min/day) increased after the protocol (26% vs. 39%; p=0.01). Although responders and nonresponders had similar physical and functional capacity, responders tended to present exertional desaturation (p=0.076), lower age (p=0.052) and live alone (p=0.089).
Conclusions: These preliminary findings suggest that around half of patients with COPD increase their level of PADL after a 12-week exercise training program. Responders tend to be younger, live alone and desaturate during exertion.

3287
Symptom experience in patients with COPD and their level of physical activity. Is there a good association?
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1Rehabilitation Sciences and Physiotherapy, KULeuven, Belgium; 2Respiratory Rehabilitation, UZ Leuven, Belgium; 3Department of Personality, Evaluation and Psychological Treatment, University of Salamanca, Spain
Rationale: Several instruments including physical activity monitors and questionnaires are used to assess the functional status in patients with COPD. The relation between objectively measured physical activity (PA) and questionnaires assessing functional status and symptoms is poorly studied.
Methods: 54 patients with COPD (age 66±7, FEV1 62±22% pred) were included. PA was assessed during 2 periods of 14 consecutive days in 6 weeks, by the dy-naport movemonitor and actigraph. The amount of steps per day and movement intensity during walking (MI) were used for this analysis. Symptom experience was measured by the MRC scale for dyspnea (MRC), COPD Assessment Test CAT, functionality subscale of the CCQ (CCQ-f) and the dyspnea subscale of the CRQ (CRQ-d), every 2 weeks. The correlations with PA were measured, both with and without inclusion of the weekends.
Results: The univariate correlations are shown in table 1. All questionnaires were significantly correlated with both the steps per day and the MI. Excluding week-ends did not increase the correlation between ‘functional status’ and steps per day and slightly enhanced the correlations with MI.
Table 1 Univariate correlations (p<0.05)

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<th>Steps/day</th>
<th>MI</th>
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<td>WE incl</td>
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<tr>
<td>WE excl</td>
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<td>r = –0.31</td>
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<td>r = –0.34</td>
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<tr>
<td>WE incl</td>
<td>PA data including weekends</td>
<td>WE excl</td>
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</table>

Conclusion: The symptoms experienced by the patients and functional status are mostly related to the amount and intensity of PA. Interventions that improve symptoms may therefore not automatically sin off in enhanced physical activity levels.
Conclusion: Comparison of two strategies using pedometers to counteract physical activity deficit likely to improve physical fitness and HRQoL after a pulmonary rehabilitation program. Twenty-eight patients (65.1%) were considered HRQoL responders and worst baseline HRQoL score, increased free-days asthma symptoms and lower depression score were significant predictors to HRQoL improvement (accuracy 81%, p < 0.001).

Results: Twenty-eight patients (65.1%) were considered responders in exercise capacity and baseline depression symptoms, ventilatory reserve (VE/VVFM) and FEV1 were significant predictors to HRQoL improvement (accuracy 81%, p < 0.001). Twenty-one patients (48.8%) were considered responders in both parameters, with baseline depression as a significant predictor (accuracy 79%, p < 0.001).

Conclusion: Asthmatic patients with impaired HRQoL, better clinical control, fewer depression symptoms and lower ventilatory limitation are significantly more likely to improve physical fitness and HRQoL after a pulmonary rehabilitation program.

Aim: A comparison of two different 5-month protocols using pedometers and informative booklets to increase physical activity in daily life (PADL) in smokers who reach or not 10000 steps/day in daily life.

Methods: PADL was re-assessed (A2), and the interventions were crossed over for 1 month, following an early intervention including lung expansion + expiratory muscle training (Active) or lung expansion + sham training (Control). Training has been set with incremental resistive load over the study period. At present, 39 patients (out of the 54 programmed) completed the study, 19 and 20 in Active and Control respectively, with one patient dropped in each group. Anthropometrics and general characteristics, type of surgery, and functional variables at baseline were similar. Training has been set with incremental resistive load over the study period.

Results: The physically active subgroup of GP+B significantly increased steps/day at A2 and maintained this increase until A4. The physically inactive subgroup of GP+B initially increased to a lesser extent, reaching borderline statistical significance at A2 and A3 (p=0.06) and statistically significant increase only at A4 (p=0.02).

Conclusions: Both strategies were effective in increasing the number of steps/day in physically inactive smokers after 5 months, although the increase was more quickly obtained in smokers who used pedometers as the first intervention.

Physical training for asthma: Which patients obtain most clinical benefits? F. Felipe Mendes1, Andreza Pinto2, Beatriz Saravia-Romanholo1, Rafael Stefanch1, Alberto Cukier1, Pedro Giavina-Bianchi2, Milton Martins3, Celso Carvalho2. 1Physical Therapy, School of Medicine, University of Sao Paulo, Sao Paulo, SP, Brazil; 2Clinical Immunology and Allergology Division, School of Medicine, University of Sao Paulo, SP, Brazil; 3Clinical Medicine, School of Medicine, University of Sao Paulo, SP, Brazil; 4InCor-Pulmonary Division, School of Medicine, University of Sao Paulo, SP, Brazil

Background: Recent studies have shown that exercise training improves exercise capacity, health related quality of life (HRQoL) and clinical control in asthma; however, not all obtain clinical relevant benefits and can be considered responders.

Objective: To investigate baseline characteristics that determines the improvement after an exercise training program in asthmatics patients.

Methods: Forty-three adults with moderate or severe asthma performed an aerobic training (35min/twice a week/3 months). It was considered exercise responders those patients that increased ≥10% in maximal aerobic capacity (VO2peak) and HRQoL responders those patients that improved ≥20% in a specific-asthma HRQoL questionnaire. Discriminant analysis was used to distinguish responders from non-responders based on patient’s baseline data.

Results: Twenty-eight patients (65.1%) were considered responders in exercise capacity and baseline depression symptoms, ventilatory reserve (VE/VVFM) and FEV1, were significant predictors to training response (accuracy 86%, p < 0.001).

Conclusion: Muscle mass and strength in pts with thoracic cancer is thought to result from loss of muscle mass and functional impairment. The latter is thought to result from loss of muscle mass and strength.

Aim: To investigate the effect of radical treatment and post-treatment rehabilitation on muscle mass and strength in pts with thoracic cancer.

Methods: Muscle mass was estimated with the fat free mass (FFM) by bioelectrical impedance and the cross-sectional area (CSA) of skeletal muscle on a single 16-mm CT-scan slice. Muscle strength was estimated by the quadriceps force (QF). All variables were measured pre-treatment (M1), after radical treatment (M2) and after either 12w of rehabilitation (RA) or control (CON) (M3). Data are presented as medians with 95% CI.

Results: Of 29 consecutive pts, 18 were allocated to RA and 11 to CON. Both groups have comparable M1 characteristics. At M2, all pts showed a significant decrease in muscle mass and strength. At M3, only RA-patients improved significantly their muscle mass. There is a good correlation between muscle CSA and FFM (r = 0.70; p < 0.001).

Conclusion: Muscle mass and strength significantly decrease with radical treatment in pts with lung cancer and mesothelioma. Muscle mass increases with rehabilitation. CT scan can substitute bioelectrical impedance for measuring muscle mass. Mature data will be presented at the meeting.

311. Paediatric respiratory epidemiology: something for everyone!

314. Expiratory muscle training in patients recovering open thoracic and cardiac surgery

Enitesto Critsulfi1, Massimo Cerulli2, Elena Venturelli3, Fabio Florini4, Nicoletta Kidomax1, Assunta De Biase1, Vittoria Firuno1, Enrico M. Clini1,2, Respiratory Medicine, Ospedale Villa Pineta, Privada srl Modena, Italy; 3Oncology Haematology Respiratory Diseases, University of Modena, Italy

Respiratory muscle training has been so far demonstrated to be effective as a rehabilitation technique in COPD patients. However, it is still not clear whether it may similarly be useful when used in patients receiving open thoracic and cardiac surgery.

We therefore undertaken a randomised 14-day trial in these patients to evaluate changes in maximal expiratory (MEP, as the primary outcome) and inspiratory (MIP) pressures, lung volumes (FEV1, FVC, CV, CI, VR), oxygenation index (PaO2/FiO2), perceived symptoms (VAS), and generic quality of life (SF36) following an early intervention including lung expansion + expiratory muscle training (Active) or lung expansion + sham training (Control). Training has been set with incremental resistive load over the study period. At present, 39 patients (out of the 54 programmed) completed the study, 19 and 20 in Active and Control respectively, with one patient dropped in each group. Anthropometrics and general characteristics, type of surgery, and functional variables at baseline were similar. Training has been set with incremental resistive load over the study period.

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Conclusions: Both strategies were effective in increasing the number of steps/day in physically inactive smokers after 5 months, although the increase was more quickly obtained in smokers who used pedometers as the first intervention.

The effect of radical treatment and pulmonary rehabilitation on muscle mass as measured by CT-scan: A randomised trial in patients (pts) with lung cancer and mesothelioma

Bhavya Sali1, Gilles Thyebeaut1, Thomas L. Malafa1, Karim Vermaelen1, Veerle F. Saimont2, Wouter Hueysse2, Georges Van Maelle3, Jan P. van Meerbeeck1, Eric Dromel1. 1Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; 2Radiology, Ghent University Hospital, Ghent, Belgium; 3Medical Informatics and Statistics, Ghent University Hospital, Ghent, Belgium

Introduction: Cancer and its treatment are known to contribute to fatigue and functional impairment. The latter is thought to result from loss of muscle mass and strength.

Methods: Forty-three adults with moderate or severe asthma performed an aerobic training (35min/twice a week/3 months). It was considered exercise responders those patients that increased ≥10% in maximal aerobic capacity (VO2peak) and HRQoL responders those patients that improved ≥20% in a specific-asthma HRQoL questionnaire. Discriminant analysis was used to distinguish responders from non-responders based on patient’s baseline data.

Results: Twenty-eight patients (65.1%) were considered responders in exercise capacity and baseline depression symptoms, ventilatory reserve (VE/VVFM) and FEV1, were significant predictors to training response (accuracy 86%, p < 0.001).

Conclusion: Muscle mass and strength significantly decrease with radical treatment in pts with lung cancer and mesothelioma. Muscle mass increases with rehabilitation. CT scan can substitute bioelectrical impedance for measuring muscle mass. Mature data will be presented at the meeting.

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Conclusions: Both strategies were effective in increasing the number of steps/day in physically inactive smokers after 5 months, although the increase was more quickly obtained in smokers who used pedometers as the first intervention.
difficulty with using reported alcohol intake to measure exposure is that under-
comes at 7 years of age. Carriers of the minor A allele drink less in pregnancy and
reporting is common and associations are likely to be confounded. In contrast, a
with asthma and hayfever than mothers who reported never drinking (OR 0.81
week or more in the last two months of pregnancy were less likely to have children
(95% CI: 0.33 to 0.75), P=0.001, N=6,701). There were no significant associations
Results: Maternal ADH1B genotype was strongly associated with childhood
asthma and atopic diseases in childhood
Foetal exposure to maternal stressful events increases the risk of having
intake are likely to be confounded.

Aim: To test whether the children of mothers who had experienced SLE during pregnancy are at an increased risk for asthma, atopic eczema and allergic rhinitis.

Methods: The association between maternal SLE (at least one among: depressive disorders, anxiety, substance abuse, or suicide attempt) and childhood asthma and atopic diseases in childhood was studied in a population (n=3854) of children, aged 0-14 years, living in Northern Italy. The parents filled in a standardized questionnaire about the children’s health and the events occurred to their mothers during pregnancy.

Results: 337 (9%) of the mothers experienced at least one SLE during pregnancy. After adjusting for potential confounders (including risk factors of the children and their families, birth complications or drug use during pregnancy and children’s characteristics at birth), the foetal exposure to SLE was positively associated with wheezing (OR: 1.45, 95%CI: 1.07-1.97), asthma (OR: 1.69, 95%CI: 1.02-2.77), allergic rhinitis (OR: 1.69, 95%CI: 1.06-2.68) and atopic eczema (OR: 1.47, 95%CI: 1.08-2.00).

Conclusion: The children of mothers who had experienced SLE during pregnancy were at a moderately increased risk of having wheezing, asthma, eczema and allergic rhinitis during their childhood. Maternal stress during pregnancy may enhance the expression of asthma and atopic phenotypes in children, strengthening the hypothesis that promness to atopy begins in utero.

2844
Clinical index to evaluate the risk of primary ciliary dyskinesia in children
Jana Djakov1, Ewa Rozezhalova1, Magdalena Havlisova1, Tamara Svobodova1, Petra Pichova1

Introduction: Primary ciliary dyskinesia (PCD) is a rare genetic disorder causing a variety of symptoms. The diagnostics of PCD is challenging as the clinical presentation can differ in particular patients. Also the methods (as high-speed videomicroscopy or electron microscopy) to diagnose PCD are usually available only in specialized centres.

Aim & objective: To find out if a simple clinical index can be used to differentiate the patients with high risk of PCD.

Methods: All patients with PCD diagnosed in our clinic (n=31) and all patients sent to the diagnostic centre as suspected of PCD in 2009-2011 (n=352) were included into the study. We randomly divided the study group into 2 subgroups. The analysis subgroup was used for model preparation and hold-out group was used for subsequent cross-validation of the model. We measured quality of the test (model) by computing area under ROC curve (AUC) and discriminant validity by computing total scores for group with or without PCD diagnosis.

Results: The clinical index included 7 yes/no questions concerning the history and clinical symptoms. One point was assigned to each yes answer. AUC for analysis sample was 0.94, AUC for hold-out subsample 0.89. Discriminant validity was measured in whole study group by non-parametric Mann-Whitney U-test: U(555,5, Z=0.08, p<0.0001).

Conclusions: A simple clinical 7-item questionnaire can be used to evaluate the risk of PCD and to discriminate the patients that should be referred to diagnostic centre.

2845
PCD with normal ultrastructure is not rare
Mikee Boon1, Anne Smits1, Mark Jongse1, Lieven Dupont1, Francois Vermeulen1, Anjela M. Pescatore2, Erol E. Gaillard1, John Henderson2, Francois Vermeulen1, Anjela M. Pescatore2, Erol E. Gaillard1, John Henderson2, Claudia E. Kuzem1

1School of Social and Community Medicine, University of Bristol, United Kingdom; 2Institute of Social and Preventive Medicine, University of Bern, Switzerland; 3Division of Pulmonary, Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom

Aim: In young children with wheeze it is common to distinguish between those who wheeze only during respiratory tract infections (episodic viral wheeze, EVW) and those who also wheeze due to other factors (multiple trigger wheeze, MTW). The stability of this classification has recently been questioned. In two population based cohort studies, we compared the prevalence and stability of these phenotypes in early childhood.

Background: Very low birth weight (VLBW) infants (<1500g) with bronchopulmon-
ary dysplasia (BPD) may suffer lung damage through mechanical ventilation and the presence of incomplete recovery of respiratory function, which can lead to respiratory and airway resistance, functional residual capacity (FRC), maximal expiratory flow at FRC and blood gas values. Tidal volume, minute ventilation, respiratory compliance and FRC determined by SF6 multiple breath washout were significantly lower in BPD infants compared to controls, but the differences vanished after normalization to body weight.

Conclusions: While somatic growth and some lung function parameter were de-
layed in BPD infants, their lung function appeared to develop along trajectories of non-BPD infants when actual body weight is being considered. Longitudinal LFT of preterm infants after discharge may help to identify BPD infants at risk of incomplete recovery of respiratory function, which can lead to respiratory problems later on.

2846
Development of postnatal lung function in very low birth weight infants with
or without BPD
Charles Roelig1, Silke Wolitzki, Hans Proesacker, Christian Bührer, Gerit Schmädlisch. Neonatology, Charité Medical Centre, Berlin, Germany

Background: Neonates born at ≤1500 g were included and divided into two groups (BPD and non-BPD). The BPD group included children with bronchopulmonary dysplasia (BPD) who had mean gestational age (GA) <30 weeks and birth weight <1500 g and had received ventilation for at least 7 days or until death. The non-BPD group included children with GA ≥30 weeks and birth weight ≥1500 g and had no or only short-term respiratory support. All infants were ventilated with conventional ventilation and received surfactant at 36 weeks GA.

Methods: All infants born at ≤1500 g were included and divided into two groups (BPD and non-BPD). The BPD group included children with bronchopulmonary dysplasia (BPD) who had mean gestational age (GA) <30 weeks and birth weight <1500 g and had received ventilation for at least 7 days or until death. The non-BPD group included children with GA ≥30 weeks and birth weight ≥1500 g and had no or only short-term respiratory support. All infants were ventilated with conventional ventilation and received surfactant at 36 weeks GA.

Results: The analysis subgroup was used for model preparation and hold-out group was used for subsequent cross-validation of the model. We measured quality of the test (model) by computing area under ROC curve (AUC) and discriminant validity by computing total scores for group with or without PCD diagnosis.

Results: The clinical index included 7 yes/no questions concerning the history and clinical symptoms. One point was assigned to each yes answer. AUC for analysis sample was 0.94, AUC for hold-out subsample 0.89. Discriminant validity was measured in whole study group by non-parametric Mann-Whitney U-test: U(555,5, Z=0.08, p<0.0001).

Conclusions: A simple clinical 7-item questionnaire can be used to evaluate the risk of PCD and to discriminate the patients that should be referred to diagnostic centre.

2847
Multiple trigger and episodic viral wheeze in early childhood: Are these
phenotypes stable over time?
Ben D. Spycher1, 2, Jonathan A. C. Sterne1, Raquel Granell1, Michael Silverman1, Ana M. Pescatore2, Erol E. Gaillard1, John Henderson2, Claudia E. Kuzem1

1Institute of Social and Preventive Medicine, University of Bern, Switzerland; 2Division of Pulmonary, Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom

Aim: In young children with wheeze it is common to distinguish between those who wheeze only during respiratory tract infections (episodic viral wheeze, EVW) and those who also wheeze due to other factors (multiple trigger wheeze, MTW). The stability of this classification has recently been questioned. In two population based cohort studies, we compared the prevalence and stability of these phenotypes in early childhood.
Methods: We included 14062 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) and 4300 from the Leicester Respiratory Cohorts (LRC). Mothers received postal questionnaires including questions on wheeze and triggers of episodes in past 12 months when children were aged 2, 4 and 6 yrs.

Results: Between ages 2 and 6 yrs, prevalence of current wheeze decreased from 18 to 10% in ALSPAC and from 23 to 10% in LRC. Among children with wheeze the proportion of those with MTW as opposed to EVW increased from 55% (both cohorts) to 70% (ALSPAC) and 74% (LRC). Among children with EVW who wheezed again 2yrs later, a considerable proportion were reclassified as MTW in both cohorts (Tables). There was less reclassification from MTW to EVW.

Table 1

<table>
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<tr>
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<th>EVW 4yrs [%]</th>
<th>MTW 4yrs [%]</th>
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<td>LRC</td>
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<tr>
<td>MTW 2 yrs</td>
<td>ALSPAC</td>
<td>LRC</td>
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Table 2

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<th>EVW 6yrs [%]</th>
<th>MTW 6yrs [%]</th>
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<tbody>
<tr>
<td>EVW 4 yrs</td>
<td>ALSPAC</td>
<td>LRC</td>
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<td>39</td>
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<tr>
<td>MTW 4 yrs</td>
<td>ALSPAC</td>
<td>LRC</td>
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Conclusion: The phenotypes EVW and MTW show limited stability through early childhood suggesting that triggers of wheeze alone are not sufficient to distinguish underlying disease processes, or that the disease processes change in some children throughout this period.

Funding: BIDS is recipient of a ERS/Marie Curie Joint Research Fellowship (MC 1614-2010).

2848 Increased risk of preschool wheeze both with higher BMI in infancy and at age 4 years
Emma Gokal1, Bernt Alm1, Rolf Pettersons2, Per Möllborg1, Ilaslo Erdes1, Nina Ahlbom1, Department of Environmental Medicine, Gothenburg, Sweden; 2Central Infant Welfare Unit, Pediatric Outpatient Clinic, Mölndal, Sweden; 3Pediatric Outpatient Clinic, Pediatric Outpatient Clinic, Skene, Sweden

Background: Overweight has been associated with wheezing and asthma both in children and adults. It is debated whether overweight early in life predisposes for later wheeze or if the association is due to asthmatic children being less active. The aim of this study was to explore the relationship between body mass index, BMI, and recurrent wheeze (≥3 episodes during the last 12 months) at preschool age.

Methods: Data were obtained from a prospective, longitudinal study of a cohort of children born in Western Sweden in 2003. 8176 families (50% of the birth cohort) were randomly selected. The parents answered questionnaires at 6 and 12 months and at 4.5 years of age. The response rate at 4.5 years was 4496, i.e. 83% of the 5398 questionnaires distributed at 4.5 years. Odds ratios were calculated with BMI as a continuous variable.

Results: In multivariate analysis, the risk of recurrent wheeze at preschool age was increased both by a higher BMI at 12 months (OR 1.2, 95% CI 1.03-1.4) and by a higher BMI at age 4 years (OR 1.2, 1.04-1.4). Adjusting for recurrent wheeze during infancy or excluding children with recurrent wheeze during infancy had no major influence on the ORs. In addition, recurrent wheeze in infancy did not increase the risk of overweight at 4 years.

The analyses controlled for preterm birth, smoking during pregnancy, family history of atopies, other allergic diseases in infancy, parental education, small for gestational age, gender and maternal overweight before pregnancy.

Conclusion: A higher BMI at 12 months or at 4 years both increased the risk of recurrent wheeze at preschool age. Wheezing during infancy did not explain the associations seen.

2849 Interactions between exposure to cigarette smoke and variations in the GSTM genotype for asthma quality of life
Steve Turner1, Roger Tavendale2, Somnath Mukhopadhyay1, Anil Mehta1, Colin Palmer3, Jon Ayres1, 1Child Health, University of Aberdeen, United Kingdom; 2Population Pharmacogenetics Group, University of Dundee, United Kingdom; 3Division of Maternal & Child Health Sciences, University of Dundee, United Kingdom; 4Child Health, Brighton and Sussex Medical School, Brighton, United Kingdom; 5Occupational and Environmental Medicine, University of Birmingham, United Kingdom

Background: Asthma is a heterogeneous condition and our hypothesis is that gene environment interactions explain some of the variation within the asthmatic population. Here we report on an interaction between exposure to second hand smoke (SHS, an oxidant stress) and variation in the gene coding for antioxidant protein GST-M for asthma outcomes.

Methods: Children with asthma were recruited from primary and secondary care across Scotland. A respiratory questionnaire and the Pardissia Asthma Quality of Life Questionnaire (PAQLQ) were completed and DNA collected. A subset underwent an assessment including spirometry and exhaled nitric oxide. Saliva was collected for cotinine analysis.

Results: From 894 children recruited, PAQLQ and DNA were obtained in 499 (56%). There were 88 children exposed to SHS. Compared to children null for GSTM who were not exposed to SHS, the overall PAQLQ score for exposed children null for GSTM was reduced (meaning worse quality of life) by a mean of -0.7 [95% CI -0.1, -1.3] p=0.020. Similar associations were present for domains of symptoms (mean difference -0.7 [-0.1, -1.3]) and emotions (mean difference -0.7 [-0.1, -1.2]) but not activities (mean difference -0.3 [95% CI -0.9, -0.3]). There were no differences in spirometry or exhaled nitric oxide between GSTM null children who were and were not exposed to SHS.

Conclusion: Our findings support the hypothesis that gene environment interactions are important to some of the heterogeneity of asthma. Whilst all children with asthma should avoid SHS exposure, parents of children null for GSTM (50% of all asthmatics) might be considered for specific intervention.

312. Recent technical developments in long-term noninvasive ventilation

2880 Pulse transit time allows a reliable non-invasive measurement of respiratory effort under non-invasive ventilation
Göran Östergard1, Claudio Carnevale2, Jean-Christian Borel3,4, AbdelKebir Sabil2,3, Renaud Tamisier2,3, Patrick Levy2,3, Jean-Paul Janssens1, Jean-Louis Pepin2,3, 1Division of Pulmonary Diseases, Geneva University Hospitals, Geneva, Switzerland; 2HP 2 Laboratory (Hypoxia: Pathophysiology), INSERM U 1042, Joseph Fourier University, La Tronche, France; 3ECFR and Sleep Laboratory, Locomotion, Rehabilitation and Physiology Department, Grenoble University Hospital, Grenoble Cedex 09, France; 4Research and Development Department, AGIR à Dom, Meylan, France

Rationale: Among respiratory events which may occur during nocturnal non-invasive ventilation (NIV), differentiating between central and obstructive events requires appropriate indicators of respiratory effort.

Objective: To assess pulse transit time (PTT) as an indicator of respiratory effort under NIV in comparison with esophageal pressure (Pes).

Methods: 1: During wake period, PTT was compared to Pes during spontaneous breathing and under NIV with or without induced leaks in 11 healthy individuals. 2: To evaluate the contribution of PTT vs Pes for differentiating central from obstructive respiratory events occurring under NIV during sleep in 10 patients with obesity hypventilation syndrome (OHS).

Results: 1: From spontaneous breathing to NIV without leaks, respiratory effort decreased significantly and with increasing level of leaks, there was a significant increase in respiratory effort. In both situations changes in PTT accurately reflected changes in Pes.

2: In the OHS patients during nocturnal NIV, intraclass correlation coefficients between Pes and PTT were 0.970 for total number of events and 0.970 for percentage of central events.

Conclusions: PTT accurately reflects the unloading of respiratory muscles induced by NIV and the increase in respiratory effort during NIV. PTT during sleep is also useful to differentiate central from obstructive respiratory events occurring under NIV.

Clinical trial registration number: NCT00983411.

2881 Validation of a method for non-invasive assessment of transdiaphragmatic pressure during support ventilation
Kristel Lopez-Navas1,2, Sebastian Brandt1, Merle Strutz1, Hartmut Gehring1, Ulrich Wenkembach1, 1Laboratory of Medical Systems, University of Applied Sciences, Lübeck, Germany; 2Department of Anaesthesiology, University Medical Center Schleswig-Holstein, Campus Lübeck, Germany

Especially during long term support ventilation continuous assessment of the patient’s work of breathing can be helpful to improve the quality of the assistance. We designed the Oeselon-Delta (O+D) method to estimate non-invasively transdiaphragmatic pressure (Pdi) and started validation in a study with volunteers.

Methods: Respiratory flow and airway pressure were recorded from 11 healthy men (21 to 68 years old) during quiet spontaneous breathing, increased effort and supported by a ventilator in ASB mode. Pdi was measured for control using a double-balloon catheter. Each 3 to 5 cycles our method was applied getting an estimation of respiratory resistance R and compliance C used to reproduce the Pdi of the coming cycles, which was compared to the measured Pdi by their respiratory pressure time products (PTT).
Results: The short occlusions required by O+D did not disturb the volunteers and produced the expected signals. The obtained R (3.2 to 7.1 cmH2O/l/s) and C (58.7 to 97.7 ml/cmH2O) remained in the usual range for healthy adults. Regression and correlation analysis revealed high agreement between methods (PTP0 = 1.00*PTPv+0.02, r=0.92, R2=0.86). The overall differences (n=2420 (220 per volunteer)) were 0.01±10.3 cmH2O/s (mean±2SD).

Conclusions: The results obtained demonstrate great potential in the developed method. A study with 30 volunteers is being carried out to complete validation.

2852
Initiation of nocturnal ventilation using an intelligent autotitrating non-invasive ventilator: Impact on ventilatory efficiency, sleep and adherence
Jay Jays, Julia Kelly, Rachel Pickerill, Michelle Chawin, Mary Morrill, Anita Simonds.
Sleep and Ventilation Department, NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, London, United Kingdom

Intro: A novel intelligent non invasive ventilator allows automated set-up & delivery of volume assured ventilation within preset pressure support boundaries adjusting to patient requirements (iVAPS). iVAPS controls nocturnal hypoventilation (NH) comparably to standard non invasive pressure support ventilation (PS) in established NIV users. We hypothesise iVAPS is as effective as PS in naive patients for controlling NH.

Methods: 18 patients with chronic obstructive or restrictive disorders & newly diagnosed NH, (mean±SD) age 51(17) yrs, mean day PaO2 9.2(1.2) kPa, PaCO2 6.4(0.7)kPa completed a randomised crossover study of iVAPS vs PS (ResMed Ltd). Baseline FEV1/FVC & respiratory muscle strength (RMS) were repeated at 1 month treatment, plus polysomnography.

Results: iVAPS used less PS for the same ventilatory outcome; 7.7(2.9) v 10.2(2.9) cmH2O (p=0.03*).

Conclusion: No differences were seen for FEV1/FVC, RMS or sleep quality; arousal index 16.9(9.2) v 18.1(12.0) (p=0.65), O2 desaturation index 7.2(6.6) v 6.4(6.9) (p=0.59).

Adherence was superior with iVAPS: 5.6(2.1) v 4.6(2.3) hrs/day (p=0.002). Patients expressed an iVAPS preference.

Conclusion: iVAPS is as effective as PS initiated by a skilled healthcare professional in controlling NH. It may facilitate NIV use without extensive prior team experience & may encourage compliance/adherence to therapy for patients newly adjusting to NIV.

2853
Impact of long-term target-volume noninvasive positive pressure ventilation on sleep quality
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Objective: Target-volume noninvasive positive pressure ventilation (TV-NPPV) was introduced to combine the advantages of volume- and pressure-preset NPPV. However, diverging results have been reported regarding a deterioration of sleep quality due to pressure variation.

Methods: 12 COPD-patients on long-term high-intensity NPPV (HI-NPPV) were switched to TV-NPPV for 10 weeks. Sleep quality and overnight gas exchange were analyzed at run-in during HI-NPPV and after 10 weeks of TV-NPPV. Two TV-NPPV-settings were tested overnight in a randomized order: 8ml/kg ideal body weight (TV1) versus 110% of individual tidal volume analyzed during follow-up HI-NPPV (TV2). Inspiratory pressures were set to -5cmH2O up to 35cmH2O. TV-NPPV-settings reflecting the lower overnight transcutaneous PCO2-values (PtcCO2) were chosen for long-term TV-NPPV.

Results: 10 patients completed the study, 2 patients refused to complete the trial using TV2-NPPV at home. Mean overnight PtcCO2 was similar during HI-NPPV and TV-NPPV (both 45±5mmHg), p=0.75. In addition, no difference was found comparing sleep quality by polysomnography regarding sleep efficiency, sleep stages, total sleep time, arousal index, apnoe-hypopnoea index or oxygen saturation.

Conclusion: After 10 weeks of TV-NPPV at home no differences regarding sleep quality or overnight PtcCO2 were observable compared to conventional HI-NPPV.

2854
Home polysomnography in the management of noninvasive ventilation in neuromuscular patients
Grazia Crescimanno, Francesca Greco, Oreste Marrone. Institute of Biomedicine and Molecular Immunology, Italian National Research Council, Palermo, Sicily, Italy

Objective: PSG in the management of NIV in NMD patients are lacking.

Design: To compare feasibility and patients’ acceptance of PSG during NIV performed either in hospital or at home.

Methods: Fifty-two consecutive NMD patients on long-term NIV were assigned to home or to unassisted hospital PSG during NIV application. A 7 item self-questionnaire was administered after PSG to explore perceived sleep efficiency, sleep quality, awakenings, and acceptance of the polysomnographic procedure. Sleep was scored according to AASM rules.

Results: One home and 1 hospital PSG were not reliable due, respectively, to insufficient sleep or to signal loss. Four hospital and three home recordings showed minor technical problems that did not affect their reliability. The remaining 43 recordings were technically excellent both as regards neurological and respiratory signals. Subjective (382.80±114.28 vs 347.94±77.3 minutes, respectively) and objective total sleep time and sleep efficiency (68.80±19.40 vs 72.03±15.86%), that were correlated to each other, were similar in the two groups. Acceptance of home PSG (8.28±1.99 on a scale from 0 to 10) was higher than for hospital PSG (6.84±2.42, p=0.02).

Conclusion: In ventilated NMD patients, feasibility and reliability of PSG, as well as subjective and objective sleep quality, do not differ if it is performed in hospital or at home. Acceptance of the procedure in the home environment is higher.

2855
Is volume assured ventilation always able to compensate volume loss in presence of leaks?
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Background: Volume assured (VTG) ventilation is a pressure targeted mode aimed to guarantee a target tidal volume (Vt) by varying the inspiratory pressure between two preset pressure values. VTG ventilation has been used to correct sleep-related periodic hypoventilations during noninvasive ventilation (NIV). However, in this setting the likelihood of non-intentional leaks (NIL) may be high.

Aim and methods: In a bench study we wanted to assess the VTG NIL compensation algorithm in three turbine driven ventilators designed to set a VTG either with an EVC or with an ILC (Vivo50, Breas; PB560, Covidien; Ventimotion, Weimann). All ventilators were tested in random order using a lung simulator (Ingmar, ASL5000) in VTG Pressure Control mode with both the ILC and the EVC.
at three level of leaks (15, 27 and 37 l/min) and at three different conditions of respiratory mechanics: normal, obstructive and restrictive.

Results: All the ventilators in the ILC configuration were able to maintain the Vtg in all simulated conditions; conversely, during all simulated leak conditions when the EVC was used a significant fall both in Vt and inspiratory pressure compared to the baseline value was observed.

Conclusions: All single circuit ventilators tested in ILC configuration were able to compensate the volume loss and to ensure the preset Vtg in all leak conditions but failed to ensure the Vtg when the EVC was used.

2856
Effectiveness of the use of heliox on nebulizer associated with noninvasive ventilation in chronic obstructive pulmonary disease patients: A randomized controlled trial
Vittoria Lima, Ceyda Reinaux, Luciana Alcoforado, Shirley Campos, Catarina Rattes, Simone Brandão, Valdecir Galindo Filho, Armêla Dornelas de Andrade, Physiotherapy, Federal University of Pernambuco, Recife, Brazil Saúde Materno-Infantil, Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Brazil

Objective: To evaluate the efficacy of nebulized bronchodilators carried by heliox associated with NIV in the pulmonary deposition of radioaerosol in patients with COPD.

Methods: A randomized controlled trial involving 37 patients divided into four groups: heliox NIV, oxygen NIV, heliox and oxygen. For scintigraphy pulmonary inhalation dose was administered a dose of diethanolaminomonoacetate labeled with technetium (99mTc-DTPA). 25 mcU combined with fenoterol brome (0.12 mg) and ipratropium bromide (0.25 mg) delivered through a bi-level noninvasive ventilation system using a face mask with two unidirectional valves and connected to the nebulizer for radioisotopes (IPAP = 10 cm H2O and EPAP=8 cm H2O). Images were acquired immediately after the intervention using a Gama camera and Regions of interest was determined.

Results: There was a higher radioaerosol pulmonary deposition in the lower third in the heliox NIV and oxygen NIV groups compared to oxygen (p=0.03 and p=0.02, respectively). We observed a higher deposition in the middle third (p=0.008) in heliox NIV group when compared to O2. Thus, there was a positive correlation gain in inspiratory capacity(IC) and the total area of the right lung (p=0.04, r=0.71) in the heliox NIV group.

Conclusions: Our results suggest that coupling heliox or oxygen with bi-level NIV reached a higher lung radioaerosol deposition in the lower third for both lungs. The association between heliox and NIV seem to be more effective to promote a higher radioaerosol peripheral deposition considering the gain of the IC. Supported by: CAPES, CNPq, FACEPE.

Table 1

<table>
<thead>
<tr>
<th>Leakage (l/min)</th>
<th>Analyzed “Breath” (n)</th>
<th>External Sensor</th>
<th>Internal Sensor (Device)</th>
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<td>VTe (ml)</td>
<td>%Predicted</td>
<td>VTe (ml)</td>
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<td>57</td>
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<td>69</td>
<td>43</td>
<td>105±36</td>
<td>21±7</td>
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Conclusions: Externally measured VT is only reliable when mask leakage is minimal. Since measurement is based on airflow inside the sensor, other derived parameters are also affected. The corrected VT from the internal sensor of the NIV device is much less susceptible to leakage but tends to overestimate the actual VT in the setup we used. When exact measurements are crucial, beforehand assessment of results under controlled conditions is advisable.

313. Tuberculosis: epidemiological and public health features

P2858 Agreement between Quantiferon-TB-Gold In Tube, T-SPOT.TB and tuberculin skin testing for diagnosing latent tuberculosis infection in a contact tracing study
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Aim: To determine the agreement between Quantiferon-TB Gold In Tube (QFN), T-SPOT-TB and TST in diagnosing LTBI in a contact study.

Methods: 753 individuals from contact tracing studies were included in the study. In all cases QFN and TST were performed, and in 141 patients the T-SPOT was also performed. TST was negative when the induration was less than 5 mm.

Results: The QFN and TST obtained concordant result in 478 cases from the 753 patients (the overall agreement was 63%), being both tests negative in 145 cases, and positive in 333 cases. From the 275 discordant results, in only one case the TST was negative and the QFN positive (corresponds with a high degree of exposure to the index case), and in 274 cases the TST was positive and the QFN negative, corresponding in 239 cases to BCG-vaccinated patients, and without significant difference between time of exposure to the index case.

With regards to the 141 patients tested with T-SPOT both in vitro tests were concordant in 120 cases (85.1%), being in 61 cases both tests negative, and in 59 cases positive. From the 21 discordant results, in 5 cases the QFN was positive and the T-SPOT negative, and in 16 cases the QFN was negative but the T-SPOT positive, being in 15 of them the time of exposure significantly higher.

Conclusions: QFN and T-SPOT-TB have a high concordance in the diagnosis of LTBI. T-SPOT-TB shows a higher number of positive results than QFN. The main discordant results between TST and QFN should be attributed to the BCG vaccination. Both tests seem useful for the diagnosis of LTBI in the contact studies. The study was supported by a grant from FIS (08/1738).

P2859 Tuberculosis in health care staff in Romania, 2006-2010
Nicoleta Cigan1, Horia Coci1, Elimara Bream. Central Coordination Unit of Romanian National Tuberculosis Program, “Marius Nasta” Institute of Pulmonology, Bucharest, Romania

Introduction: Health care staff represents a well recognized high risk group for TB.

Objective: To analyze characteristics of TB cases out of health care facilities in Romania during 2006-2010 by demographic, clinical, bacteriological parameters and treatment outcomes.

Methods: Retrospective descriptive study of TB cases notified among health care staff in Romania from 2006 to 2010. Data and information used was obtained from the National TB Register.

Results: Total number of TB cases reported in health care workers in Romania from 2006 to 2010 was 843, declining from 224 in 2006 to 139 in 2009 and slightly increasing (to 150) in 2010. Most of them were aged from 25 to 39 years. Conversely to the general population, female gender was predominant (over 70%).
as the residence in urban area (over 70% as well). Even the staff in TB network varied between 2006 and 2008 from 12.9% to 7.7% of all medical staff. TB incidence rate in this group was 114.5‰, versus 51.3‰ in other medical staff, in 2010. Pulmonary cases were from 74.0% to 85.9% in 2008. New cases and relapses represented over 96% of all cases (96.8% in 2006 and 99.3% in 2010). In the five years have been reported 18 MDR-TB cases – from in 2008 (6.9%) and positive pulmonary cases) to 3 in 2010 (respectively 3.8%) and none in 2007. Overall success rate was 98.3% in 2007 and 89.3% in 2006.

Conclusions: TB incidence rate in health care staff in TB facilities is 2.2 times higher than in the personnel in other health care facilities. New pulmonary cases were predominant, with a few MDR-TB cases and a therapeutic success rate over 89%.

P2860 Pattern of tuberculosis (TB) notifications among health care workers (HCW) attending a revised national TB control programme (RNTCP) unit in Kottayam Medical College (Kerala India)
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Background: There is paucity of data with regard to pattern of TB in HCW

Aim: To study the pattern of TB among HCW.

Study setting: RNTCP unit of a Medical College in Kerala, India from October 2009-March 2011.

Methods: Clinical profile of patients referred to RNTCP unit with a proven diagnosis or with a clinical and radiologic diagnosis made by a specialist medical teacher were gathered by a preset oral questionnaire and clinical examination.

Result: Out of 1222 TB patients 5.72% (n=70) were HCW-90% of HCW (n=63) were nurses or nursing students, 10% (n=7) were paramedics or doctors and medical students registered in control programme for treatment. 68.6% (n=48) had extra pulmonary TB & 31.4% (n=22) pulmonary TB (OD 2.725). 63.6% (14/22) of pulmonary TB was smear positive. Occurrence of TB lymphadenitis (n=24) and extra pulmonary TB (n=5) were more common among HCW compared to general category patients (p value of <0.05). 92.8% were newly diagnosed (n=65), 4.2% (n=3) retreatment & 2.8% (n=2) MDR. None had brain or meningcal TB. 92.8% were BCG vaccinated.

Conclusion: TB lymphadenitis was more common among HCW compared to general category patients. Majority of HCW coming for treatment in RNTCP were nurses or nursing students. No doctors registered for treatment in control programme.

References:

P2861 Tuberculosis (TB) notifications in healthcare workers (HCW) in Liverpool, UK
Nicholas Cousins1, Syed M.H. Kazmi2, Sean Mackin3, Clifford Bisacre2, Peter Davies2.* School of Medicine, University of Liverpool, Merseyside, United Kingdom; 2York Centre, Liverpool Community Health, Liverpool, Merseyside, United Kingdom

Background: The number of overseas HCW in Liverpool has grown sharply in recent years. In 2005, an audit demonstrated a rise in the number of TB notifications 6 years later to assess the impact of improved TB screening.

Methods: Clinical profile of patients referred to RNTCP unit with a proven diagnosis or with a clinical and radiologic diagnosis made by a specialist medical teacher were gathered by a preset oral questionnaire and clinical examination.

Result: Out of 1222 TB patients 5.72% (n=70) were HCW-90% of HCW (n=63) were nurses or nursing students, 10% (n=7) were paramedics or doctors and medical students registered in control programme for treatment. 68.6% (n=48) had extra pulmonary TB & 31.4% (n=22) pulmonary TB (OD 2.725). 63.6% (14/22) of pulmonary TB was smear positive. Occurrence of TB lymphadenitis (n=24) and extra pulmonary TB (n=5) were more common among HCW compared to general category patients (p value of <0.05). 92.8% were newly diagnosed (n=65), 4.2% (n=3) retreatment & 2.8% (n=2) MDR. None had brain or meningcal TB. 92.8% were BCG vaccinated.

Conclusion: TB lymphadenitis was more common among HCW compared to general category patients. Majority of HCW coming for treatment in RNTCP were nurses or nursing students. No doctors registered for treatment in control programme.

References:

P2862 Tuberculosis among health care workers
Maya Zbekovka, Biljana Bievcska Poposka, Ismail Vati. TB Department, PHI Institute for Lung Diseases and Tuberculosis, Skopje, Macedonia, The Former Yugoslav Republic of

Background: The number of overseas HCW in Liverpool has grown sharply in recent years. In 2005, an audit demonstrated a rise in the number of TB notifications 6 years later to assess the impact of improved TB screening.

Methods: Clinical profile of patients referred to RNTCP unit with a proven diagnosis or with a clinical and radiologic diagnosis made by a specialist medical teacher were gathered by a preset oral questionnaire and clinical examination.

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Conclusion: TB lymphadenitis was more common among HCW compared to general category patients. Majority of HCW coming for treatment in RNTCP were nurses or nursing students. No doctors registered for treatment in control programme.

References:

P2863 Risk of latent tuberculosis infection among healthcare trainees
Anja Schablon1, Gema Diner2, Ute Anskे2, Felix Ringshausen2, Albert Nienhaus1,3. *Vaccination Competence Centre for Epidemiology and Health Service Research in Nursing, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; 2Occupational Safety and Health, Vivantes, Berlin, Germany; 3Pneumology, University Medical Centre, Hannover, Germany

Objective: The prevalence of latent tuberculosis infection (LTBI) and the risk of tuberculosis infection in nursing students in Germany are unknown. Therefore trainings were followed over a three-year period for the prevalence and risk of LTBI.

Method: In a prospective cohort study, all trainees (n=194) who began training as a nurse or carer at the Vivantes Healthcare Training Institute in Berlin on 1 October 2008, and 1 April 2009, were IGRA-tested at three different times. IGRA results were performed at the start of training and at the end of the first and third years of training. Socio-demographic data and possible risk factors were recorded.

Results: The cohort consisted of 154 IGRA-negative trainees (n=154) who began their training) of a total of 194 trainees. 70% were female. The average age was 23. The LTBI prevalence was 2.1% (4/194). 40 trainees quit before completing their training. In the first follow-up test, 2 out of 154 tested IGRA-negative. The prevalence of LTBI was 1.3%.

Conclusion: The prevalence rate of LTBI was 2.1% in this cohort. The LTBI prevalence rate was lower than expected. Therefore IGRA testing in this low risk group is feasible. However, screening should focus on trainees with personal risk factors for TB. All others should only be tested after they have been in close contact with a TB index patient.

P2864 The effect of the introduction of IGRA in screening French healthcare workers for tuberculosis
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Introduction: In France pre-employment screening for tuberculosis (TB) is performed for healthcare workers (HCW). Screening is repeated, when exposure to TB patients or infectious material occurs. The results of the TB screenings were analysed in a retrospective analysis.

Method: TB screenings were performed with Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (Quantiferon Gold in tube QFT). If TST was >5mm or TST increased by >10 mm, X-ray and pneumology consultation regarding preventive treatment of latent TB infection was performed. The screening results of 637 HCWs on whom QFT was performed were extracted from the files of the University Hospital of Nanterre.

Results: In 3 (0.5%) HCWs the QFT was indeterminate. In 22.2% the QFT was positive. A second QFT was performed in 118 HCWs. Reversion rate was 42% (5 out of 17). Conversion rate was 6% (6 out of 98). TST was performed in 466 (73.5%) of the HCWs. TST >10mm results were 77.4%. In those with TST <10mm, QFT was positive in 14% and in those with TST >10mm, QFT was positive in 26.7%. When based on QFT results, X-ray and pneumology consultation could have been reduced to 28.6% of those selected by TST.

Conclusion: TST overestimated the prevalence of LTBI in this cohort. The de-
cision on X-ray and consultation regarding preventive treatment should be based on QFT rather than TST results. The high reversion rate should be taken into consideration when consulting HCWs regarding preventive treatment.

P2865
Contact screening in tuberculosis. Can we identify those with higher risk?

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Introduction: Contact tracing is part of the tuberculosis (TB) elimination strategy. It is important to know which risk factors are associated with a positive screening.

Objectives: To identify risk factors associated with a positive screening.

Material and methods: During 2011, contacts of patients with pulmonary TB (sputum or broncho-alveolar lavage smear or culture positive), followed for screening in a TB reference centre, were questioned about their exposure to the index case. Positive screening was defined as active TB or latent infection. Contacts with incomplete characterization of exposure, unfinished screening or a past history of TB were excluded. A binary logistic model was used to analyze the variables.

Results: We observed 509 contacts of which 359 (153 men, median age: 32 years) were included in the analysis. 76 had a positive screening. Positive screening was associated with a positive sputum analysis of the index case (OR=2.62, 95%Ci=1.33-5.14) and with coinhabitation (OR=3.42, 95%Ci=1.66-7.07). Each additional year in age of the contact implied an increase in the odds for infection of 3% (OR=1.03, 95%CI=1.02-1.05) and each additional day of symptoms by the index case, previous to treatment, implied an increase in the odds for infection of 3% (OR=1.03, 95%CI=1.02-1.05). No significant differences were found regarding size and ventilation of the exposure site.

Conclusions: This study shows that there is a significant increase in the risk of TB transmission to contacts for every day that the diagnosis of the index case is delayed. Increased risk was also shown for coinhabitants, contacts of older age and the presence of positive sputum smear or culture of the index case.

P2866
Approaching tuberculosis in a vulnerable group

Elmira Ibraim1, Nicoleta Cioran1, Nicoleta Popescu2, Florentina Liguia Pârămucă1, NTPI, Marius Năstase Institute of Pulmonology, Bucharest, Romania; 2Medical Department, Samusocial, Bucharest, Romania; 3Public Health and Management, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

Introduction: The homeless represents a high risk group for TB, with poor access to health care services. TB prevalence among the around 5,000 homeless estimated to live in Bucharest is not known.

Aims and objectives: To detect active TB cases in homeless population in Bucharest.

Methods: A screening program was developed based on partnership between the National TB Programme and Samusocial Romania (NGO providing medical, psychological and social support to homeless people). Persons coming to the surgery service of Samusocial have been screened for TB in TB facilities. Any homeless giving a positive informed consent has been included and only exclusion criterion was having another chest X-ray in the previous 6 months.

Results: In the 248 cases registered from January to June 2011, 83.9% were males, mean age was 43.9 years (from 18 to 73 years old), 30.2% didn't have any ID document and half were at first medical consultation. TB has been suspected in 44.4% by clinical criteria, but from eligible persons only 48% were screened by chest X-ray, 14.1% refused and 35.5% didn't come back for screening. Active TB has been found in 8 cases (6.7% from the screened persons, 2 of them negative to clinical examination. None was previously examined even though they have free access to TB services. All cases were admitted in long-stay hospitals for treatment and monitoring.

Conclusions: In this project the prevalence of active TB was found very high in the homeless population (6,700/1000). Providing free access to TB services is not sufficient to detect TB cases in this high risk group and active screening programs are necessary.

P2867
Tuberculosis and migration: Predictors of epidemiological trends

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Last years economic migration to the big cities of Russian Federation (RF) from other regions of RF and former Soviet republics has considerably increased. Since 2011 free diagnosis of tuberculosis (TB) and free TB-treatment are not available for foreigners in St. Petersburg, RF.

Objective: To determine the impact of health care changes on the incidence of TB.

Methods: The study was conducted in the district of St. Petersburg. The population of this district was 178,000. From 01.01.2008 an office for migrants has opened at the TB dispensary. All persons including migrants who addressed the TB dispensary during 2008-2011 were examined. The causes for examination were symptoms of tuberculosis or casual radiological findings. Examinations and treatment were free for all patients. Until 2008, there was no systematic recording of TB in migrants.

Results: During 2008-2010 the number of new TB cases in local population decreased, the number of infectious TB has decreased in local population and in migrants. The number of new cases of TB in children (local population and migrants) has decreased. In 2011, the trend reversed.

Conclusions: To ensure effective control of tuberculosis free access to health care is required for all TB patients, including migrants.

P2868
New-entrant screening for tuberculosis at port of entry in the U.K.: Is it time to change policy?

Vikas Panaminty1, Henke Kunst, Martin Dedicoat, Joy Troko. Department of Respiratory Medicine & Physiology, Heart of England NHS Foundation Trust, Birmingham, West Midlands, United Kingdom

Background: It is shown that 20% of tuberculosis (TB) cases are diagnosed in persons entering UK within 2 years & in 45% within 5 years of arrival. Therefore the first 2.5 years of arrival in UK presents a period of high risk of reactivation of new-entrants with LTBI. This clearly indicates the importance of early screening & reducing the risk of active TB by giving chemoprophylaxis to patients with LTBI.

UK policy at the moment advocates identification of active TB by chest x-ray for all new arrivals intending to stay for > 6 months from countries with a TB incidence 40/100,000; however, screening is very arbitrary & not standardised. The results are forwarded to local NHS TB services where new entrants intend to settle for complete screening.

Methods: A retrospective review was conducted of all new-entrants who were referred to our institution during a 2 year period, from January 2010, with supposed abnormal chest x-ray at port of entry. All new-entrants were screened for active & latent TB by TST or IGRA

Results: 103 patients, 51 females & 52 males were referred, however only 42 patients (40.7%) were referred to our institution during a 2 year period, from January 2010, with supposed abnormal chest x-ray at port of entry. All new-entrants were screened for active & latent TB by TST or IGRA

Conclusions: Screening new-entrants at port of entry is inadequate. New-entrants often do not attend clinic appointments since they have moved elsewhere or do not understand the necessity of being screened for latent or active TB.

P2869
Impaired pulmonary function and the risk of tuberculosis – A population based cohort study

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Background: Even though COPD is a frequent co-morbid condition in elderly with active tuberculosis relatively little is known to what extent impaired lung

5225
function increases the incidence of active tuberculosis in excess of the direct effect

Introduction:

Methods:

P2870

Incidence of tuberculosis: The application of capture-recapture method to compare two sources of information

Francisco Muñiz1, María López2, Nellieta Carracedo3, Sara Raposo2,
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Objectives:

Methods:

The true incidence of tuberculosis is higher than that in national and international records. Underreporting is estimated to vary between 7% and 27% according to studies.

Conclusion:

The SIVE data on the incidence of tuberculosis in the study area underestimate the true incidence rate. The source of information that involves recording cases of tuberculosis in the community is underused. The capture-recapture method, the annual incidence for 2008 was 48.14 (95% CI 37.85 - 56.44) and for 2009 of 34.17 (95% CI 30.19-38.17). In each of the years studied the number of cases obtained from the pharmacy register was higher.

Conclusions:

The incidence obtained in 2008 using the SIVE data was 18.80 x100000 and the rate using the pharmacy register was 26.77. In 2009, the SIVE data gave an estimate of 18.23 and the pharmacy register 22.50. When applied the capture-recapture method, the annual incidence for 2008 was 44.14 (95% CI 37.85 - 56.44) and for 2009 of 34.17 (95% CI 30.19-38.17). In each of the years studied the number of cases obtained from the pharmacy register was higher.

Conclusions:

P2872

Efficiency of molecular methods for epidemiological investigation in tuberculosis (TB)

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Introduction:

High prevalence of tuberculosis in Poland may related to active transmission.

Objectives:

Methods:

Results:

Adverse drug reactions (ADRs) can lead to a patient interrupting tuberculosis (TB) treatment before completion, and contribute to avoidable morbidity, treatment failure, loss in quality of life, or death. While many national TB control programmes have a long tradition of monitoring patient care, the surveillance of drug-related problems, or pharmacovigilance, has not been systematic. The increasing worldwide use of more extensive regimens for drug-resistant TB, the concomitant use of antiretroviral therapy in patients with HIV-associated TB, and the imminent release on the market of new classes of medicines to treat TB make the case for pharmacovigilance even stronger.

WHO produced guidance this year on pharmacovigilance for TB through the financial support of the European Commission Seventh Framework Programme. The manual discusses how pharmacovigilance can be effectively implemented in a programme through key stakeholders, and provides a step-by-step approach on how to identify signals, assess relationships between an event and a drug, determine causality, and communicate findings. It presents three methodologies of pharmacovigilance which can be applied for the detection, assessment, understanding and prevention of adverse events or any other drug-related problem under field situations. The first two - spontaneous and targeted spontaneous reporting - can be built into national programmes of routine pharmacovigilance and/or tuberculosis control. The third type, cohort event monitoring (CEM), is an active form of surveillance, similar in design and management to an epidemiological cohort study. CEM would be particularly well suited to the post-marketing surveillance of new drugs.

P2874

Administration of BCG vaccination: Survey of practice in the Mersey region, UK

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Introduction:

Method:

Amongst 1853 patients who received a patient history and 183 patients were included in the questionnaire survey. The blood pressure was measured with an automated blood pressure monitor.

Conclusions:

P2875

Reducing patient safety: New WHO guidance on pharmacovigilance in tuberculosis care

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Results:

Questions Guidelines Compliance (%)

Administration of BCG at sites other than upper arm

Prior assessment of HIV status

Prior evaluation of anaphylaxis risk

Availability of resuscitation equipment

Formal training of staff in paediatric resuscitation

* The other sites used were right upper arm or upper thigh. Reasons included patient preference or confusing scar.

There were no recorded episodes of anaphylaxis in the past 12 months. All centres referred patients with severe adverse local reactions appropriately.

Our survey demonstrates that NICE recommendations and their implementation were essential in elucidating areas of uncertainty in the administration of BCG vaccination and subsequently the practice is now uniform across the Mersey region. We intend to extend this survey to national level.
314. Trials in COPD: novel treatments and insights

**P2876**

**Quantification and treatment patterns of real-world patients classified by the GOLD 2011 strategy**

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**Objectives:** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 Strategy classifies COPD patients into 4 categories: A: low risk, low symptoms; B: low risk, more symptoms; C: high risk, low symptoms; D: high risk, more symptoms. Based on risk (FEV1 < 20%, 50% predicted and/or exacerbation history < or ≥ 2 per year) and symptoms (COPD Assessment test [CAT] score < or ≥10 or ≥15), 1007 medical research centers (mRC) dyspnea scale < or ≥2.

We examined the proportion of patients in each category when evaluated by CAT or mMRC, and corresponding pharmacological treatment (CAT classification).

**Methods:** GOLD 2011 criteria were applied to a real-world international COPD population sampled from the Adelphi Respiratory Disease Specific Programme undertaken June to September 2011. Physicians and patients completed matched questionnaires.

**Results:** 2392 patients completed a questionnaire, of which 1508 with all 4 GOLD classification parameters were analyzed. The proportion of patients in categories A, B, C, and D were using a long-acting β2-agonist (LABA) alone (8, 6, 0, and 1%), long-acting muscarinic antagonist (LAMA) alone (37, 25, 8, and 5%), inhaled corticosteroid plus LABA (ICS/LABA) alone (22, 18, 8, and 8%), and ICS/LABA plus LAMA only (11, 20, 46, 43%).

**Conclusion:** CAT assessment increased the number of patients in the more symptomatic categories (B and D), compared with mMRC. Contrary to the GOLD 2011 recommendations, by CAT assessment, a high proportion of low-risk patients (A and B) were using ICS/LABA.

**P2877**

**Differential dropout may affect exacerbation risk estimates differently in moderate-to-severe COPD**

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**Background:** Differential withdrawal of patients from clinical trials (dropout) complicates interpretation of the effect of intervention on the exacerbation frequency in COPD studies. We examined the impact of differential dropout on exacerbations in moderate-to-severe COPD (GOLD grades 2–4).

**Methods:** Patients in 3 pooled COPD studies were randomised to budesonide/formoterol (B/F 320/μg bid) or placebo (P) via Turbuhaler®. Exacerbations, dropouts and a composite of the two outcomes were examined over the first 3 months of treatment.

**Results:** 1583 COPD patients were studied (24% moderate; 61% severe, 14% very severe). B/F improved time to first exacerbation in moderate and severe but not very severe COPD (HRβ/FP: 0.43 [95% CI 0.25–0.72], 0.45 [0.33–0.63] and 0.58 [0.32–0.95]) vs. P. Time to dropout was improved by B/F vs. P, the differences being larger with increasing COPD severity (HRβ/FP: 0.62 [0.34–1.11], 0.56 [0.39–0.81] and 0.38 [0.18–0.80]). A composite measure of time to first exacerbation or dropout showed a significant effect of B/F in all severities.

**Conclusions:** Differential study dropout (greater with P than B/F) increased as the severity of COPD worsened. This should be considered when interpreting clinical COPD trial data.

**References:**


**P2878**

**A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD**

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**Background:** TD-4208 is a potent and selective inhaled muscarinic antagonist with functional lung selectivity and long duration in preclinical models of bronchodilator.

**Aims:** To investigate the bronchodilatory profile, safety and tolerability of nebulized TD-4208 in patients with COPD and when evaluated by CAT assessment, a high proportion of low-risk patients (A and B) were using ICS/LABA.

**Methods:** Thirty-two patients aged 45-75 years with moderate or severe COPD were randomized in a double blind, complete 4-way crossover study. Single doses of 350 μg or 700 μg TD-4208, ipratropium (500 μg) or placebo were administered using a PARLC® Plus nebulizer in each period. Baseline and serial post-dose spirometry assessments (0-25 hrs) were performed. Safety evaluation included AEIs, vital signs, ECGs, and clinical lab results.

**Results:** A statistically significant improvement in peak FEV1 versus placebo of 174 mL (95% CI: 112, 235) was observed (p<0.001 for each comparison). Similar to ipratropium, onset of action on TD-4208 was rapid and bronchodilation was sustained over the 25-hr monitoring period. FEV1 difference from placebo at 12 hrs was 112.5 mL, 123.4 mL, and 15.3 mL; p <0.001, <0.001 and 0.669, and at 24 hrs was 102.8 mL, 136.6 mL, and -24.2 mL; p <0.001 and 0.327, for TD-4208 350 μg, 700 μg, and ipratropium, respectively. AEIs were generally mild and occurred with similar frequencies in all groups, with the most common being headache and dyspnea. No SAEs occurred.

**Conclusions:** TD-4208 was well tolerated and demonstrated significant peak bronchodilation with rapid onset that was sustained over 24 hrs suggesting a once daily dosing regimen.

**P2879**

**Association of β2-adrenoceptor genotypes with prevention of COPD exacerbations by tiotropium or salmeterol in the POET-COPD® trial**

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**Background:** β2-adrenoceptor (ADRB2) polymorphisms are found at positions B16 (G16R) and B27 (Q27E). The POET-COPD® trial allowed assessing the effects of these polymorphisms on exacerbations in patients treated with tiotropium (Tio) or salmeterol (Sal).

**Methods:** RCT comparing Tio 18 μg qd vs Sal pMDI 50 μg bid over 1 y. 7376 COPD patients aged ≥40 y, with a smoking history ≥10 pack-y, postBD FEV1 <70% pred., FEV1/FVC ratio <0.7, ≥1 exacerbation in past year.

**Results:** Genotype distribution and baseline characteristics of 5125 patients (89.5%) (Tio 2564; Sal 2561) who consented to genotyping were balanced between groups. Exacerbations in the Tio group were unaffected by B16 or B27 genotypes. While B27 did not affect Sal outcomes, B16 significantly modified the efficacy of Sal. The fraction of patients with ≥1 exacerbation was 32.3% in R16R, 39.8% in G16R, and 42.1% in G16G carriers (log rank P-values vs R16R: 0.0130 and 0.0018, respectively). Among R16R carriers, exacerbation risk was lower between groups, while for G16G and G16R, Tio was more effective than Sal.

**Conclusions:** In R16R carriers (16.5% of patients), Sal prevented exacerbations as effectively as Tio. In the majority of patients (83.5%), Tio was superior to the...
**P2880**

**Effects of high dose N-acetylcysteine in COPD patients**

Wilfried De Backer¹, Cedric Van Holsbeke¹, Anna Sadowska², Jan De Backer¹, Rita Claes², Wim Vos², ³

**Aim:** Studies suggest that NAC can reduce inflammation and hyperinflation in COPD patients, but little data is published about effects of high dose NAC (3x500mg daily) on airway remodeling. Since hNAC may induce high levels of GSH, this study focuses on the effect of hNAC on airway structure/function in relation to GSH.

**Method:** A double blind randomized placebo-controlled 2way crossover pilot study in 12 GOLDII patients was performed. Patients were treated twice for 3m with either hNAC or placebo (provided by Zambon S.p.A.) on top of their usual medication according to GOLD guidelines. Respiratory functional imaging (RFI) was used to assess airway volume (iVaw) and resistance (iRaw) (De Backer et al. Radiol. 2010;257(3):854-862). Data was collected at baseline and after both treatment periods.

**Result:** A clear drop in iRaw is seen in patients with a higher anti-oxidant reserve (i.e. low baseline GPx) despite lack of overall improvement in the entire population. This drop in iRaw is observed in patients that were already treated according to GOLD criteria.

**Conclusion:** For the first time reduction in iRaw caused by anti-oxidant mucolytic drug is shown using highly sensitive RFI methods. It would be interesting to study in a larger population whether this indicates recovery of the β₂-receptor sensitivity subject to oxidative impairment. The results demonstrate the potential of using RFI to assess anti-inflammatory characteristics of existing and newly developed compounds.

**P2881**

**Acute effect of erdosteine on preventing recurrence of exacerbation in COPD patients after hospital discharge**

Maurizio Moretti¹, Maria Ballabio², ³

**Introduction:** Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) are frequent cause of hospital admission and associated to high risk of recurrence. Preventing exacerbations is a key treatment goal.

**Objectives:** To evaluate the effect of erdosteine, an anti-oxidant mucolytic agent, given on acute setting during hospitalization for severe AE-COPD to prevent subsequent recurrence of exacerbations.

**Methods:** 15 COPD patients hospitalized for severe AE-COPD randomly received erdosteine 900mg daily or placebo for 10 days in combination with standard treatment. Recurrence of exacerbations after hospital discharge was assessed at 30 and 60 days. Data were correlated to pulmonary function indices and serum C-reactive protein (CRP) measured at 10 and 30 days after hospitalization.

**Results:** Table 1. The mean exacerbation recurrence was significantly higher (p < 0.05) in the placebo group. The recurrence of exacerbation was inversely correlated to FEF25-75% value at 10d (p < 0.05), 30d (p < 0.05) and positively correlated to serum CRP marker of systemic inflammation at 10d (p < 0.05) and 30d (p < 0.05).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CRP mg/100ml</th>
<th>FEF25-75%, mL/sec</th>
<th>No. exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 d</td>
<td>30 d</td>
<td>10 d</td>
<td>30 d</td>
</tr>
<tr>
<td>Erdosteine</td>
<td>0.38</td>
<td>0.29</td>
<td>619</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.36</td>
<td>0.67</td>
<td>375</td>
</tr>
</tbody>
</table>

Data are mean values. *p < 0.05 vs. placebo.

**Conclusions:** Treatment with erdosteine plus standard therapy in severe AE-COPD reduced their early recurrence after hospital discharge. These results were related to improvement in small airway obstruction and decrease of serum CRP at recovery from AECOPD. Mucolytic agents with relevant antioxidant activity may improve clinical outcome after AECOPD by reducing the burst of airway inflammation.

**P2882**

**Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat® inhaler in patients with COPD**

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**Background:** Dual administration may provide improved bronchodilation with conventional once-daily dosing.

**Objective:** To determine the optimum once-daily combination of T+O delivered via the Respimat® inhaler in patients with COPD.

**Methods:** In a randomised, double-blind, 4-period, incomplete crossover study, patients with post-bronchodilator forced expiratory volume (FEV1) of ≥30% and <80% of predicted normal received combinations of T and O, with both agents delivered via separate Respimat® inhalers, as well as O monotherapy.
once daily for 4 weeks (NCT 01040403). The primary end point was trough FEV1 response (L) at the end of week 4.
Results: In total, 232 COPD patients (133 male; 99 female) received treatment. FEV1 responses (tong and up to 6 h post-dose) for O 5 and 10 μg monotherapy were similar. For all doses of T, FEV1 responses were significantly increased when added to O 5 and 10 μg. Dosing order for T when added to O was evident. No safety or tolerability concerns were identified.
Conclusions: Addition of T to O resulted in significant improvements in FEV1 versus O alone. These data support further investigation of T 2.5 and 5 μg combined with O 5 μg in the Phase III T+O clinical trial programme.

P2885
Once-daily NVA237 reduces exacerbations and improves symptoms in COPD patients: A pooled analysis of the GLOW1 and GLOW2 studies.
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Introduction: NVA237 (glycopyrronium bromide) is a safe and once-daily (QD) inhaled long-acting muscarinic antagonist for the maintenance treatment of COPD.
Methods: This is a pooled analysis of the GLGlycopyrronium bromide in COPD airways clinical studies (GLOW1 and 2) which assessed the efficacy of NVA237 50 μg QD vs placebo (PBO) and open-label tiotropium 18 μg QD (TIO) over 26 to 52 wks in COPD patients. Results include exacerbations, symptoms (transition dyspnea index [TDI]) and Health Status (St George’s Respiratory Questionnaire [SGRQ]).
Results: 1854 patients were analyzed (NVA237=1059, TIO=267, PBO=528). NVA237 statistically significantly prolonged the time to first moderate/severe exacerbation vs PBO (WK 26: hazard ratio [HR] 0.64; WK 52: HR 0.67, both p<0.001), which was comparable to TIO (WK 26: HR 0.70, p=0.026; WK 52: HR 0.61; both p<0.001). NVA237 had a statistically significantly lower rate of moderate/severe exacerbations vs PBO (WK 26: rate ratio [RR] 0.66; WK 52: RR 0.66; both p<0.05), while TIO was not significantly different from PBO (WK 26; RR 0.74, p=0.085 and WK 52; RR 0.80, p=0.179). Treatment difference in TDI total score was significant for NVA237 (WK 26: 0.93 and WK 52: 0.57) and TIO (WK 26: 1.05 and WK 52: 0.66) vs PBO, all p<0.05. SGRQ score (LS Mean [SE]) at Wk 52: -3.32 [1.04], p<0.001 and TIO (WK 26: -2.43 [1.01] and WK 52: -2.84 [1.15], p<0.05) vs PBO.
Conclusion: NVA237 once daily significantly reduced COPD exacerbations and improved symptoms vs PBO over 52 wks. Overall, the effects of NVA237 were similar to tiotropium.
Results: In 35 patients analyzed, bronchodilation did not significantly increase 
tar retention (-4.5%, p=0.20), or nicotine retention (-2.6%, p=0.11).
Bronchodilation did not significantly affect our secondary outcomes. Secondary
analysis revealed potentially less retention due to bronchodilation: tar retention
-3.8% (p=0.13), and nicotine retention -3.4% (p=0.01).

Conclusions: Our results do not support the hypothesis that bronchodilation in-
creases cigarette tar and nicotine retention in COPD patients. Instead, we observed
a possibility for less retention.

P2887
Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in
patients with COPD: Mid-high dose assessment
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Rationale: FF/VI is a novel once-daily (OD) inhaled corticosteroid/long-acting
beta2 agonist in development as combination therapy for COPD.

Objective: To evaluate the efficacy and safety of FFVI (2000 and 1000/25) vs
placebo (PBO), FF (200 and 100mcg) and VI (25mcg), given OD via novel dry
powder inhaler in moderate-severe COPD patients for 168 days.

Methods: A multicentre, randomised, PBO-controlled, double-blind, parallel-
group study (N=1224 (ITT)). Co-primary endpoints: weighted mean (wm) FEV1
(0–4h). Addition of FF to VI provided numerical improvements only
in trough FEV1 (0-4h). Additional endpoints to assess the contribution of VI, and
trough FEV1 (Day 169) to assess the contribution of FF and 24h duration of VI. Additional
endpoints included CRQ-SAS dyspnoea, and safety.

Results: Co-primary endpoints, see Figure. Treatment differences from PBO for
dyspnoea scores were -0.12, -0.01, 0.07, 0.24 and 0.10 for FF 100, 200, VI 25,
FFVI 100/25, 200/25, respectively. On-treatment AEs were similar between active
treatment groups (38-47%) and PBO (47%). No treatment effects on 24h urinary
cortisol, laboratory values, or cardiac monitoring parameters were seen.

Conclusions: Addition of FF to VI reduced the annual rate of MSE and time to
onset of 1st MSE, with evidence of a consistent effect of the 100/25mcg strength
in individual studies and the pooled analysis. Lung function improved at all strengths
of FF/VI vs VI in pooled analysis. The safety of the combination is reported
separately.

Funded by GSK: HZC102871: NCT01009463, HZC102970: NCT01107952.

P2889
Efficacy of combination fluticasone furoate/vilanterol (FF/VI) and
salmeterol/fluticasone propionate (SFC) over 12 weeks in patients with COPD
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Introduction: The novel combination of FF, an inhaled corticosteroid and VI, a
long-acting beta2 agonist, is under development as a once-daily (OD) therapy for
COPD and asthma.

Objectives: To compare the efficacy of OD FF/VI and twice-daily (BD) SFC in
moderate-to-severe COPD.

Methods: In a randomised, double-blind, double-dummy, parallel-group study,
COPD patients (mean post-bronchodilator predicted FEV1, = 48%) received
FF/VI 100/25mcg OD AM (N=266) via a novel dry powder inhaler or SFC 50/500mcg
BD (N=262) via DISKU™. Primary efficacy: change from baseline in 0–24h weighed mean (wm) FEV1. Secondary endpoints included time to
100mL improvement on baseline on Day 1 (speed of onsets), SGRQ-C,
safety endpoints included adverse events (AEs).

Results: There were non-significant trends favouring FF/VI (130mL) versus SFC
(100mL) for wmFEV1 (22mL, [95%CI: –18.63, p=0.282) and speed of onset;
FF/VI=161mL, SFC=281mL (p=0.280). A clinically meaningful improvement (≥4.8)
in SGRQ-C score was seen with FF/VI, but not SFC (-3.3), though the
difference (-1.5 [95%CI: –3.9, 0.9]) was not statistically significant (p=0.215).
Both treatments were well tolerated. 13 (4%) and 6 (2%) patients in the FF/VI
and SFC arms experienced serious AEs; the same numbers withdrew as a result of
on-treatment AEs. Safety profiles, including pulse rate, were similar.

Conclusions: OD FF/VI and BD SFC improved lung function in patients with
moderate-to-severe COPD without substantial safety concerns. Primary and sec-

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Introduction: FF/VI is in development as once-daily (OD) combination therapy
for COPD.

Objectives: Assess effect of FF/VI on exacerbation rates in COPD compared
to VI. Safety is described separately.

Methods: In two replicate 1 year studies (HZC871:N=1622, HZC970:N=1633),
after a 28 day run-in with ADVAIR DISKUS® 250/500mcg subjects received FF/VI
50/25, 100/25, 200/25mcg or VI 25mcg OD. Primary endpoint was the annual rate
of moderate/severe exacerbations (MSE). Secondary efficacy endpoints included
time to first 1st MSE and trough FEV1.

Results: Rate ratios (95%CI) for MSE with FF/VI vs VI (by-study & pooled
data) are shown (Figure). There was a reduction in risk in time to 1st MSE vs
VI (p<0.036) for FF/VI 200/25 (HZC970 & pooled) and 100/25mcg (all). Trough
FEV1 vs VI at week 52 was greater (p<0.011) for all FF/VI strengths in HZC871
(50/25=41mL, 100/25=58mL, 200/25=64mL) and pooled data (50/25=38mL,
100/25=42mL, 200/25=46mL) but for 50/25 only (34 mL, p=0.034) in HZC970.

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527s
P2090
Effects of twice-daily aclidinium bromide in COPD patients: A long-term extension of ACCORD-COPD I
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Introduction: The long-term effects of twice-daily (BID) aclidinium 200 μg and 400 μg were assessed in patients with moderate-to-severe COPD.

Methods: In this 52-week, double-blind, extension study, COPD patients on aclidinium 200 μg or 400 μg BID during the 12-week lead-in continued the same treatment while patients in the placebo group were re-randomized (1:1) to aclidinium 200 μg or 400 μg BID. Baseline was prespecified as Visit 2 of the lead-in study. Spirometry, SGRO, and adverse events (AEs) were assessed.

Results: A total of 467 patients completed the lead-in study and 291 patients volunteered for the extension study. At study end, placebo patients re-randomized to aclidinium 400 μg and those on either dose of continuous aclidinium treatment showed improvements from baseline in trough FEV1. All groups showed improvements from baseline in SGRO Total score (range, 4.85-7.92 point improvement).

The percentages of patients with an AE were similar for both doses. Incidence of anticholinergic AEs was low and similar for both groups; dry mouth occurred in 1 patient (400 μg). The incidence of cardiac AEs was low across treatments (<5%, any event) and did not occur in a dose-related manner. The incidence of serious AEs (SAE) was comparable in the 200 μg (14.6%) and 400 μg (13.2%) groups; the one SAE reported in the placebo group was COPD exacerbation. One patient from each treatment group died during the study and both deaths were deemed unrelated to treatment.

Conclusions: Patients continuing long-term treatment with aclidinium 200 μg or 400 μg BID maintained improvements in lung function and health status compared to baseline. Aclidinium was well tolerated throughout this 1-year extension study.

P2091
Pooled analysis of twice-daily aclidinium bromide in COPD patients: Dyspnea and health status in the ACCORD-COPD I and ATTAIN trials
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Introduction: Aclidinium is a novel, long-acting muscarinic antagonist in development for COPD treatment. Pooled analyses of dyspnea and health status data from the ACCORD and ATTAIN trials are shown here.

Methods: Patients (N=1389) were randomized (1:1) to aclidinium 200 μg, 400 μg or pbo BID for 12- and 24-weeks for the ACCORD and ATTAIN, respectively. Endpoints included change from baseline in FEV1 over 3h postdose on Day 1 as well as trough and peak FEV1 at Week 12.

Results: Mean (SD) baseline and % predicted FEV1 were 1.45 (0.525) and 85 (14.3), respectively. Significant improvements in lung function were seen following the first dose, as measured by change from baseline in FEV1 at 0.5h postdose (first time point assessed) on Day 1 (200 μg, 99 mL; 400 μg, 128 mL; both p<0.0001 vs pbo). The long-term effects of twice-daily (BID) aclidinium 200 μg and 400 μg were sustained throughout the study. Both doses resulted in statistically significant improvements from baseline to Week 12 in trough FEV1; a greater improvement and a clinically significant effect in trough FEV1 was seen with the higher dose (200 μg, 80 mL; 400 μg, 112 mL; both p<0.0001 vs pbo). Mean change from baseline to Week 12 in peak FEV1 was 167 mL and 191 mL for 200 μg and 400 μg, respectively (both p<0.0001 vs pbo), with numerically greater improvements following treatment with the 400 μg vs 200 μg dose at all measured time points from 0.5h to 3h postdose.

Conclusions: Both doses of aclidinium produced significant improvements in lung function in COPD patients, with the 400 μg dose being consistently more effective. Maximal improvements in lung function were seen at Day 1 and were maintained over 12 weeks.

P2092
Twice-daily aclidinium bromide in COPD patients: A pooled analysis of lung function in the ACCORD-COPD I and ATTAIN trials
Edward Kerwin1, Paul Jones2, Anthony D’Urzo3, Ludmila Rekeda4, 
1Clinical Research Institute, Medford, United States; 2Division of Clinical Sciences, St. George’s University, London, United Kingdom; 3Family & Community Medicine, University of Toronto, Canada; 4Biostatistics, Forest Research Institute, Jersey City, United States; 5R&D Centre, Almirall, S.A., Barcelona, United States; 6Clinical Development, Forest Research Institute, Jersey City, United States

Introduction: Aclidinium is a novel, long-acting muscarinic antagonist being investigated for maintenance treatment of COPD. Pooled analyses of lung function data from the ACCORD and ATTAIN trials are presented here.

Methods: Patients (N=1389) were randomized to aclidinium 200 μg, 400 μg, or pbo BID for 12- and 24-weeks for ACCORD and ATTAIN, respectively. Endpoints included change from baseline in FEV1 over 3h postdose on Day 1 as well as trough and peak FEV1 at Week 12.

Results: Mean (SD) baseline and % predicted FEV1 were 1.45 (0.525) and 85 (14.3), respectively. Significant improvements in lung function were seen following the first dose, as measured by change from baseline in FEV1 at 0.5h postdose (first time point assessed) on Day 1 (200 μg, 99 mL; 400 μg, 128 mL; both p<0.0001 vs pbo). The long-term effects of twice-daily (BID) aclidinium 200 μg and 400 μg were sustained throughout the study. Both doses resulted in statistically significant improvements from baseline to Week 12 in trough FEV1; a greater improvement and a clinically significant effect in trough FEV1 was seen with the higher dose (200 μg, 80 mL; 400 μg, 112 mL; both p<0.0001 vs pbo). Mean change from baseline to Week 12 in peak FEV1 was 167 mL and 191 mL for 200 μg and 400 μg, respectively (both p<0.0001 vs pbo), with numerically greater improvements following treatment with the 400 μg vs 200 μg dose at all measured time points from 0.5h to 3h postdose.

Conclusions: Both doses of aclidinium produced significant improvements in lung function in COPD patients, with the 400 μg dose being consistently more effective. Maximal improvements in lung function were seen at Day 1 and were maintained over 12 weeks.

Table

<table>
<thead>
<tr>
<th>Baseline values</th>
<th>Aclidinium 200 μg</th>
<th>Aclidinium 400 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, L (Mean (SD))</td>
<td>1.44 (0.57)</td>
<td>1.37 (0.64)</td>
</tr>
<tr>
<td>FEV1, % of predicted (Mean (SD))</td>
<td>47.45 (13.93)</td>
<td>45.52 (14.26)</td>
</tr>
<tr>
<td>Morning Pre-dose (Trough) FEV1, change from baseline</td>
<td>0.064</td>
<td>0.091</td>
</tr>
<tr>
<td>Week 1, L, LSM (SE)</td>
<td>(0.011)</td>
<td>(0.018)</td>
</tr>
<tr>
<td>Week 24, L, LSM (SE)</td>
<td>0.062</td>
<td>0.101</td>
</tr>
<tr>
<td>(0.014)</td>
<td>(0.014)</td>
<td></td>
</tr>
<tr>
<td>Peak FEV1, at Week 52, change from baseline, L, LSM (SE)</td>
<td>0.185</td>
<td>0.214</td>
</tr>
<tr>
<td>(0.015)</td>
<td>(0.015)</td>
<td></td>
</tr>
<tr>
<td>Normalized (ACCRD) FEV1, at Week 52, change from baseline, L, LSM (SE)</td>
<td>0.116</td>
<td>0.144</td>
</tr>
<tr>
<td>(0.015)</td>
<td>(0.015)</td>
<td></td>
</tr>
<tr>
<td>SGRO Total Score at Week 52, change from baseline, LSM (95% C.I.)</td>
<td>-5.3</td>
<td>-5.2</td>
</tr>
<tr>
<td>(6.8 - 3.8)</td>
<td>(6.7 - 3.8)</td>
<td></td>
</tr>
<tr>
<td>EuroQol, at Week 52, change from baseline, LSM</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>Weighted State Health Index</td>
<td>0.91</td>
<td>0.91</td>
</tr>
</tbody>
</table>
ized FEV1,AUC0−3, and change from baseline to Week 52 in SGRQ and EuroQol scores.

Results: A total of 605 patients were randomized to this study. Both aclidinium 200 μg and 400 μg BID resulted in improvements from baseline to Week 52 in trough and peak FEV1 (Table), with numerically larger increases seen with the 400 μg dose. At study end, change from baseline in normalized AUC0−3 FEV1 was also improved for both groups, with greater improvements seen with the higher aclidinium dose (Table). Both treatment groups showed clinically significant improvements in SGRQ Total score and improvements in EuroQol, parameters from baseline to Week 52 (Table).

Conclusions: Treatment with aclidinium 200 μg or 400 μg BID results in benefits in lung function and health status in COPD patients over 1 year.

315. Pharmacological and non-pharmacological management of COPD

P2894

Effect of inhalation of tobramycin on reduction of hospitalisation rate in severe COPD

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Introduction: Exacerbation in severe COPD often requires hospital treatment and has a negative impact on patients prognosis. An important cause of frequent exacerbations is lower airway bacterial colonisation in stable disease. In addition moderate bronchectasis are present in up to 50% in severe COPD. The study investigated the effect of daily inhalation of tobramycin on hospitalisation rate in severe COPD.

Methods: At six centers we randomly assigned 44 patients (30 males) with severe COPD (FEV1 of predicted value 42.8±7.1 Tobra and 33.5±10.3 placebo) and a minimum of two hospitalisations in the year before inclusion. Patients inhaled twice daily for 12 months 80 mg tobramycin (GERNEBRICIN®) or isotonic saline ( placebo) with a jet nebulizer (Puri Boy SX). Primary endpoint was hospitalisation rate in the period of study, secondary endpoints time to first hospitalisation and 6 MWD.

Results:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Tobra</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>n (ITT 1)</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>n (PP)</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65.5±10.1</td>
<td>63.9±8.8</td>
</tr>
<tr>
<td>Hospitalisations in the period of study (n)</td>
<td>4.3±2.6</td>
<td>2.5±1.9</td>
</tr>
<tr>
<td>Time to first hospitalisation (days)</td>
<td>104±38</td>
<td>173±26</td>
</tr>
<tr>
<td>6 MWD (m) study entry</td>
<td>398</td>
<td>380</td>
</tr>
<tr>
<td>6 MWD (m) end of study</td>
<td>272</td>
<td>328</td>
</tr>
</tbody>
</table>

ITT = number of patients which took study medication for at least 28 days.

Conclusion: Inhalation with 160 mg tobramycin by means of a nebulizer over a 12 month period didn’t reduce the hospitalisation rate for patients with severe COPD and a minimum of two hospitalisations compared to placebo. The statistical relevance is reduced by a high drop-out rate specifically in the tobramycin-group unrelated to side effects during inhalation of tobramycin. However, the underlying reason remains unexplained.

P2895

Discharge coordinator intervention prevents hospitalisations in patients with COPD: A randomized controlled trial

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Background: Discharge planning is key element in the healthcare continuum that seeks to bridge the gap between hospital and patient home environment. As limited data is available for COPD, we conceived this study to determine the effectiveness of discharge coordinator intervention in reducing the risk for COPD hospitalisation.

Methods: This was a randomized, controlled trial that compared discharge coordinator intervention with usual care. Patients were enrolled within 48 hours following admission due to COPD exacerbation. Discharge coordinator intervention included educational and self-management sessions with patients and caregivers and liaison with health and social care providers in patient home environment. Patients in control group received standard management.

Results: Of the 253 eligible patients (71.49 years, 72% men, 87% GOLD III/IV), 118 were assigned to intervention and 135 to usual care group. During follow-up of 180 days, fewer patients receiving intervention were hospitalized due to COPD (14% vs 31%; p=0.002). In time to event analysis, intervention was associated with lower rates of COPD hospitalisations (p=0.001). Cox model of proportional hazards adjusted for sex, age, GOLD stage, heart failure, cancer, and long term oxygen treatment demonstrated that intervention reduced risk of COPD hospitalisation (hazard ratio 0.43, 95% confidence interval 0.24-0.77, p=0.002).

Conclusions: Among patients hospitalized for COPD exacerbation, discharge coordinator intervention reduced COPD hospitalisations. Hospital management programs should consider discharge planning to improve outcome in patients with COPD.

P2896

QVA149 administered once daily provides significant improvements in lung function over 1 year in patients with COPD: The ENLIGHTEN study

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Background: QVA149 is a once-daily, fixed-dose combination of the long-acting β2-agonist indacaterol and the long-acting muscarinic antagonist NVA237 (glycopyrronium bromide) in development for the treatment of COPD. This study evaluated the long-term effect of QVA149 on lung function in patients with COPD.

Methods: In a multicenter, double-blind, placebo-controlled study, patients with moderate-to-severe COPD were randomized (2:1) to receive QVA149 (110/50 μg) or placebo (PBO) via a single-dose dry powder inhaler (Breatherhaler®) for 52 weeks. Treatment was taken in the morning at the same time of day. Lung function was measured as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) at 30 and 60 min post-dose at clinic visits over 52 weeks. Missing values were not imputed.

Results: 338 pts (77% male, mean age 63 years; mean post-salbutamol FEV1 57%; predicted, FEV1/FVC 54%) were randomized to receive QVA149 (n=225) or PBO (n=113); 86% and 79% of patients respectively completed treatment. QVA149 significantly increased FEV1 and FVC vs PBO at all assessment points (Table). QVA149 vs PBO differences in FEV1 and FVC (mL) (all p<0.001):

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Week 3</th>
<th>Week 6</th>
<th>Week 12</th>
<th>Week 26</th>
<th>Week 39</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>156</td>
<td>246</td>
<td>268</td>
<td>235</td>
<td>271</td>
<td>231</td>
</tr>
<tr>
<td>60 min post-dose</td>
<td>201</td>
<td>267</td>
<td>276</td>
<td>256</td>
<td>275</td>
<td>257</td>
</tr>
<tr>
<td>FVC</td>
<td>30 min post-dose</td>
<td>221</td>
<td>333</td>
<td>340</td>
<td>268</td>
<td>333</td>
</tr>
</tbody>
</table>

Conclusion: QVA149 once daily provided rapid and clinically meaningful bronchodilation compared with PBO. No tachyphylaxis was observed and the bronchodilator effect was sustained over the 52-week treatment period.

P2897

Pneumonia in COPD patients treated with fixed ICS/LABA combinations

Kjell Larsson1, Kjell Larsson1, Karin Lisper1, Björn Ställberg2, Georgios Stratelis4, Gunilla Telg4, Leif Jörgensen4, Gunnar Johansson1.

1Department of Medical Scinces, Respiratory Medicine, Uppsala University, Uppsala, Sweden; 2Unit of Lung and Allergy Research, National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; 3Deposed Department of Public Health and Caring Sciences, Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden; 4Department of Asthma, Northern Region, Sweden; 5Department of Public Health and Caring Sciences, Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden

Background: Inhaled corticosteroids (ICS) in combination with long-acting β2-agonists (LABA) improve quality of life and reduce exacerbations in chronic obstructive pulmonary disease (COPD). Increased prevalence of pneumonia has been identified during treatment with fluticasone but not with budesonide, but no direct comparions have been performed.

Objectives: To investigate occurrence of pneumonia in a COPD population treated with fixed ICS/LABA combination; budesonide/formoterol (BfF) or fluticasone/salmeterol (SfS) (NCT01146392).

Methods: Medical records’ data from primary care patients ≥ 18 years was linked to Swedish hospital and drug register data for 1999 – 2009. Index date was first prescription of a fixed ICS/LABA combination post COPD diagnosis. Propensity score matching was done at index date.

Results: The total sample covered 9,893 patients. Matching gave two equivalent populations (2,734 patients/group) using either BfF or SfS at index. Mean prescribed daily steroid dose was 562 μg budesonide and 786 μg fluticasone. In all, 15,353 pneumonia diagnoses were seen. 44% of all patients had experienced
pneumonia within 8 years post COPD diagnosis. Yearly rate of pneumonia for B/F was significantly lower, 0.062 compared to 0.11 for F/S; 44% difference (p<0.0001). Yearly rate of hospitalisations due to pneumonia was 0.041 vs 0.074 (+45%), days at hospital/year 0.34 vs 0.63 (+86%) for B/F vs F/S, respectively. Time to first diagnosis of pneumonia showed a hazard ratio of 0.794 (95% CI 0.706, 0.892) in favor of B/F.

**Conclusion:** In this observational register study, COPD patients treated with budesonide/formoterol experienced fewer pneumonias than patients treated with fluticasone/salmeterol.

**Study sponsor:** AstraZeneca.

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**P2999**

Estimates of demand and use for home oxygen for COPD in England and Wales

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**Introduction:** There are an estimated 60,080 patients (40% of GOLD IV) who require home oxygen in England and Wales. It is unknown whether this need is met, or whether assessment and/or review of all home oxygen users would be beneficial.

**Methods and results:** To estimate the prevalence of COPD among home oxygen users, a survey of 2,845 patients was undertaken with patients asked about the single condition for which they were prescribed oxygen. It is calculated that they received it for COPD and 15% gave a reply of “Not Known” or “Not Stated” or ticked two conditions. Thus 68%, from 58%/11.0.15), of all home oxygen were estimated as having COPD. This equates to 5825 patients. It suggests that either supply is matching demand, or that some COPD users may be being inappropriately prescribed home oxygen, and that there are others with an unmet need.

Further data was obtained on oxygen concentrator electricity consumption and cylinder deliveries to 71,078 patients (with varied diagnoses) over a 6-month period from three oxygen providers. A total of 16,657 or 24% patients with a home oxygen prescription used no oxygen, 16,524 used less than 20% prescribed and 5,124 between 20% – 40% prescribed. In addition, 2,664 patients were prescribed Short-Burst Oxygen Therapy (SBOT) without clinical trial evidence that SBOT is effective and for many patients, in addition to their oxygen concentrator.

**Discussion:** These data suggest the importance of research to the home oxygen user in England and Wales and inclusion of clinical assessment and review (HOS_AR) schemes to improve the accuracy of prescription, patient adherence and by withdrawing unnecessary home oxygen, particularly SBOT, ensure that supply matches demand.

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**P2999**

Target lobar volume reduction and COPD outcome measures after endobronchial one-way valve therapy

Archanaj Vajirapalan1, Felix J.F. Herth2, Gerard J. Criner3, Jean Michel Vergeon4, Jonathan Goldin5, Frank Sciruba6, Armin Ernst7, 1Department of Respiratory and Critical Care Medicine, Ludwig-Boltzmann Institute for COPD and Respiratory Epidemiology, Ott-Wagner Hospital, Vienna, Austria; 2Pneumology and Critical Care Medicine, Thoraxklinik, Heidelberg, Germany; 3Temple Lung and Critical Care Medicine, Thoraxklinik, Heidelberg, Germany; 4Center for Computer Vision and Imaging Biomarkers, Department of Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States; 5School of Medicine, University of Pittsburgh, PA, United States.

**Introduction:** Clinical effectiveness of endobronchial one-way valve therapy in patients with emphysema appears to be related to the extent of lobar volume reduction.

**Methods:** Data derived from a multicentre study from 416 patients with severe emphysema (62% male, age 63.4±7.7, FEV1 30±8%), who were randomized to valve therapy (n = 284) or conservative treatment (n = 132), were analyzed. Pulmonary function, exercise capacity, dyspnea scores, and CT analysis of target lobar volume reduction (TLVR) were assessed before and after 6 months of valve therapy.

**Results:** Of patients randomized to the treatment group, 49 (17%) showed >50% target lobar volume reduction, 57 (20%) demonstrated TLVR between 20% and 50%, and 178 patients (56%) > 20% TLVR at 6 months post intervention (p < 0.001). Patients with TLVR > 50% demonstrated greater improvements in lung function parameters, exercise capacity (6-MWT), quality of life (SGRO) and dyspnea score (mMRC) compared with the other groups. Consequently, BODE index was significantly improved by 1.4±1.1, 0.2±1.3, and 0.1±1.3 points in patients with TLVR > 50%, < 50% TLVR > 20%, and TLVR < 20%, respectively, whereas it worsened by 0.3±1.2 points in controls after 6 months (p < 0.001 for inter-group differences). Logistic regression analysis identified target lobar volume reduction as the strongest independent predictor of improved BODE index scores from baseline to 6 months.

**Conclusions:** The extent of lobar volume reduction predicts improvement in BODE index and health outcomes associated with bronchoscopic lung volume reduction using one-way valves.
P2902
Hospital admitted COPD patients treated at home using teledermatology — A randomised, multi-centre trial
Anna Svarn Jakobsen, Lars Christian Laursen, Birte Østergaard, Susan Rydahl-Hansen, Christina Emme, Lone Schou, Klaus Viengpheth Phanareth. Telemedicine Research Unit, Frederiksborg University Hospital, Frederiksborg, Denmark; Medical Department 6, Herlev University Hospital, Herlev, Denmark Research Unit of Nursing, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark Research Unit of Clinical Nursing, Bispebjerg University Hospital and Frederiksberg University Hospital, Bispebjerg, Denmark Telemedicine Research Unit, Frederiksborg University Hospital, Frederiksberg, Denmark Telemedicine Research Unit, Frederiksberg University Hospital, Frederiksberg, Denmark

Background: COPD Patients with acute exacerbations are frequently admitted to emergency wards causing the patients to feel anxiety, loss of control and stress, and also causing considerable healthcare costs for the society.

Aim: We investigated whether patients with COPD exacerbations admitted to a hospital following discharge can be future-safe and safely be treated at home by means of teledermatology technology (TT).

Methods: Fifty-seven patients with severe COPD, who fulfilled the inclusion criteria and consented to participate within 24 hours of a hospital admission, were randomised to receive either standard treatment at the hospital or standard treatment at home using TT. The equipment consisted of a video conference system and a webcam, measuring equipment (spirometer, thermometer, and pulsoximeter), 24 hour online web-service, access to oxygen, nebulizer and medical therapy. Two university hospitals participated. Readmission within 30 days after discharge was selected as primary outcome.

Results: Twenty-nine patients were allocated to the TT group and 28 patients received usual care in the hospital. There were 10 readmissions in each group involving eight patients in the TT group and six patients in the control group. Readmission rate was 27.6% (95% CI 11.3 to 43.9) in the TT group and 21.4% (95% CI 6.2 to 36.6) in the conventional group. No statistically significant differences between groups in readmission rate, use of antibiotics or systemic steroids were seen. No deaths occurred during the study period.

Conclusion: We propose that a considerable segment of patients with COPD exacerbations admitted to hospital can be safely treated at home using the TT solution.

P2903
COPD self management: The impact of implementing self management plans & rescue medications across 3 hospitals
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Introduction: Guidelines for COPD suggests that patients should be given self-management advice and rescue medication.

Aims & Objectives: Assess if a unified self management strategy, consisting of a self management plan, education and rescue medications, reduces hospital readmissions at 30 and 90 days.

Methods: A six month project, across three acute hospitals was carried out. All patients admitted with a COPD exacerbation, unless contra-indicated were given self management advice and rescue medication. Guidelines for COPD suggests that patients should be given self-management plan and rescue medication.

Results: 491 patients were recruited. 53.3%, 54.6% and 25.2% of patients received a self management plan and rescue medication across the three hospitals respectively, with a mean of 36.5%. Common reasons for not receiving these were language barriers and concordance issues.

Conclusions: Unified self management plans and rescue medications in COPD reduces 30 and 90 readmission rates by 12.1% and 5.7% respectively.

P2904
Clinical phenotypes in patients with concomitant obstructive sleep apnea and chronic obstructive pulmonary disease
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1Respiratory Care Clinic, Nippon Medical School, Tokyo, Japan; 2Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

Rationale: Concomitant obstructive sleep apnea syndrome (OSAS) and COPD (overlap syndrome, OLS) may result in the presentation of different clinical phenotypes of each disease.

Objectives: To examine the clinical phenotypes of COPD in OLS cases.

Methods: We conducted a prospective cohort study including 204 patients recruited in 8 years. All the subjects underwent the examinations: pulmonary function tests; polysomnography (PSG); blood chemistry tests, including a KL-6 test; nutritional assessments; computed tomography (HRCT) to assess emphysema (LAAV%); and 6-minute walk tests (6MWT). Subjects with symptomatic airflow obstruction were classified as COPD patients, and the apnea-hypopnea index (AHI) was calculated for assessing OSAS. We analyzed the association between the variables recorded during the examinations.

Results: The overall cohort included 138 male subjects and 23 female subjects (mean age, 54.8 years). The mean FEV1/FVC ratio, mean body mass index (BMI), and mean AHI were 0.77, 25.3, and 30.3 respectively. The AHI values were as follows: 0.5 (n = 9), 5–15 (n = 36), 15–30 (n = 50), and >30 (n = 66). The subjects were divided into the OLS group (n = 34), OSAS alone group (n = 118), COPD alone group (n = 0), and neither group (n = 9). The mean age, BMI, and AHI in the OLS were 66.4, 24.5, and 34.7, respectively. AHI was significantly associated with BMI in the OSAS alone group. This association was not seen in the OLS group, in which there was a trend that low FEV1% predicted was associated with low AHI and AHI was significantly associated with KL-6 (p = 0.0002).

Conclusions: We concluded that OLS did not affect the clinical phenotypes of OSAS and COPD.

P2905
Costs and effectiveness of a disease management program for chronic obstructive pulmonary disease
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1Respiratory Medicine, ASLI Massa e Carrara, Carrara, Italy; 2Internal Medicine, ASLI Massa e Carrara, Carrara, Italy; 3Medical Direction, ASLI Massa e Carrara, Carrara, Italy; 4Primary Care Medicine, ASLI Massa e Carrara, Carrara, Italy

Introduction: The effect of disease management for COPD is not well established.

Objectives: The effect of integrated care intervention (ICI) on hospital admission was examined and a cost analysis was performed.

Methods: 208 COPD patients recruited by general practitioners in Massa-Carrara sanitary district from January 2009 were followed up prospectively. Interventions included individually tailored care plan following GOLD guidelines, educational program on self-management of the disease, treatment supervision during scheduled reviews, home visits and phone contacts by specialised nurses.

Results: Data from the 2-year follow-up were compared with the year prior to its initiation. ICI decreased the frequency of hospitalization and the mean number of hospitalization days in 1-year follow-up period: these results remained stable after 2 years (table 1). The best clinical results were detected in GOLD 2 and 3 stages. Mean daily cost of pulmonary drugs increased (€ 3.1/patient/year vs € 1.3 in the pre-enrolment year), while mean daily cost of hospitalization decreased from € 5.1/patient/year to € 2.2 (p < 0.001).

Table 1

<table>
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<th>1-year Pre-enrolment</th>
<th>1-year Follow-up</th>
<th>2-year Follow-up</th>
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<tr>
<td>Hospital admissions</td>
<td>Hospitalization days</td>
<td>Hospitalizations</td>
<td>Hospitalizations</td>
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<tr>
<td>30.9%</td>
<td>5.20**</td>
<td>0.20</td>
<td>0.26</td>
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<td>2.92</td>
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Data are mean values. *p<0.001 vs 1yr and 2yr follow-up; **p<0.01 vs 2yr follow-up.

Conclusions: The study shows that a standardised ICI based on share-care intervention between primary care and hospital team in COPD patients effectively decreases hospitalizations for exacerbation and total disease costs after 1 year follow-up; these positive results do not change after 2 years.

P2906
Cardioselective beta-blockers are not only safe in patients with COPD, but may also improve the responsibility of FEV1 to beta-agonist: A meta-analysis of randomized controlled double-blind trials
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Objective: To assess the effect of cardioselective beta-blockers on respiratory function of patients with COPD
Methods: The EMBASE, MEDLINE, and the Cochrane Controlled Trials Register were searched comprehensively to identify all relevant clinical trials in humans published between 1986 and May 2011. Randomized, blinded, controlled trials that studied the effects of cardioselective beta-blockers on the forced expiratory volume in 1 s (FEV1) and responsibility of FEV1 to beta-agonist in patients with COPD were included in the analysis. Outcomes measured were the FEV1 and the change of FEV1 after the use of beta-agonist. Results: Sample size for the cardio-selective beta-blockers was 85 cases, non-selective beta-blockers 46. The results showed that FEV1 declined 0.14L with the use of non-selective beta-blockers (z = 6.78, p < 0.0001), and with the use of cardio-selective beta-blockers declined 0.03L (z = 2.08, p = 0.04). Non-selective beta-blockers decrease the response to beta-agonist of FEV1 by 13.42% (z = 10.68, p < 0.0001). Cardio-selective beta-blockers produced no significant change in response to beta-agonist of FEV1 (z = 0.46, p = 0.65). A sensitivity analysis was performed to evaluate the effect of excluding a trial which had a great weight and the result showed an opposite result of the responsibility of FEV1 to beta-agonist, although not statistically significant. Conclusion: Our meta-analysis suggests that cardioselective beta-blockers is not only safe in patients with COPD, but may also improve the responsibility of FEV1 to beta-agonist.

P2007
Continuance and effects of self-training at home using a bicycle ergometer with long-term oxygen therapy
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Rationale: Regular exercise is an important therapeutic modality for advanced chronic obstructive pulmonary disease (COPD). However, daily mobility is severely restricted in patients with COPD. Aim: We evaluated whether self-training at home using a bicycle ergometer with oxygen therapy is an effective therapeutic modality for COPD. Methods: We recruited 129 patients with advanced COPD. After an observation period, each patient was given a bicycle ergometer as per the advice of health care professionals. The patients were instructed to use the ergometer for 20 min each in the morning or afternoon, with oxygen therapy (2L/min), and to maintain the maximum pulse rate at <110 beats/min. Before self-training was undertaken, each patient was examined to assess the effects of the training. We compared the data recorded after 6 months of self-training. Results: The subjects were divided into 2 groups: those using a bicycle ergometer (Group E) and those performing usual exercise (Group U). Group E was further divided into 2 groups: those showing good adherence (Group EG) and those showing poor adherence (Group EP). In Group EG, the mean age, BMI, FEV1%, and walking distance covered in 6 minutes were 72.3, 21.3, 0.4, 42.2, and 43.2, respectively, whereas in Group EP these values were 73.8, 21.1, 4.8, 4, and 407, respectively. The walking distance significantly improved in Group EG. Continuance was 51.4%, and the major reasons for discontinuance were lumbago and arthralgia. Conclusions: Self-training using a bicycle ergometer with oxygen therapy might be useful in select subjects.

P2008
COPD: Disease coping styles
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It is generally known that desadaptative coping plays an important role in deterioration of medical patients’ quality of life (QoL). However, rehabilitation of COPD patients in general is performed uniformly, while individual psychological features of the patient remain ignored. Aim: To identify the basic styles of disease coping in COPD patients. Methods: 43 COPD therapeutic inpatients (male n=36; mean age 65.6±10.4 yr.) were included into the study. All patients were examined by a pulmonologist and clinically interviewed by a psychiatrist. Psychometric scales Beck Depression Inventory (BDI), Temperament and Character Inventory (TCI-125) and NEO-Five Factor Inventory (NEO-FFI), SF-36, Index of Cooperation (IC - developed by Moscow Research Institute of Pulmonology) were also used. Results: Three styles of disease coping were identified: maladaptive denial of physical illness (n=21, 48,8%), health anxiety (n=18, 41,8%), and depression (n=4, 9,3%). Maladaptive denial was comorbid with clinically diagnosed dissocial personality disorder (PD) (n=9, 20,9%), low NEO-FFI Agreeableness and Conscientiousness scores, low TCI-125 Self-Directedness score. Health anxiety and depression were often comorbid with histronic PD (n=7, 16,3%), or avoidant PD (n=4, 6,4%). QoL decrease was prominent in health anxiety and depression groups. Maladaptive denial patients showed relatively fair QoL scores (measured by SF-36), had disturbance of social compliance (measured by IC). Discussion: On the assumption of typology described, we propose developing patient-centered rehabilitation programs, according to the individual COPD patient’s coping style: QoL-oriented program for health anxiety/depression patients, and compliance-oriented for maladaptive denial patients.

P2009
Disease management program for COPD patients with frequent exacerbations
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Objectives: To determine if a disease management program focused on early recognition and self-treatment of COPD exacerbations can reduce hospital admissions due to COPD exacerbation. Methods: We included outpatients with stable COPD who had two or more COPD exacerbations in the previous year. Patients attended an individual education session conducted by a specialized respiratory nurse that included general information about COPD, direct observation of inhaler techniques, smoking cessation counselling and encouragement of regular exercise. Subjects were instructed to recognize signs and symptoms of an exacerbation and to begin action plan medications for symptoms that were substantially worse than usual. Each subject received an individualized written medical action plan and the telephone number to contact the case manager. The nurse made monthly phone calls to patients. Scheduled medical visits were made every three months and after exacerbations. Results: 31 patients were included in the program (94% male; mean age 74 SD 7 years; post-bronchodilator FEV1% predicted 39 SD 11; 100% ex-smokers). The average duration of follow-up was 13.5 (5.5) months. During this period of time a mean of 8 DS 4 phone calls and 5 SD 2 medical visits were made. The frequency of hospitalizations and emergency visits for COPD were lower than the previous year before beginning the program (mean 0.26 SD 0.6 vs. 0.97 SD 1.1, p<0.000). The total COPD exacerbations were significantly lower than the previous year (mean 2.35 SD 1.8 vs. 3.61 SD 1.4; P=0.001). Conclusions: A disease management program focused on early recognition and self-treatment of COPD exacerbations can reduce hospital admissions due to COPD exacerbation.

P210
Daytime risk factors of nocturnal hypoxemia in COPD patients unqualified for long-term oxygen therapy
Yui Wang1, Liang Tiao2, Guochao Shi, Huanying Wan, Xiaoting Cai, Haixing Zhu, Pulmonary Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
Objective: To identify daytime variables that are predictive to nocturnal hypoxemia among COPD patients unqualified for long-term oxygen therapy (LTO). Methods: Forty-eight stable COPD patients with daytime SaO2 ≥95% were enrolled to this study and regarded as patients unqualified for LTO. Patients were divided into 4 groups depending on daytime SaO2: SaO2≥98%, group 1; SaO2≥97%, group 2; SaO2≥96%, group 3; 90%<SaO2<95%, group 4. All patients underwent lung function examinations during daytime. Their nocturnal oxygen saturations were monitored with overnight pulse oximetry (PO). Results: Daytime oxygen saturation was positively correlated with nocturnal mean SaO2 (r=0.79, P<0.0001), while negatively correlated with time spend with saturation below 90% (TB90) (r= -0.75, P<0.0001). No significant relationship was found between lung function parameters and nocturnal SaO2. Patients with daytime oxygen saturation between 90% and 95% were more likely to have lower nocturnal oxygen saturation and longer TB90 (P<0.05). Table 1. Spearman rank correlation coefficient between daytime SaO2 Variables r P value Nocturnal MSaO2 0.79 <0.0001 TB90 -0.75 <0.0001 ODI 0.28 0.0552
Table 2. K-W test and SNK test among different SaO2 levels of COPD patients Variables r2 P value Multiple comparison Nocturnal LSaO2 0.7585 <0.0059 group 1 vs group 4 TB90 0.9115 0.0020 group 1 vs group 4 ODI 0.3640 0.5030 none
Conclusions: Daytime oxygen saturation may effectively predict the occurrence of nocturnal hypoxemia in stable COPD patients unqualified for LTO. To reduce COPD complications and improve prognosis, we suggest a relative indication of LTO for patients with a high oxygen saturation between 90% and 95% and connected with nocturnal hypoxemia.
P2911
Multiple dimensional analysis of arterial blood gas and pulmonary function in patients with COPD
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Introduction: Blood gas analysis is very important and often used to evaluate the hypothesis and hypercapnea in chronic obstructive pulmonary disease (COPD) patients, but little attention has been given to the relationship among blood gas analysis, pulmonary function, body composition and symptoms.

Objectives: To identify the predictor of dyspnea, hypoxemia, hypercapnea in COPD patients, we investigated COPD patients cross-sectionally on multidimensional aspects.

Methods: A total of 309 Japanese COPD patients (334 male, age 71 (64-76), with a smoking history of at least 10 pack-years underwent comprehensive measurements, including medical examination, arterial blood gas analysis, pulmonary function tests, and modified Medical Research Council (MMRC) dyspnea scale. Patients with long term oxygen therapy or non-invasive ventilation were excluded. Possible predictors of MMRC, PaO2 and PaCO2 were analyzed with both univariate and multiple regression methods.

Results: All of PaO2, PaCO2, and MMRC associated significantly with age, various pulmonary function, and/or BMI. In addition, multivariate regression analysis of stepwise manner revealed that PaO2 was able to be explained by %FEV1, %Kco, BMI and age (R^2=0.20, p<0.001). PaCO2 could be explained by %FEV1, %FVC, RV/TLC and age (R^2=0.15, p<0.001). Then MMRC could be explained by %FEV1, %Kco, %FVC, %IC, age and PaO2 (R^2=0.14, p<0.001).

Conclusion: We showed that %FEV1, %Kco and age were important to dyspnea and the estimation of blood gas analysis in COPD patients.

316. Treatment of lung cancer

P2912
Synergistic therapy for NSCLC: Additive preclinical efficacy of interleukin-6 inhibitor madindoline A with crizotinib
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Backgrounds and aims: Crizotinib has also demonstrated the development of acquired drug resistance. Despite secondary mutation, resistance of crizotinib may also be influenced by tumor microenvironment. Senescent cells display a senescent-associate secretory phenotype (SASP) involving the production of inflammatory cytokines that alter tumor microenvironment. Here, we analyzed the level of IL-6 and its signaling pathway in NSCLC cells and assessed the efficacy of IL-6 inhibitor madindoline A in combination with crizotinib in vivo.

Methods: We detected senescence, SASP, IL-6/STAT3 and PI3K/AKT/mTOR signaling after crizotinib treatment in the presence or absence of madindoline A. In addition, multivariate regression analysis of inflammatory cytokines that alter tumor microenvironment. Senescent cells display a senescent-associate secretory phenotype (SASP) involving the production of inflammatory cytokines that alter tumor microenvironment. Here, we analyzed the level of IL-6 and its signaling pathway in NSCLC cells and assessed the efficacy of IL-6 inhibitor madindoline A in combination with crizotinib in vivo.

Results: Crizotinib induced tumor cellular senescence with senescent characteristics including increased senescence-associated f-actin cytoskeletal activity and high expression SASPs. Depletion of the key IL-6 signaling component STAT3 by clinical practice obtained from 166 pts who were treated with pemetrexed in the 1st line treatment.

Methods: We retrospectively investigated the clinicopathological characteristics of 26 NSCLC patients who had undergone BEV therapy in Saitama Medical University International Medical Center and Saitama Medical University Hospital.

Results: The patients had a median age of 64 years (range, 33 to 72 years), and 19 males and current smokers. Epidermal growth factor receptor gene mutations were found in 6 patients (23%). Combined with BEV, each half of 26 patients received the chemotherapeutic regimen of either carboplatin/paclitaxel or carboplatin/pemetrexed. Objective response rate was 54% and disease control rate was 96%, and median progression free survival and overall survival were 100 days and 202 days, respectively. Adverse events included 4% of arthralgia, 27% of hyperpertension, 8% of lower gastrointestinal bleeding, 19% of nasal bleeding, and 23% of proteinuria. Using Kaplan-Meier survival curves and logrank tests, therapeutically influenced neither progression free survival nor overall survival, whereas longer overall survival was observed in NSCLC patients treated with pemetrexed-containing chemotherapy after failure of BEV.

Conclusion: Therapeutic response to BEV does not predict survival benefit of BEV-treated NSCLC patients. Meanwhile, it may be a novel therapeutic option for NSCLC patients who have failed BEV treatment.

P2914
Improved results after preoperative concurrent chemotherapy and high dose radiation therapy in selected cases with stage III N2 lung cancer
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Objective: Optimal management of stage IIIA-N2 non-small cell lung cancer remains controversial. The use of neoadjuvant chemoradiotherapy can present challenges in the perioperative management of patients undergoing lung resection for non-small cell lung cancer. Preoperative chemoradiotherapy may reduce tumor size and lymph node involvement, and can result in significant fibrosis around key anatomic structures, making dissection difficult and hazardous.

Methods: This is a retrospective study of 40 consecutive patients with T3-1 N2 M0 lung cancer who underwent induction chemoradiation before surgical intervention from January 2005 through December 2011. Induction chemotherapy consisted of cisplatin, etoposide, and concurrent radiotherapy to a mean dose of 54.3 Gy. Lung resection was performed within 6 weeks of completion of chemoradiation.

Results: Twenty-five patients were submitted to pneumonectomy, simple or intrapulmonary one, 10 to lobectomies and 5 either to segmentectomies or atypical resection. R0 resection was achieved in 75% of cases. The median perioperative mortality rate was 2.5% (one died in the lobectomy group). No important morbidity was noted and the overall hospital stay ranged from 7 to 14 days.

Conclusion: Chemoradiation before pulmonary resection in carefully selected patients with surgically resectable stage IIA (N2) non-small cell lung cancer can be performed with low mortality and morbidity and might lead to improved overall and disease-free survival.

P2915
Pemetrexed in the first line treatment in non-smell cell lung cancer (NSCLC): A multicentre prospective analysis of data from clinical practise of Czech Republic
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Background: Pemetrexed is a novel multi-targeted antifolate that is used in the treatment of NSCLC. This analysis presented examines data from Czech Republic obtained from 166 pts who were treated with pemetrexed in the 1st line treatment.

Methods: Pts with advanced NSCLC were treated between 12/2008 and 12/2011 in 10 institutions with pemetrexed 500mg/m2 and cisplatin 80 mg/m2 on day 1 every 3 weeks. We evaluated efficacy and toxicity.

Results: From 166 pts were 47% men and 53% women, median age 62 years. Non-smokers were 32.5%, stop-smokers 26.5% and current smokers 41.0%. Pts 0 was in 18.1%, PS 1 in 76.5% and PS 2 in 5.4%. Stage IV had 86.2% pts. Adenocarcinoma was confirmed in 84.9%. CR was confirmed in 1.5%, PR in 26.3%, SD in 41.6%, 21.9% progressed and 8.8% pts were not evaluated. Major toxicities (grade 3-4) were neutropenia in 10.8%, leucopenia in 4.8%, anemia...
in 6.0% and thrombocytopenia in 1.2%, pts, but the therapy was finished due to toxicity only in 6 (4.4%) patients. Median OS (95% CI) was 12.5 months (7.5; 17.5). Probability of one-year survival was 52.2%. PFS (95% CI) was 3.9 (3.4; 4.5) and probability of 6-months PFS was 38.9%. The best OS survival (13.5 months) was in pts with adenocarcinoma. We don’t find the differences between groups of pts according smoking (p=0.532), sex (p = 0.696) and PS (p = 0.131).

Conclusions: The treatment with cisplatin as the first line treatment was well tolerated (only 4.4% of pts finished therapy due to toxicity), with evidence of antitumour activity in adenocarcinomas. The results from clinical practise of Czech Republic are comparable with the results of registration study.

P2916
Non-small cell lung carcinoma-advanced disease (NSCLC-AD): Effectiveness of subsequent therapeutical lines and predictive factors of poor outcome
Lídia Fernandes, Inês Sanches, Catarina Ferreira, Ana Figueiredo, Fernando Barata. Pneumology, Centro Hospitalar Universitário de Coimbra, Hospital Geral, EPE, Coimbra, Portugal.

Five years observational study (2006-2010) of a cohort of patients with NSCLC-AD (1st line monotherapy excluded). Epidemiology, histology, performance status (PS), therapy, response – disease control (DC) or progression (n-DC), progression free survival (PFS) and overall survival (OS) after each therapy were evaluated.

We also tried to assess predictors for DC and OS.

Results: We included 276 patients, 77.9% men, mean age 63.1 years (±10.9), most of them smokers (36.6%) with PS 1 (89.1%). The most frequent histology was adenocarcinoma (59.8%). Metastasis in L, 2 or 3 organs was found in 65.2%, 31.2% and 3.6% of the patients. All patients were initially treated with a platinum-based duplet; Pemetrexed or Erlotinib or Erlotinib in 2nd-line setting (53.9% of the patients) and Erlotinib in 3rd (15.6% of the patients). There was a progressive reduction of the DC rate along the 3 lines: 71.7%, 67.1% and 51.2%

The median PFS and OS for each line were: 1st: 4.53M ± 0.54, 2nd: 2.89M ± 0.21 and 1st 9.1M ± 0.66, 3rd: 4.47M ± 0.68 and 10.42M ± 3.35. Prognostic factors were: smoking status (HR 1.54, p-value 0.016), the presence of metastasis≥1 organ (HR 1.50, p-value 0.003), PS2 (HR 3.62, p-value<0.001) and n-DC after 1st line (HR 2.71, p-value<0.001). The presence of DC after each line did not predict subsequent DC (p-value 0.05), but the PFS after 1st line correlates with the following PFS (p-value 0.001).

Conclusions: There is an increase in OS and PFS in the 3rd line, probably reflecting the influence of new biological treatments. Strong predictors for a poor outcome were PS 2 and n-DC after 1st line.

P2917
Prevalence and effectiveness of third-line therapy for advanced non-small cell lung cancer (A-NSCLC)
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Background: Systemic chemotheraphy is the main option for A-NSCLC. Few patients receive third-line therapy and in this setting little is known about outcomes.

Objectives: Evaluate demographics, histology, performance status (PS), sites of metastases, toxicity, response (DC or progression), progression-free survival (PFS) and overall survival (OS) in patients with A-NSCLC treated with third-line therapy.

Methods: We reviewed 5 years of clinical practice (Jan 2006 - Dec 2010): 676 patients with A-NSCLC were diagnosed and 330 received systemic chemotherapy. Of these, 44 completed 3 lines.

Results: 73% male, mean age 61.8y (±9.4). Smoking status: 36% non-smokers, 36% former-smokers and 28% active smokers. Histology: 66% adenocarcinoma, 27% squamous cell carcinomas, 5% large cell carcinomas and 2% NSCLC-NOS. Initially all patients had PS 0-1. Main sites of metastases: lung (80%) and bone (43%), with 34% of patients with ≥ 2 metastatic foci. First-line platinum-based duplet: 50% achieved an objective response, 30% had stable disease, PFS 6.4M. Second-line setting (docetaxel/pemetrexed/erlotinib): partial response (PR) 30%, stable disease (SD) 52%, PFS 5.4M. Third-line (erlotinib/pemetrexed): PR 14%, SD 36%, PFS 4.2M. Hematological toxicity: 18% in 1st-line, 16% in 2nd-line and 7% in 3rd-line. None of the hematological toxicities was 16% in 1st-line, 20% in 2nd-line and 14% in 3rd-line. OS was 24.05M.

Conclusions: Third-line therapy was used in 6.5% of the patients. 1st-line platinum-based chemotherapy with new-generation agents like pemetrexed and erlotinib in the subsequent lines had good efficacy with less toxicity and strongly contributed to the 24 months in overall survival in our patients.

P2918
A study on chemotherapy induced intestinal lung disease in patients with unresectable non-small cell lung cancer complicated by combined pulmonary fibrosis and emphysema
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Chemotherapy-induced anemia is a frequent complication of LC Platinum-based chemotherapies (CT) particularly impair erythropoietin production. One option for the management of this anemia is the administration of recombinant human erythropoietin (RHE) which stimulates red blood cell (RBC) formation.

We compared the efficacy and safety of two types of RHE: epoetin alpha (Eprex) and epoetin beta (NeoRecombin) in anemic patients with LC. Thirty eight patients (mean age 62.1 years, receiving CT for a LC (stage III and IV) with anemia (hemoglobin level ≤11g/dl) were included: 19 patients in group 1 treated by Eprex 4000IU/week and 19 patients in group 2 treated by NeoRecombin 3000IU/week for 6 weeks. A hematopoietic response was defined as an increase in hemoglobin concentration ≥2g/dl or hemoglobin (Hb) concentration ≥12g/dl in the absence of the RBC transfusion. The mean Hb levels at baseline were identical: 10 g/dl in group 1 and 9.8 g/dl in group 2. Each group was divided into two subgroups (transfused and non-transfused). 15.8% of patients in the first group required a RBC transfusion versus 36.8% in the second group (p=0.26). The mean changes in hemoglobin level during treatment in non-transfused patients were 0.83 g/dl for group 1 (p=0.003) and 0.31 g/dl for group 2 (p=0.13) without statistical difference among groups (p=0.08). While 12.5% patients in group 1 had a significant hematopoietic response, none was observed in group 2. Two patients in group 2 developed thrombotic events.

The tested erythropoietic agents increased the Hb level in anemic patients with LC. In our study epoetin alpha was better in terms of efficacy and safety than epoetin beta.

P2920
Docetaxel-related peripheral neuropathy is a dose-dependent event; a retrospective study in a Greek population with NSCLC
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Introduction: Neurotoxicity is the most important non-hematologic toxicity of taxanes. It presents as peripheral neuropathy with tingling, numbness and pain with a “glove and stocking” distribution and influences the daily activities of patients treated with taxanes.

Aim: To record peripheral neuropathy in relation with the dosage of docetaxel in NSCLC.

Method: We retrospectively studied 700 consecutive files of patients from the archive of the oncology unit of our institution in treatment from December 2006 until May 2008. Election criteria includes patients with NSCLC, PS 0-2, any stage, treated with docetaxel in any combination. We evaluated peripheral neuropathy with CTCAEv3.0

Results: We found 105 patients,84 males(80%),21 females(20%), median age 62.94(9.29, smokers 95(90.5%), median dose of docetaxel 74.4(52.7,78.8)mg/m², median aggregate dose 427.13(282.9, dose intensity 32.63(5.88mg/m²/week, median treatment duration 12.6±7.9weeks. Peripheral neuropathy presented in 28 (26.7%) patients, mild or moderate severity, mainly sensory neuropathy in 75%, after 2.64(1.18 cycles. The group of patients who received docetaxel ≥ 80mg/m² presented neuropathy at 37.5% versus 21%(p=0.09). The group with dose intensity ≥37.5mg/m²/week presented neuropathy at 47.1% versus 16%(p=0.001). In the group of aggregate load dose ≥600 mg, 51.6% presented neuropathy versus 16% with <600 mg(p=0.0001). Neurotoxicity was a reversible adverse event in 25 of 28 patients.

Conclusion: Peripheral neuropathy is a dose-dependent adverse event that increases with the accumulation and the dose intensity of docetaxel. Symptoms usually resolve after treatment or by decreasing the dosage.
Tumor-infiltrating lymphocytes (TIL) were isolated from tumor tissue by culturing in 1 out of 6 patients, XAGE-1b induced proliferation in LN XAGE and IFN-γ release in LN XAGE and TIL. In another patient, XAGE-1b induced proliferation (PBMC and LN nsg, but no IFN-γ release). In 3 out of 6 patients, a p53-induced proliferation was observed in LN p53, which was accompanied by IFN-γ release in 2 patients. In one patient, p53 induced TNF-α release in TIL. These preliminary data show T-cell immunity to XAGE-1b and p53 in lung adenocarcinoma indicating that these antigens are potential targets for immunotherapy. More patients are needed to define strength, breadth and phenotype of this antigen-specific response and its relation with antigen expression in the primary tumor.

P2924

Elderly lung cancer patients profit from radical mediastinal lymphadenectomy? Kalliopi Athanassiadi1, Vassiliki Karamen2, Irini Mavromiti3, Ilia Samiotis3, Maria-Kalliopi Konstantinoudou1, Despina Viotidak1, Dimitra Riga2, Dimitris Lioumpas1, Dimitris Roudou2, Ion Hellenis1, 2Thoracic Surgery, General Hospital “Evangelismos”, Athens, Greece; 3Anaesthesiology, General Hospital “Evangelismos”, Athens, Greece; 4Pathology, General Hospital “Evangelismos”, Athens, Greece

Objective: The therapeutic impact of a radical mediastinal lymphadenectomy (RLA) associated with a pulmonary resection for lung cancer remains controversial. Our objective is to investigate the impact of radical lymphadenectomy on overall survival compared to the overall survival for elderly lung cancer patients and assess whether the non-performance of an RLA could be justified in the surgical treatment for this group.

Material: We analysed the records of 60 patients aged 75 years and older (41 males, 19 females) who underwent surgery for non-small-cell lung cancer. They were divided into two groups, according to the performance of a radical mediastinal lymphadenectomy, the radical systematic lymphadenectomy (RLA Group, n=36) and the Sampling (SLN group, n=24) groups. A Cox proportional hazards model and the Kaplan-Meier method were used for the survival analyses.

Results: RLAs had no protective effect on mortality; the hazard ratio for the RLA group in comparison to the SLN group was 0.93 in the multivariate analysis. The 3-year survival for the SLN group, was marginally better than that of the RLA group. There was no significant difference in the overall survival between the two groups (p=0.05).

Conclusions: There was no survival benefit for the Radical Mediastinectomy. Although in some reports a significant mediastinal lymphadenectomy is recommended for correct staging, a pulmonary resection with non-performance of radical lymphadenectomy could be an acceptable surgical treatment for the increasing number of elderly lung cancer patients.

P2925

Lung cancer in Berlin – Therapeutic concepts and their impact on survival in patients with NSCLC stage II/III from 2000 to 2008 Torsten Blinn1, Stephan Egginger1, Christian Gogoll1, Christian Grab1, Günter Schöner1, Christian Greil2, Christian Fischer1, 2Thoracic Surgery, Charité, Berlin, Germany; 3Gastroenterology, Charité, Berlin, Germany

Objectives: To evaluate the effect of changing therapeutic concepts on survival times in patients with newly diagnosed NSCLC stage II/III from 2000 to 2008.

Methods: In this retrospective case study, the pooled data of the TZB of pts. with newly diagnosed lung cancer during 2000 and 2008 were analyzed. Pts. were divided into three 3-year groups (G1: 2000-2002, G2: 2003-5 and G3: 2006-8). Results: The total cohort comprised 14,302 pts. For pts. with NSCLC stage II/III, the proportions of pts. with surgery and adjuv. therapy increased in G2 and G3 (Figure 1, see p. 536s). Kaplan-Meier survival analysis could not demonstrate significant differences between G1 and G2/3 in general, but for pts. with NSCLC stage II and III (Figure 2, see p. 536s).

Conclusions: According to the pooled data of the TZB, the analysis of therapeutic concepts spotted an increase of surgery and adjuv. therapy among pts. with NSCLC stage II/III over time corresponding with an improvement in survival in these groups.
P2926
Treatment modalities in lung cancer patients with brain metastasis
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Forty lung cancer patients with diagnosed brain metastasis were evaluated at the Institute of Lung diseases at Sremska Kamenica in the period of three years. Duration of survival in such patients was evaluated and compared according to the treatment employed as well as to the histology, number of metastasis and presence/absence of synchronous or other visceral metastasis. Treatment modalities included: irradiation, surgery, and chemotherapy for chest tumor, and for the brain metastasis, and symptomatic treatment. There were 34 male (85%) and 6 female (15%). 72.5% have had solitary metastases, while 27.5% presented with multiple metastasis. Mean survival was 3.2 months from the diagnosis of brain metastasis (range 0-14 months). Irradiation of thorax underwent 57.5%, chest operation (15%). 72.5% have had solitary metastases, while 27.5% presented with multiple metastasis, and symptomatic treatment. Thirty percent were treated only symptomatically. Sixty percent were without other visceral metastasis. Statistical significance in terms of longer survival was found in patients who had solitary compared to multiple metastases p<0.026, in patients with irradiated brain metastasis p<0.015 and in patients operated for brain metastasis p<0.003.

Although prognosis of patients with lung cancer and brain metastasis is gloomy, our investigation suggests longer survival with employed brain surgery or brain irradiation.

MONDAY, SEPTEMBER 3RD 2012

P2927
Prodomal face of a study: High dose rate endobronchial brachytherapy (HDREB) as a first step introductory treatment of a multimodality therapy approach in non operable NSCLC with endobronchial obstruction
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Introduction: Lung cancer patients frequently present with advanced stage. HDREB has always been used as a palliative treatment option in end-stage disease, and has not yet been thought of as a first-step therapeutic approach of a multimodality treatment strategy. We strongly feel that HDREB could be the method of choice in carefully selected patients with endobronchial obstruction, prior to other treatments.

Aim: HDREB could be used as a first-step, introductory treatment in selected patients with inoperable obstructive endobronchial carcinoma of the lungs.

Methods: A catheter is placed through bronchoscopy in the obstructed lumen. HDREB is delivered in two sessions separated by one week. Bronchoscopy is performed 3 weeks later. Pulmonary function tests are performed before and after HDREB monthly. Evaluation of quality of life is assessed with Saint Georges Respiratory Questionaire. Obstruction score is also evaluated before and after treatment.

Results: Six patients with previously untreated, inoperable NSCLC associated with endobronchial obstruction, were treated with HDREB as an introductory treatment of a multimodality therapeutic approach. We found significant improve- ment on symptoms (cough, dyspnoea, hemoptysis) and intraluminal reduction of the obstruction.

Conclusions: HDREB is a low-cost, semi-invasive, and well-tolerated method that has been applied with a limited palliative purpose, whilst it could provide an improvement of performance status and partial disease regression early enough, giving the patient the opportunity of a better outcome of treatment, overall.

P2928
Non-small cell lung cancer – Advanced disease: Barriers to inclusion in clinical trials and its impact on survival
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Introduction: Inclusion in clinical trials allows patients to submit to innovative therapies and a meta-analysis showed that this may be associated with increased rates of survival.

Aims: Identify reasons that hindered the inclusion of patients in clinical trials of first-line therapy; Compare overall survival (OS) and progression-free survival (PFS) between groups of included and excluded patients.

Methods: This study was conducted over 36 months in a central hospital. Patients with well defined histology and candidates to chemotherapy were considered eligible for clinical trials. Reasons for non inclusion have been detailed. OS and PFS were compared.

Results: We identified 199 eligible patients, mean age 64.9 ± 10.7 years, 75.9% males, 61.8% with non-squamous cell carcinoma. From these 22.1% were included in trials. Among those not included 18.7% had performance status (Zubrod) 2 and 66.5% had other exclusion criteria, mainly heart disease (22.5%), respiratory disease (21.4%), brain metastases (15, 5%) or second malignancy (15.5%). About 15% of patients refused to be involved in trials. Of patients who had performance status 0/1 (N = 170), there was no statistically significant difference in analysis of OS or PFS between those included in trials and the excluded, whether by criteria (Cox Regression: OS p=0.705/PFS p=0.807) or by refusal (Cox Regression: OS p=0.026, PFS<0.000).

Conclusion: Liberalization of exclusion criteria and recognition of causes that lead to refusal are possible determinants of increased participation in clinical trials. Bibliography: CA Stiller(1994). Centralised treatment, entry to trials and survival. Br J Cancer 70,352-362.

P2929
Intratumoral injection of plasmid-encoded flagellin inhibits growth of NSCLC-cells in murine lung cancer model
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Lack of progress in the treatment of NSCLC urges to look for experimental therapeutic methods, such as gene therapy. Currently used therapeutic vectors can cause adverse effects, or have a limited potential to transduce cells. The aim of this work was 1) to construct a vector suited for gene therapy allowing for selective transduction of only tumor cells 2) to assess therapeutic potential of Salmonella flagellin (FlFC).

Engineered plasmid vector was obtained by PCR synthesis. For the purpose of tumor-specific transcriptional activity it was necessary to design a two-step promoter unit system based on telomerase minimal promoter.

Influence of FlFC on NSCLC cells was assessed by measuring proliferation of transfected cells and by phenotyping of maturation markers on DCs incubated with
A549 cells. NSCLC tumors in mice were injected with empty or FliC-coding vector. Tumor growth and survival of the mice were analyzed. FliC-transfected A549 cells had significantly lower proliferative potential. Such cells enhanced maturation of MφDC as suggested by higher expression of CD80 and CD83. NSCLC-inoculated mice administered with a vector containing FliC gene had a significantly longer survival time (p < 0.002) and slower tumor growth (p < 0.001) compared to the control group. Designed two-step promoter unit allows for efficient and tumor-selective expres- sion of therapeutic gene. Results suggest that NSCLC transduction with FliC gene may inhibit tumor growth in vitro and tumors, FliC (Carefusion, Hochberg, Germany) was attached to the tube of the rigid bronchoscope. IOS was performed in real time during interventional procedures under spontaneous breathing. Resistance at Shs (R5) and 20H (R20) measurements were recorded during inspiration and expiration. The cross-sectional area (CSA) at the narrowest segment was recorded using ziostation (Ziosoft, Tokyo, Japan) before bronchoscopic intervention.

Methods: IOS was performed on 14 patients with tracheal stenosis in the endo- scopic suite between April 2009 and December 2011. After patients were intubated with a rigid bronchoscope (FIMER, La Ciotat, France), IOS (Carefusion, Hochberg, Germany) was attached to the tube of the rigid bronchoscope. IOS was performed in real time during interventional procedures under spontaneous breathing. Resistance at Shs (R5) and 20H (R20) measurements were recorded during inspiration and expiration. R5 on inspiration revealed the strongest correlation with the narrowest segment of the cross-sectional area (r = 0.61, p < 0.05). There was little difference between R5 and R20 during inspiration and expiration.

Conclusion: IOS could evaluate airway narrowing in real time during interven- tional bronchoscopy.

Surgical treatment of descending necrotizing mediastinitis
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Surgical treatment of descending necrotizing mediastinitis remains one of the most complex and unresolved problems in thoracic surgery. High level of mortality (up to 70%) is indicative for its actuality. Material and methods: The study based on an analysis of treatment 158 patients with descending necrotizing mediastinitis of following localization: upper anterior – 45, upper posterior – 28, upper total – 20, total anterior – 20, total posterior – 15, total – 30. Results: Surgical treatment undergone 152 patients (six was not operated and died within two hours after admission). Overall mortality was 37.7%, postoperative - 35.5%. The results of clinical application of new methods of draining of anterior and posterior mediastinum are presented. Conclusions: Surgery method remains the main in the treatment of descending mediastinal necrotizing mediastinitis. The results of treatment can be improved by timely diagnostics, adequate mediastinal draining, adequate homeostasis correction, “open” cervical wound treatment, tracheosthomy only in cases of impossibility of intubation.

A rare case of mediastinal inflammatory myofibroblastic tumor
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The inflammatory myofibroblastic tumor (IMT) or the inflammatory pseudotumor is a rare benign tumor composed of spindle cells that is known to develop in various locations such as lung, skin, breast, gastrointestinal tract, pancreas, bone, epididymis, peritoneum. Mediastinal localisation of the tumor is very rare. We present the case of a 16 years old female with such pathology. Methods: The patient was admitted into our clinic with a history of pain in the right hemithorax, mild dyspnea and irritative cough. The chest x-ray showed a great ascension of the right hemidiaphragm. Abdominal ultrasound revealed the presence of heterogeneous formations, bulk with liver parenchyma dislocation and fluid collection. The Chest CT examination showed a giant formation in the right hemithorax having hypodense mass effect on the liver, trachea, mediastinum and lung parenchyma. A right posterostral approach was used re- vealing a giant tumoral formation (4/13/12 cm) originating from the mediastinum. Total surgical ablation was performed. Results: The postoperative outcome of the patient was good, with no complications and lung reexpansioning. The hospital stay was 7 days. Immunohistochemistry was positive for desmin, VIM, CD 34, CD 68, Ki67, and was diagnosed with inflammatory myofibroblastic tumor. No tumoral recurrence was noticed at the one year and two year follow-up. Conclusions: The mediastinal inflammatory myofibroblastic tumor is a very rare pathology. It can raise a series of problems, from technical problems related to its location. If total surgical ablation is possible the patients have a favorable outcome.

Mediastinal metastases from non-lymphomatous extra-thoracic tumours. A multicenter series of a rare condition
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Introduction: Most mediastinal metastases are from lung, esophagus or medi- astinum itself. Non-lymphomatous extra-thoracic tumours rarely give place to mediastinal metastases. The purpose of this study was to investigate the way this rare condition is managed and its prognosis.

Materials and methods: Thoracic surgeons from 7 different centers in Spain and France put together their series to perform a retrospective study of this kind of mediastinal metastases.

Results: A total of 16 cases was recorded (11 women and 5 men). Age ranged between 32 and 72 years in women (M=49) and between 31 and 76 in men (M=49). Among women, the primaries were: 4 sarcomas, 3 breast, 2 kidney and 2 ovary. Among men, the primaries were: 2 testicular and 1 melanoma, 1 digestive and 1 feochromocytoma. The time between treatment of the primary tumor and the diag- nosis of mediastinal metastasis was 16 months in breast origin (0-24), 84 months in sarcomas (12-132) and 19 months in kidney cases (14-92). Other metastases were rare, only pulmonary in 3 cases of sarcoma and one case of retroperitoneal metastasis in a testicular case. The mediastinal metastases were treated through thoracotomy in 11 patients (9 right, 2 left), 2 right videothoracoscopies and 3 sternotomies. Survival was of 67 months for the already dead patients and 58 months for the still alive patients.

Conclusions: Mediastinal metastases of non-lymphomatous extra-thoracic tumors are more frequent among women, normally the mediastinal metastasis is solitaire except in sarcomas, and their prognosis is not as bad as expected.

Thymic tumours: Diagnostic and therapeutic approach
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Introduction: Thymic tumours represent 0.2-1.5% of all malignancies, with an incidence of 0.15 cases per 100,000 populations. We present our experience in the management of patients (pts) with thymic tumours.

Materials and methods: We evaluated retrospectively the records of 16 consecu- tive pts who underwent thymectomy in our department. All but one pts underwent radical thymectomy, through a median sternotomy. The upper and lower thymic poles were traced and all fatty tissue between the phrenic nerves was resected. Diagnostic procedures included contrast enhanced CT of thorax and/or MRI and in the case of 2 pts, F-18 FDG PET-CT was performed. Malignancy grading was present in 2 pts (12.5%).

Results: There were 8 male and 8 female pts (mean age: 42.8 years). The histopathology revealed 11 thymomas, 1 endocrine carcinoma and 4 hyperplasias. Type A thymomas were found in 2 pts (12.5%), AB in 3 pts (18.75%), B1 in 1 pt (6.25%) and B3 in 3 pts (6.25%), while 4 thymomas (25%) were unclassified. The mean diameter of the resected masses was 8.31 cm. Two pts were classified as Masaoka IIA stage (12.5%) and one as Masaoka IIB (6.25%), who received adjuvant radiotherapy. All the others were classified as Masaoka I. All tumours

5375
were totally resected. The 5 year survival was 100%. There was recurrence of the endocrine carcinoma within 5 years. Conclusions: Tumours of the thymus are a heterogeneous group of tumours, ranging from relatively benign thymomas to highly aggressive carcinomas. Surgery continues to be the mainstay of treatment and complete resection of the tumour remains the most important prognostic factor. A recurrence should be completely resected whenever possible, because this approach is associated with good long-term survival.

P2935 Surgical treatment of superior vena cava syndrome caused by thymic carcinoma
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Introduction: Thymoma and thymic carcinoma are a rare disease, but they are the most common tumor of the anterior mediastinum in adults. They are asymptomatic until late. There are some potentially life-threatening manifestations of thymic neoplasms like myasthenia gravis and superior vena cava syndrome. The palliative treatment of the medastinal malignancies have poor prognosis and radical surgical therapy is the only option. Resection and reconstruction of the great medastinal vessels in case of involved are technically challenging.

Materials and methods: We report the case of a 63 year-old Caucasian female patient, who presented superior vena cava syndrome derived from a medastinal neoplasm compromising intrinsically and extrinsically the superior vena cava, right and left brachiocephalic vein. After evaluation the patient underwent radical resection of the tumor on blex with the involved vessels and reconstruction with Y-shaped gore-tex graft. Cardiopulmonary bypass wasn’t used. The histological analysis of the surgical specimen was diagnosed as thimic carcinoma, stage III (Yamakawa-Masaoka staging). The patient was discharged after 25 days of hospitalization without chemotherapy and radiotherapy after the operation. Results: The postoperative observation was conducted for a period of 2 and 6 months. There were no signs of recurrent disease or thrombosis of the prosthetic graft. The patient performed his daily chores without difficulty. Conclusion: Extensive resections of the tumor tissue with involved adjacent organs and vessels are feasible, safe, and improve satisfactory survival in invasive thymomas. Radiation therapy and chemotherapy in case of radical resection are not necessary.

P2936 Cryotherapy plus chemotherapy or radiation offers increased survival and quality of life in advanced stage lung cancer patients with endobronchial obstruction: Analysis of 160 patients treated with the rigid bronchoscope
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Athanasios Stamatepoulos, Gerasimos Georgopoulos. General Thoracic Surgery, General Hospital of Attica KAF, Athens, Attiki, Greece; General Thoracic Surgery, Sotiria Chest Disease Hospital, Athens, Attiki, Greece

Objective: The objective of this clinical study is to evaluate the efficacy of Bronchoscopic Cryotherapy plus chemotherapy or radiation therapy of patients with advanced stage lung cancer with endobronchial obstruction.

Methods: 160 lung cancer patients with stage IIIA, IIIB, IV and endobronchial tumor, were included in a protocol of three sessions of rigid bronchoscopical cryotherapy. From 2001-2011 142 men (44-82 yrs old) and 18 women (45-66 yrs old) were treated in our Department. After each cryotherapy one cycle of chemotherapy or radiation therapy followed. Patients age, sex, type of tumor, stage, symptoms of dyspnea, cough, hemoptysis, pain plus lung functional studies, performance status and survival time, were recorded. Follow up was at least two years.

Results: Symptoms of dyspnea, cough, hemoptysis and pain improved significantly in 73%, 68%, 69% and 42% of patients respectively (p<0.001). Lung function improved 15-20%, Fev1 from 1.41±0.5 to 1.9±0.57lt, Fvc from 1.5±0.6 to 2.24±0.7lt after treatment (p<0.05). Performance status increased from 62±5 to 75±3 (Karnofsky scale, p<0.05) and from 3.15±0.9 to 2.3±0.5 (WHO scale, p<0.05).

Survival increased considerably to 6-2 months (mean 16+) for stages IIIA, IIIB (Kaplan-Meier, 95% interval). We had 2(1.25%) in hospital deaths.

Conclusions: Bronchoscopic Cryotherapy is a safe palliative method for inoperable lung cancer with endobronchial obstruction and combined with chemotherapy or radiation offers better survival and increased quality of life.

P2937 The effect of locally applied TGF-BETA3 on wound healing and stenosis development in tracheal surgery
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Introduction: Tracheal stenosis constitutes one of the most frequently seen problems in thoracic surgery. Although many treatment modalities to prevent tracheal stenosis have been attempted, an effective method has not been found yet. In this study, TGF-beta/chitosan combination was used for that purpose.

Material and method: A film shaped slow releasing preparation, which contains TGF-beta3 with basal substance of chitosan was created. Thirty “Westar Albino” rats were divided into 3 groups. Full vertical incision was made in the anterior side of trachea between 2 and 5. tracheal rings. Membranous trachea was preserved. Tracheal incision was sutured. Group A was evaluated as control group. In group B, a chitosan based film substance was placed on the incision line. In group C, a chitosan-TGF-β3 combination slow-release film coated substance was placed on the incision line. The rats were sacrificed on 30th day, the tracheas of the rats were excised by cutting between the lower edge of the thyroid cartilage and the upper edge of the 6th tracheal ring together with oesophagus. Histopathализation, fibroblast proliferation, angiogenesis, inflammation and collagen levels were evaluated histopathologically by the same histopathologist (Figure).

Results: It was not found statistically significant difference between three groups. Cold abscesses were observed at the incision area in both TGF3/chitosan combination and chitosan groups and they were thought to form because of chitosan.

P2938 Use of helium and small size endotracheal tubes for surgery of severe tracheal stenoses (STS)
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Heliox improves ventilation by reducing density dependent resistance due to high kinematic viscosity and high diffusivity.

Objective: To present our experience and evaluate feasibility to maintain adequate ventilation using Heliox through small size endotracheal tubes during the initial period of operations for STS until the trachea is divided below the stenosis.

Methods: 4 patients with postintubational STS were intubated spontaneously breathing He-O2 (70/30) after topicalization and light sedation. In 3 of them (high stenoses) we used microlaryngeal tubes; for one (low stenosis) we designed double-size tubes.

Results: Results for the period of Heliox ventilation.

P2939 Technical aspects of mini-invasive transcervically right main bronchus approach
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We present the mini-invasive transcervical approach of the right main bronchus as operative technique.

We have used this method at a MDR patient for whom we first staple and cut the right main bronchus in order to allow the proper treatment to be administered without the risk of TB spilling. Using a Cooper suprasternal retractor we have open an access to the mediastinum as described by Zielinski for Temla and encircled the right main bronchus and after staped and cut it.

538s
of the stent with at least one pathogen. A total of 11 different pathogens were found; Staphylococcus aureus (6), Alpha haemolytic streptococci (5), Pseudomonas aeruginosa (3), Haemophilus influenzae (2), Coagulase negative staphylococcus (2), Moraxella catarrhalis (1), Non haemolytic streptococcus (2), HRSa (1), Neisseria (1), Clostridium (1), Corynebacterium striatum (1).

Conclusion: Prophylactic control in the form of antibiotic-impregnated stents and modified antibiotics post stent deployment using specific microorganisms may be beneficial in reducing granulation tissue formation.

P2943
Comparative assessment of endobronchial valve lung volume reduction in patients with COPD

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Objective: To compare the results of surgical lung volume reduction in patients with COPD with the results of endobronchial lung volume reduction valve.

Methods: Aims: To identify the different endobronchial interventions used in the treatment of airway malignancies at St. George’s Hospital, and document associated complications.

Results: 36 (73%) patients had stent deployment, 7 (14%) had laser ablation with large airway pathology. It is usually well tolerated and rarely contraindicated even for patients with advanced malignant disease.

Aims: To study whether specific microorganisms are associated with granulation tissue formation in patients post endobronchial stent deployment.

Methods: We conducted a retrospective review of all endobronchial stent insertions performed for benign conditions between January 2005- November 2011. Stents used in the procedure were covered and uncovered Ultraflex expandable metal stents (Micro-invasive, Boston Scientific, Watertown, MA). Follow up bronchoscopies determined which patients had developed granulation tissue formation. Biopsies, sputum and lavage were then taken for microbiological analysis. Microsoft excel was used to collect and analyse data.

Results: Thirty patients had endobronchial stents deployed. Ten patients developed granulation tissue proliferation and all of these had bacterial colonisation.

Background: Following endobronchial stent insertion granulation tissue formation may occur, which can occlude the airway. It has been postulated that bacterial colonisation causes granulation tissue formation and its subsequent proliferation.

Aim: To study the effects of antibiotics on the incidence of granulation tissue formation post endobronchial stent deployment.

Methods: Thirty patients had endobronchial stents deployed. Ten patients developed granulation tissue proliferation and all of these had bacterial colonisation of the stent with at least one pathogen. A total of 11 different pathogens were found; Staphylococcus aureus (6), Alpha haemolytic streptococci (5), Pseudomonas aeruginosa (3), Haemophilus influenzae (2), Coagulase negative staphylococcus (2), Moraxella catarrhalis (1), Non haemolytic streptococcus (2), HRSa (1), Neisseria (1), Clostridium (1), Corynebacterium striatum (1).

Conclusion: Prophylactic control in the form of antibiotic-impregnated stents and modified antibiotics post stent deployment using specific microorganisms may be beneficial in reducing granulation tissue formation.

P2944
Endobronchial interventions used in the management of large airway malignancies and their associated complications: An audit

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Introduction: Endobronchial intervention is an expanding specialty involving a Multi- Disciplinary Team, which diagnoses and treats a diverse group of patients with large airway pathology. It is usually well tolerated and rarely contraindicated even for patients with advanced malignant disease.

Aims: To identify the different endobronchial interventions used in the treatment of airway malignancies at St. George’s Hospital, and document associated complications.

Methods: Data relating to endobronchial stenting, laser ablation and forceps debulking, and any short-term complications, were collected from the St. George’s Hospital patient database for 49 consecutive patients with airway malignancy.

Results: 36 (73%) patients had stent deployment, 7 (14%) had laser ablation and 3 (6%) had tumours debulked using forceps. Complications occurred in 9 (18.4%) patients and were granulation tissue formation (3), mucus retention (3), stent migration (2) and bleeding (1). All complications were effectively treated.

Conclusions: Stenting is the endobronchial intervention of choice for the treatment of large airway malignancies at St. George’s Hospital. Although it has the greatest associated complications, they are usually effectively treated. Furthermore, it is safe, well tolerated and achieves good symptomatic relief.

P2945
Lung volume reduction surgery (LVRS) after endoscopic lung volume reduction (ELVRY) in severe emphysema – A case series

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Background: LVRS as well as ELVRY can improve patients symptoms, wellbeing and pulmonary function testing. ELVRY can be performed in upper and lower lobe emphysema. LVRS is currently not recommended for patients with very low FEV1 or lower lobe emphysema. LVRS is currently not recommended for patients with very low FEV1 or lower lobe emphysema.

Objectives: Case series to establish if surgical lobectomy after initially successful ELVRY is effective.

Methods: 6 patients (4 female, mean age 60.3 y, mean FEV1 640±214 ml)
with severe lower lobe emphysema received ELVR and showed an initial but not persistent improvement. Hence a lobectomy was performed for surgical lung volume reduction. Pulmonary function tests (PFT), 6-minute-walk-test (6MWT) and dyspnea score (mMRC) were performed 90 days after surgery and safety issues were assessed.

**Conclusion:** In all cases lobectomy of one lower lobe (5 left, 1 right side) was performed for patients with severe lower lobe emphysema for volume reduction. Pulmonary function tests (PFT), 6-minute-walk-test (6MWT) and dyspnea score (mMRC) were performed 90 days after surgery and safety issues were assessed.

**Successful ELVR can be used as a pretest for adequate patient selection.**

**MONDAY, SEPTEMBER 3RD 2012**

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**P2948**

Inhaled racemic adrenergic versus saline in acute bronchiolitis, a multicenter randomized double-blind clinical trial

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**Background:** The efficacy of inhaled racemic adrenaline (iRA) versus general supportive therapy in acute bronchiolitis in infants is questioned.

**Aims:** To assess efficacy of iRA versus saline and regular vs. on demand therapy in hospitalized infants with acute bronchiolitis.

**Subjects and methods:** A multicenter (n=8) randomized double-blind controlled trial (pharmaceutical company independent) of iRA vs saline further randomised into regular vs on demand inhalations (up to every second hour) included 404 children (<12 months of age (mean 4.2 months), 29.3% boys, with moderate to severe acute bronchiolitis in Norway in 2009-11. A validated clinical score (0-10, 0 best) was used pre-and post inhalation daily. Inclusion required a score ≥ 4. Supportive therapy (oxygen, nasogastric feeding (NG) or ventilatory support) were recorded. The primary outcome was length of stay (LOS) (hours until deemed ready for discharge). Analyses were by intention to treat except for LOS.

**Results:** Infants treated with iRA vs saline had no significant difference in LOS (54.9 (52.8; 57.0) vs. 60.9 (59.2; 62.5) hrs, p=0.14). There was a trend in shorter mean LOS (54.9, 47.9-62.0 vs. 68.1, 60.4-75.7 hrs, p=0.05). Several SNPs with smoking in pregnancy, such as MBL2 region other than MBL2 reached genome-wide significance. We found significant gene-environment interaction of MBL2 SNPs with smoking in pregnancy, such as for the downstream SNPs rs10824787 and rs3821968 (p=0.036 and p=0.044, respectively).

Smoking during pregnancy lowers MBL levels in CB alone and in a joint effect with MBL2 SNPs. Our results may explain a link between genetic and environmental effects on early respiratory morbidity.

**P2947**

Joint effects of smoking during pregnancy and polymorphisms in the MBL2 gene on cord blood levels of mannose-binding lectin

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Smoking in pregnancy may affect the developing immune system and is associated with respiratory disease in the offspring. Also levels of mannose-binding lectin (MBL), a soluble innate immune mediator, are related to early respiratory morbidity. Yet, a joint effect of smoking in pregnancy and single-nucleotide polymorphisms (SNPs) in the MBL2 gene on MBL levels in cord blood (CB) is unknown.

MBL was measured in CB in N=221 participants of a birth cohort of unselected, unknown. MBL2 SNPs were quantified with MBL levels in CB. Using the Illumina® MBL2 gene-environment interaction of MBL2 SNPs with smoking in pregnancy, such as for the downstream SNPs rs10824787 and rs3821968 (p=0.036 and p=0.044, respectively).

Smoking during pregnancy lowers MBL levels in CB alone and in a joint effect with MBL2 SNPs. Our results may explain a link between genetic and environmental effects on early respiratory morbidity.
Conclusion: We have characterised biofilm-forming capacity in all 4 H. influenzae isolates from PCM patients. 2 isolates from chronically colonised patients (over 4 years) consistently formed thicker, cell dense and structurally more complex biofilms than the other, more recently isolated, strains. These data suggest that H. influenzae is capable of biofilm formation and that PCM patients, like cystic fibrosis, might harbour bacteria in biofilms.

P2950 Evidence of increased pathogenicity of HRVC compared with HRVA and B: Comparisons between children with an acute lower respiratory illness and controls

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Introduction: Recent studies suggest that human rhinovirus group C (HRVC) is more pathogenic in young children than HRVA and B. However, the relative frequency of isolation of these HRV groups between children presenting to an emergency department (ED) with an acute lower respiratory illness (ALRI) and healthy community controls has not been determined.

Aim: To compare isolation rates for HRVA, B, and C between children with an ALRI presenting to ED and health community controls.

Methods: Children aged 0-5 years presenting with an ALRI to the ED of a tertiary paediatric hospital along with healthy children from a local childcare centre were prospectively recruited. A nasal sample was collected at recruitment from which RNA was extracted and reverse transcribed. From cDNA, a 2-step PCR of the HRV 5'NCR was used for HRV detection and molecular typing.

Results: There were no differences in isolation rates for HRVA between ALRI cases and controls. Isolation rates for HRVB were low and slightly higher in controls than cases. For HRVC, not only were isolation rates higher than for HRVA or B, but rates were substantially higher for cases versus controls (48.5 vs 8.7% p<0.001).

Conclusions: HRVC is the most common HRV group causing ALRI in this group of young children, but is relatively uncommon in healthy children. In contrast, HRVA and B were not more common in children with ALRI than controls. These data provide support for HRVC being more pathogenic than HRVA and B.

P2951 RSV hospitalization in Down syndrome in the Canadian Registry of Synagis (CARESS) following prophylaxis (2006-2011)

Ian Mitchell1, Benoîte Côté1,2, Aymée Castonguay1,2, Ian Mitchell1, (CARESS) following prophylaxis (2006-2011)

Background: RSV hospitalization was not different among the groups following prophylaxis. Palivizumab may be efficacious in reducing RSV in DS compared to reported historical untreated controls in a similar Danish cohort of DS patients (untreated; 7.6% vs treated; 1.6% - 77% reduction).

Results: 10,061 infants were enrolled (DS: 299, 3.0%; infants with MD: 1247, 11.0%; infants without congenital heart disease: 8475, 86.9%). Rates of hospitalization for respiratory illnesses and RSV-related hospitalization did not differ among the groups following prophylaxis.

Conclusions: RSV hospitalization in Down syndrome in the Canadian Registry of Synagis (CARESS) following prophylaxis (2006-2011) was not different among the groups following prophylaxis. Palivizumab may be efficacious in reducing RSV in DS compared to reported historical untreated controls in a similar Danish cohort of DS patients (untreated; 7.6% vs treated; 1.6% - 77% reduction).

P2952 Role of probiotics in attenuation of acute respiratory tract infections in preschool and primary school children

Serghei Gerazim1, Orysa Cucur2

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Background: Probiotics have been shown to reduce incidence, duration and symptom scores of acute respiratory tract infections (ARTIs).

Objective: To study a potential of probiotics in prevention of ARTI in children.

Materials and Methods: 96 otherwise healthy children aged 3-12 years closely contacted to a household with ARTI were randomized to receive 1 g of a powder containing 5 billion CFU of L. acidophilus DDS-1, B. lactis and 50 mg fructooligosaccharide (DDS Junior, UAS Laboratories) (group I, n=48) or rice maltodextrine powder (group II, n=48) once daily for 30 days. During one-month follow-up, we recorded incidence, duration, and clinical course of ARTI using Canadian acute respiratory illness and flu scale (CARIFS).

Results: At baseline groups I and II were comparable on age, number of social contacts, history of attending daycare/school, and history of previous ARTI (85.5% of children in the group I and 90.6% in the group II developed ARTIs, p=0.368). In sick children at group I 50.6% clinical recovery from baseline value of CARIFS occurred on day 6.2(1.9), while in the group II on day 7.2(1.1) (p=0.025). For the group I return to normal health was observed on day 8.5(3.3) vs 10.7(3.9) in the group II (p=0.007). In the group I nasal decongestants, throat preparations, and antipyretics were used for a shorter course than in the group II (2.5(1.2) vs 3.2(1.7) p=0.007; 1.9(1.1) vs 2.9(1.6) p=0.046; 2.7(1.2) vs 3.5(1.5) p=0.049, respectively.

Conclusions: At tendency toward prophylactic potential in limitation of household spread, probiotics have a clear attenuating effect on the clinical course of ARTI in young children and shorten use of flu/cold drugs.

P2953 Active cytomegalovirus infection in non-immunosuppressed children with chronic respiratory disease

María Teresa Romero Rubio1, David Navarro Ortega1, Raquel Lucas Sendra2, Beatriz Almendral1, Olmo Carrión3, Amparo Escrivano Montanés4

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Cytomegalovirus (CMV) is reactivated in lower respiratory tract in the context of local or systemic inflammatory processes, increasing its morbimortality.

Objective: To set the incidence of acute CMV infection in children with chronic respiratory diseases and no acute exacerbation.

Material and methods: Mixed retrospective-prospective study (May 2009- September 2011) of non-immunosuppressed children who underwent a diagnostic bronchoscopy. The serological test for the CMV was performed using CLIA (Diasorin, Italy).Detection and quantification of DNA in respiratory samples and plasma by PCR QRT-PCR in the m2000RT system (Abbott Diagnostics, USA).

Results: 36 patients (45% male; mean age 5.5 years. Underlying diseases were cystic fibrosis, B, and pulmonary hemosiderosis. 11 patients were IgG positive. CMV DNA detection was 10.7 (3.9) in the group II (p=0.007). In the group I nasal decongestants, throat preparations, and antipyretics were used for a shorter course than in the group II (2.5(1.2) vs 3.2(1.7) p=0.007; 1.9(1.1) vs 2.9(1.6) p=0.046; 2.7(1.2) vs 3.5(1.5) p=0.049, respectively.

Conclusions: At tendency toward prophylactic potential in limitation of household spread, probiotics have a clear attenuating effect on the clinical course of ARTI in young children and shorten use of flu/cold drugs.

P2954 The microbiology of lung disease in ataxia telangiectasia (A-T)

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Background: A-T is a progressive, neurodegenerative disease causing immunodeficiency, an increased risk of malignancy & respiratory system complications, like chronic sinusopulmonary disease, bronchiectesis, interstitial lung disease & aspiration. The high early age mortality is due to cancer & respiratory disease. Little is known about what causes lung infections in A-T (Ped Pul 2010:45:874-59).

Aim: To describe the microbiology of Respiratory tract in patients attending the UK National A-T clinic in order to guide blind antimicrobial therapy, to discuss future studies to improve the evidence base for A-T treatment.

Methods: We prospectively obtained cough swabs or sputum cultures as age...

541s
appropriate & throat swabs for virology. We collected data on new treatment prescribed, current maintenance antibiotic or immune replacement therapy.

Results: 56 children (68 consuls) were seen in the clinic (May 09 to January 12). We could not obtain a sample in some children (Bacteria, n=14; Viruses, n=25).

Table 1. Microbiology

<table>
<thead>
<tr>
<th>Virus (n=55 consuls)</th>
<th>Rhinovirus</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metapneumovirus</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No Resp. viruses</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Bacteria (n=54 consuls)</td>
<td>Resp commensals</td>
<td>47</td>
</tr>
<tr>
<td>H influenza</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>H. influenza B</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>B. pertussis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>B. cepacia</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>756/children (12.2%)</th>
<th>Immunoglobulin infusion</th>
<th>15/88 (22%) consuls (n=9 Intravenous, n=8 Oral, n=2 nebulized &amp; oral)</th>
<th>Acute antibiotic</th>
<th>41/56 (children (73%) (n=33 Azithromycin, n=8 Other)</th>
<th>Maintenance antibiotic</th>
</tr>
</thead>
</table>

Conclusions: Our findings are similar to smaller series (n=15) (Acta Pediata 2007;96:1021–24) but with no opportunistic infections; bacterial infection is common and current management is based on deaggravation from other lung diseases. A-T specific evidence based guidelines are urgently needed.

P2955 Host and viral factors predicting severity of rhinovirus-associated wheeze Giulia Cangiano1, Elena Pontetti1, Marie Noelle Krog1, Elisabeth Kromtg1, Mari Giorgiev2, Maria Teresa Barbani1, Laurent Kaiser3, Caroline Tapparel1

Background: Rhinovirus (RV) is a common cause of wheeze in childhood. Person- nal history of atopy, presence of siblings and day care attendance are known risk factors for severe RV-associated wheezing but objective markers predicting disease severity are lacking. We aimed at identifying such markers in a cohort of preschool children hospitalized for RV-associated wheezing.

Methods: Direct immunofluorescence for RV and other viruses was performed on nasopharyngeal aspirates (NPA) within the first 24 hours of hospitalisation of children aged 6-6 years. RV load, interferons (IFN) and cytokines (IL-4, IL-8, IL-15, IP-10) were quantified by RT-PCR and ELISA and related to clinical parameters.

Results: Within a 4-years period (2007-2011), we included 126 children (median (range) age: 1.66 (0.40-5.81) years). Presence of RV was confirmed by RT-PCR in all NPA samples. RV load was inversely related to age (r=0.22, p=0.02) and correlated with the pro-inflammatory cytokines IL-8 (r=0.23, p=0.01) and IL-6 (r=0.35, p<0.001). There was no relationship between RV load or any IFNs cy- tokine level and clinical outcome parameters (clinical severity scores, length of hospitalisation and duration of oxygen therapy). Post-hoc analysis revealed a trend towards higher IL-6 levels of children with prolonged oxygen need (>1 vs. ≤1 days): (135 (5.789) vs.16 (5.244) pmol/L, p=0.07).

Conclusions: In our cohort, RV load and related antiviral and pro-inflammatory responses were not associated with disease severity. This may be due to the wide range of subjects studied. Whether IL-6 levels in NPA may help to predict clinical outcome in subgroups of children with RV-associated wheezing illnesses needs to be evaluated in further studies.

P2956 Modulation effect of beta-glucan isolated from Pleurotus ostreatus in children with recurrent respiratory tract infections

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Introduction: Recurrent respiratory tract infections (RRTI) present very frequent problem in pulmonologist practice. Several natural preparations have been used for their prevention, but only few of them have scientific evidence for a real clinical efficacy.

Objectives: The aim of the study was to evaluate the preventive effect of Imunoglukan P4H®, syrup containing imunoglukan – beta-glucan from Pleurotus ostreatus, on the frequency of RRTI in children.

Methods: In double-blind, placebo-controlled study, 175 children (5.65±2.39 years) with ≥5 respiratory infections in previous 12 months were studied. Children were treated for 6 months with Imunoglukan P4H® or with artificial syrup with vitamin C (placebo group). During three visits questionnaires were fulfilled and immune parameters in blood were evaluated.

Results: In active group, 36% of the children did not suffer from any respira- tory infection during the treatment compared to 21% in placebo group (p<0.05). Imunoglukan P4H® significantly decreased the frequency of flu and flu-like dis- eases and also lower respiratory tract infections. 65% of physicians evaluated the effect of Imunoglukan P4H® as excellent (significant decreased morbidity) compared to 39% for placebo (p<0.05). We observed a significant modulation effect of Imunoglukan P4H® on humoral and cellular immune response.

Conclusions: Our study provided relevant evidence for preventing effect of Imunoglukan P4H® on the incidence of respiratory infections and revealed its com- plex immunomodulating activity. This is the first double-blind, placebo-controlled study in children with RRTI aimed on the preventive effect of beta-glucans on respiratory morbidity.

P2957 Community-acquired pneumonia in pediatric patients with heritable connective tissue disorders: Novel phenotypic variants

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Background: The prevalence of heritable connective tissue disorders (HCTD) changed manifestations of community-acquired pneumonia (CAP) in pediatric patients, leading to diagnostic and therapeutic errors.

Objectives: To study clinical features of CAP in children with HCTD.

Material and methods: 105 patients aged 3-18 years, with clinically, serologically and radiographically diagnosed CAP were followed up for two years. Patients had persistent moderate asthma (A). All pediatric patients had HCTD manifestations.

Results: CAP caused by Mycoplasma pneumonia (Mp) was in 89.1% of patients, by Cytonmegalo virus (CMV) - in 26.7%, by Chlamydophilla pneumonia (CP) - in 21.9%. CAP was caused by association of Mp, Cm and Cm in 38.1% of children. CAP in asinhatic patients occurred with longer duration of respiratory symptoms and bronchial obstruction (11±5.2 days). Pulmonary hypertension (PH) was in 51.7% of patients with CAP and A, with pulmonary fibrosis (PF) in 48.3% of this group of patients. 26.7% of children with PH and PF had CT evidence of em- physematous bullae (EB). Patients with CAP and A received antibiotic treatment (macrolides) (ABT) besides controller therapy for achievement of A control.

Conclusions: 1) Close relationship between CAP, caused by intracellular pathogens, and HCTD is revealed. 2) CAP provoked A exacerbation in 57.4% of patients. 3) CAP in asinhatic patients had more long-term and severe clinical course. 4) PH was diagnosed in 51.7% of patients with CAP, A and HCTD, 48.3% of them had PF. 5) 26.7% of patients with PH and PF had EB. It is advisable to consider CAP associated with HCTD and A as clinical phenotypes of CAP.

P2958 Effect of short-chain fatty acids and pH on aerobic and anaerobic growth of Pseudomonas aeruginosa

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Background: Pseudomonas aeruginosa (PA) is one of the most common pathogens in patients with cystic fibrosis (CF) lung disease. PA and other anaerobic bacteria produce short-chain fatty acids (SCFAs) as byproducts of anaerobic fermentation. SCFAs are more volatile at low pH values, and reports have shown that CF patient sputum in acidic. Recently, we detected SCFAs in the low millimolar range in the sputum of CF patients.

Aim: To determine if SCFAs affect bacterial growth at different pH levels.

Methods: The laboratory strain PA01 and a clinical isolate PAS08 were used for experiments with and without the addition of SCFAs (acetate, propionate, butyrate) at a range of concentrations between 3.125-100 mM and pH values from 5.5-7.0 in tryptic soy broth. Optical density at 600 nm was measured every 30 minutes for a 6 hour period, as well as viable colony counts after the period of incubation. Anaerobic/macro aerobic conditions were generated by sealing microplates with anaerobically-clear PCR film.

Results: Acetate showed a significant inhibition in growth above 50 mM (p<0.05). Acetate at <50 mM showed a significant increase in growth above 12.5 mM acetate (p<0.05). Propionate had the highest inhibition, followed by butyrate and acetate. Anaerobic conditions resulted in lower growth overall and showed similar trends in growth inhibition. Results were consistent for both PA strains tested.

Conclusion: SCFAs increase the growth of laboratory and clinical strains of PA at concentrations found in CF patient sputum, but inhibit growth at high con- centrations. SCFAs produced by anaerobic bacteria may provide an indication of increased virulence of PA.
P2959
Longitudinal microbiology of children with primary ciliary dyskinesia
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Experimental Sciences, Faculty of Medicine, University of Southampton, United
Kingdom; 2Primary Ciliary Dyskinesia Diagnostic Service, University Hospital
Southampton NHS Foundation Trust, Southampton, United Kingdom

Introduction: Longitudinal changes in the respiratory microbiology of cystic fi-
brosis is well characterised; *Staphylococcus aureus* & *Haemophilus influenzae* are
initially isolated before chronic *Pseudomonas aeruginosa* colonisation. However
there is a paucity of similar microbiological data for primary ciliary dyskinesia
(PCD).

Aims: Longitudinal assessment of respiratory microbiology in paediatric PCD
patients in a UK specialist centre.

Methods: Results of sputum and cough swab microbiology from PCD patients
(aged 2.1–19.3 years old, n=17) between January 2003–January 2012, were re-
viewed. Results were divided into 5-year cohorts corresponding to patient age at
time of sample acquisition (Table 1).

Results: 168/341 (49.1%) cultures were positive. *H. influenzae* was most prevalent
(61/168, 36.3%) followed by *S. aureus* (32/168, 19%), *Streptococcus pneumoniae*
(27/168, 16%) and *P. aeruginosa* (16/168, 9.5%). The predominance of *H. influen-
zae continued throughout childhood apart from in 5–10 year olds where there were
equivalent numbers of *H. influenzae*, *P. aeruginosa*, *S. aureus* & *S. pneumoniae*
(Table 1).

Conclusion: *H. influenzae* is the predominant pathogen in our PCD patients
throughout childhood, particularly >10 years old. The progression to chronic *P.
aeruginosa* colonization seen in CF is not evident in our PCD population.

Table 1. Percentage prevalence of bacteria in PCD children in a tertiary follow up clinic in the
UK (overall and in age bands)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Overall (n=168)</th>
<th>0–5 yrs (n=28)</th>
<th>5–10 yrs (n=67)</th>
<th>10–15 yrs (n=47)</th>
<th>15–20 yrs (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>36</td>
<td>32</td>
<td>18</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>19</td>
<td>15</td>
<td>22</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>16</td>
<td>11</td>
<td>24</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>10</td>
<td>7</td>
<td>19</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fungi and yeast</td>
<td>7</td>
<td>14</td>
<td>6</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>14</td>
<td>6</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>
3074 The second therapeutic intervention in malignant effusion trial (TIME2): A randomised controlled trial to assess the efficacy and safety of patient controlled malignant pleural effusion drainage by indwelling pleural catheter compared to chest drain and talc slurry pleurodesis

Eleanor Mistry1, Helen Davies1, John Wrightson1, Andrew Stanton1, Amar Guhan2, Christopher Davies3, Jamal Graezer3, Richard Harrison3, Anjani Prasad4, Nicky Crosthwaite4, Y.C. Gary Lee5, Robert Miller6, Brennan Khan7, Najah Rahman1,1 Oxford Respiratory Trials Unit, University of Oxford, Oxfordshire, United Kingdom; 2Dept. of Respiratory Medicine, University Hospital of Wales, Cardiff, United Kingdom; 3Dept. of Respiratory Medicine, Great Western Hospital, Swindon, United Kingdom; 4Dept. of Respiratory Medicine, James Cook University Hospital, South Tees, United Kingdom; 5Dept. of Respiratory Medicine, Royal Berkshire Hospital, Reading, United Kingdom; 6Dept. of Respiratory Medicine, Hospital Provincial, Castellón, Spain; 7Dept. of Respiratory Medicine, University Hospital of Wales, Cardiff, United Kingdom; 8Dept. of Respiratory Medicine, Royal Berkshire Hospital, Reading, United Kingdom; 9Dept. of Respiratory Medicine, University Hospital of Wales, Cardiff, United Kingdom; 10Dept. of Statistics, Medical Research Council, London, United Kingdom

Introduction: Malignant pleural effusions (MPEs) can be treated by indwelling pleural catheter (IPC) or chest drain and talc pleurodesis (usual care). This is the first direct, randomised comparison of these techniques as initial therapy assessing patient reported outcomes.

Methods: Randomised trial of IPC versus usual care (1:1) in patients with symptomatic MPE. IPCs were inserted as day cases, followed by patient education and home drainage. Usual care was admission for chest drain and talc pleurodesis in patients with good lung re-expansion. The primary outcomes were daily visual analogue scale (VAS) scores of breathlessness and chest pain over 42 days (100mm line, 0mm = no breathlessness/chest pain, 100mm = maximum breathlessness/pain).

Results: 106 patients were randomised. Dyspnoea improved in both arms, with no significant difference in intensity (mean VAS: IPC 24.4mm (SD 18.9), usual care 24.4mm (SD 17.0), difference 0.16mm, 95% CI -0.6 to 0.96). Dyspnoea decreased by mean 37mm (SD 27.1) IPC arm and 30mm (SD 27.7) usual care arm. Chest pain decreased from baseline in both arms (mean VAS: IPC 20.5mm (SD 18.2), usual care 17.6mm (SD 16.0), difference 5.4mm, 95% CI -3.0 to 13.8, p=0.21). Preliminary analysis demonstrated lower initial hospital stay in the IPC group (median days 0 (IQR 0-1) versus 4 (IQR 2-6)).

Discussion: IPC and usual care are comparable effective treatments for the relief of breathlessness in patients with MPE. The pain profile of IPC and usual care is similar over 6 weeks.

Conclusions: IPC is a useful tool that increases QoL in the palliative management of advanced malignancies with MPE.

3076 Mesothelioma in Sunderland UK 1998-2011: Chemotherapy usage and impact on survival

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Background: UK and European guidelines on treatment of mesothelioma recommend combination chemotherapy with Cisplatin/Pemetrexed (CP) in patients with good performance status. In Sunderland CP chemotherapy has been the standard treatment for mesothelioma in selected patients since 2006. The aim of this study was to ascertain the usage of CP for mesothelioma and impact on survival.

Method: Study conducted at Sunderland Royal Hospital. Patients diagnosed with malignant mesothelioma between 1998-2011 were included. Data collected: demographics, performance status, comorbidity, histology, treatment. Patients were stratified by date of diagnosis: 1998-2005 and 2006-2011. Factors affecting survival were assessed by Cox’s regression analysis.

Results: N=209, median (IQR range) age 66 (63-77) years, male 81.8%. Histology: Epithelioid 48%; Sarcomatoid 12.6%, Mixed 5.2%, Unspecified 34.2%. Propor- tion treated with chemotherapy 1998-2005 29.3%, 2006-2011 62.9%; OR 3.65 (CI 2.03-6.5). Median (IQR) survival: 1998-2005 8.2 (3.7-19.3) months, 2006-2011 all patients 9.8 (3.7-15.8) months, patients given CP chemotherapy 12.7 (9.8-22.7) months p > 0.05. On regression analysis treatment with CP appeared to confer a survival benefit HR 0.95 (95% CI 0.30) (0.21-0.43). But overall survival was unchanged between 1998-2005 and 2006-2011 HR 0.98 (0.72-1.3).

Conclusion: Most patients with malignant mesothelioma are now treated with carboplatin/pemetrexed combination chemotherapy. However overall survival has not improved significantly and the apparent benefit of treatment may be due to patient selection.

3077 Efficacy and safety of autologous blood pleurodesis versus talc pleurodesis in patients with malignant pleural effusions: Preliminary results

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Autologous blood pleurodesis in clinical practice has not been evaluated in the treatment of malignant pleural effusions. The aim of this ongoing study is to determine the efficacy and safety of autologous blood pleurodesis versus talc pleurodesis in patients with malignant pleural effusions.

A prospective, randomized trial was carried out in a single centre. Our study has been conducted since March 2009 and by now comprised 21 patients with recurrent malignant pleural effusions. Patients were randomized to autologous blood and talc pleurodesis group. A blood sample of 3 ml/kg was obtained from the patients' brachial vein and immediately given into the intrapleural space. Four grams of talc mixed in 150 ml of normal saline was administered via tube thoracostomy. Patients were followed up with chest radiographs at 3 days and 1 month after pleurodesis.

Eight patients were randomly assigned to the autologous blood-treated group and 11 to the talc-treated group until January 2012. Two patients were ineligible due to rapid progression of systemic disease and death. The median age was 60.7 years. The success rate was 75% (6/8) in autologous blood group and 82% (9/11) in talc group. There was no statistically difference between the groups in regard to success rates (p=0.574). No severe or life-threatening adverse experiences were noted in the study. Chest pain is the most frequent minor complication in talc group. According to these preliminary results, we have found that pleurodesis using both autologous blood and talc showed high efficacy for controlling malignant pleural effusions.

3078 Time to diagnosis and time to therapy in patients with malignant pleural mesothelioma (MPM) compared to patients with lung cancer in Denmark 2007 to 2011. A quality assurance analysis

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In Denmark patients with pleural diseases are usually first seen by doctors taking care of patients with suspected lung cancer. When “diagnostic packages” were published in 2008 by the National Board of Health a 28 days maximal time to diagnosis and a 42 days maximal time to treatment were stated for lung cancer
as well as for MPM. We wanted to study how well these time frames are fulfilled for MPM. For the 5-year period 2007 to 2011, we have found 146 MPM patients in the pathology registry of Odense University Hospital. This is about 30% of all incident cases in Denmark in the period. MPM was confirmed by histology in 92% of the cases. Five patients died before the final diagnosis was known. Forty-two (30%) of 141 patients were treated by best supportive care. Two patients were lost for follow-up. In the three patients therapy was initiated at progression, but in 94 patients therapy began as soon as possible after the diagnosis. Eighty-three had chemotherapy, 10 had radiotherapy, and one had resection as the first step of the treatment. For the 141 patients the median time to diagnosis was 38 days (range: 6-127 days). Only 30% of the patients were diagnosed within 28 days. The median time to therapy for the 94 patients was 58 days (range: 19-142 days) - 21% were treated within 42 days. Among the 77 MPM patients from our primary uptake area 42% were diagnosed within 28 days and 17 out of 54 (32%) were treated within 42 days. In the same period, 84% of patients with lung cancer from our primary uptake area were diagnosed within 28 days and 74% had started treatment within 42 days. 

3081 A dual-acting muscarinic antagonist, β2-agonist [MABA] molecule (GSK961081) improves lung function in COPD. A randomised trial on moderate and severe COPD subjects. GSK961081 was safe and well tolerated. Introduction: GSK961081 is a dual pharmacophore demonstrating both muscarinic antagonist and beta agonist activities in one molecule (MABA). Recent COPD treatment guidelines have recommended that combining bronchodilators with different mechanisms may increase the degree of bronchodilation for equivalent or lesser side effects (GOLD 2010). Methods: This was a 4-week, multicentre, randomised, double blind, double dummy, placebo and salmeterol controlled parallel group study. Dose ranging across three twice-daily (BD) doses and three once-daily (QD) doses were assessed in moderate and severe COPD subjects. Through FEV1, at day 29 was the primary endpoint. Other efficacy endpoints, included serial FEV1 over 24h, FVC, and rescue salbutamol use. Safety endpoints included heart rate, glucose and QTc. Results: The study recruited 436 subjects. GSK961081 showed statistically and clinically significant differences from placebo in all doses and regimens for FEV1, trough on day 29 (155-277ml p<0.001). The optimal daily dose was 400mcg, either as once (400mcg QD) or as twice a day (200mcg BD) dosing with an improvement in Day 29 trough FEV1 of 21.5ml (95%CI) (-140,290) p<0.001 and 249ml (170,320) p<0.001 respectively. Other efficacy endpoints, including serial FEV1 over 24h, FVC and rescue salbutamol use were assessed. Safety endpoints included heart rate, glucose and QTc.

Rationale: Osteopontin (OPN) is overexpressed in mesothelioma tissue and has been associated with impaired patient survival. However, whether OPN is involved in mesothelioma growth and regulation of tumor-stimulated immune reaction is unknown. Aim: To examine the functional importance of OPN in experimental malignant pleural mesothelioma. Methods: AE17 murine mesothelioma cells which express high levels of OPN, engineered to stably express short hairpin RNAs (shRNAs) targeting the OPN transcript. To mimic pleural mesothelioma we intrapleurally injected syngeneic C57Bl/6 mice with AE17/OPNshRNA or AE17/vector cells. Tumor size and pleural fluid were harvested 15 days post-injection. The presence of pro-tumor cells including CD11b+CD206+ macrophages and CD11b+Gr(+) myeloid suppressor cells were evaluated using FACS. Results: Pleural tumors in mice injected with AE17/shRNAs were significantly smaller than those developed in mice injected with AE17/vector (mean tumor weight 428±41.2mg versus 107±2.25 mg, P<0.05). In addition, animals bearing AE17/shRNAs tumors had significantly less pleural fluid compared to those bearing control tumors (45.8±4.8g/1 versus 41.67±4.52g/1, P< 0.05). Pleural fluid CD206+ macrophages were significantly less in mice with AE17/shRNAs tumors compared to those with AE17/vector. Similarly, pleural fluid CD11b+Gr(+) myeloid-suppressor cells were significantly reduced respectively. Conclusion: OPN promotes experimental pleural mesothelioma growth and formation of malignant pleural effusion. Importantly, OPN substantially contributes in pro-tumor inflammatory cell recruitment in the mesothelioma-affected pleural cavity.

The overall survival of the MPM patients with lower pleural effusion MMP-3 levels was longer than that of those with higher pleural effusion MMP-3 levels. Our data suggest clinical role of pleural effusion MMP-3 levels in malignant pleural mesothelioma. 

3079 Clinical role of pleural effusion MMP-3 levels in malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive malignant tumor of mesothelial origin associated with asbestos exposure. MPM displays a limited response to conventional chemotherapy and radiotherapy, so early diagnosis of MPM is very important. Malignant tumor progression requires destruction of the basement membrane (BM), which is constructed from extracellular matrix (ECM) materials. Matrix metalloproteinases (MMP) are thought to be important due to their role in ECM degradation and cellular invasion. MMPs are involved in the progression of various diseases, including cancer, atherosclerosis, and immune responses. In particular, MMP-3 is known to play a crucial role in cancer progression and invasion.

In this study, we measured the pleural effusion MMP-3 concentrations of 52 MPM patients and 67 non-MPM patients. We demonstrated that the MPM patients had significantly higher pleural effusion MMP-3 levels than the population with non-malignant pleuritis. This finding suggests that high MMP-3 levels in pleural effusion might be a useful biomarker for diagnosing MPM.

The study also examined the clinical significance of pleural effusion MMP-3 levels. The results showed that patients with higher MMP-3 levels had a significantly shorter survival time compared to those with lower levels. This finding supports the clinical relevance of MMP-3 levels in MPM.

In conclusion, our study reveals that high pleural effusion MMP-3 levels are associated with a poorer prognosis in malignant pleural mesothelioma. These findings underscore the importance of MMP-3 as a potential biomarker and therapeutic target for MPM.

345. New bronchodilators and other novel drugs for asthma and COPD

3082 Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: Low-nadir dose assessment

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Rationale: FF/VI is in development as a novel once-daily (OD) inhaled corticosteroid/long-acting beta2 agonist combination therapy for COPD.
Objective: To evaluate the efficacy and safety of FF/VI (100/25 and 50/25mcg) vs placebo (PBO), FF (100mcg), and VI (25mcg), given OD as a novel dry powder inhaler for 168 days in moderate-severe COPD patients.

Methods: A multicentre, randomised, PBO-controlled, double-blind, parallel-group study (N=1030 (ITT)). Co-primary endpoints: weighted mean (wm) FEV1 (0-4h). Addition of FF to VI provided numerical improvements only in wmFEV1 (0-4h). Additional endpoints included CRQ-SAS dyspnoea and safety.

Results: Co-primary endpoints: see Figure. FF/VI 100/25 was numerically superior to components on dyspnoea score (treatment differences from PBO =-0.38 vs -0.06 [FF] and 0.14[VI]). On-treatment AEs were more frequent with active treatment (54–60%) than PBO (48%). There were no treatment effects on 24h urinary cortisol, laboratory values, or cardiac monitoring parameters.

Conclusions: Addition of VI to FF produced a clinically significant improvement in wmmFEV1 (0-4h). Addition of FF to VI provided numerical improvements only in trough FEV1. Combination therapy was superior to PBO for both co-primary endpoints. All treatments were well tolerated. Funded by GSK (HESC112206; NCT01053988).

3084 Efficacy and safety of BI 671800, an oral CRTH2 antagonist in controller-naïve patients with poorly-controlled asthma

Objective: To investigate the efficacy and safety of BI 671800 versus placebo and fluticasone propionate (FP) in controller-naive patients with poorly-controlled asthma.

Methods: Adults with asthma (FEV1 < 60% and ACQ >1.5) were enrolled in a randomized, double-blind, parallel arm study comparing BI 671800 50, 200 or 400 mg bid with matching placebo bid or FP 110 μg bid for six weeks. The primary study outcome was change in trough FEV1.

Results: 385 patients were randomised (mean age 37–4 years, FEV1 72%, ACQ 2.9). Changes from baseline in adjusted mean (SE) trough morning FEV1% predicted versus placebo were 3.08% (1.65), 3.59% (1.60) and 3.98% (1.64) for 50, 200 and 400 mg BI 671800 respectively, and 8.61% (1.68) for FP (one-sided p = 0.02 for 200 and 400 mg bid and FP), achieving the primary efficacy outcome for the study. Change in ACQ mean (SE) scores versus placebo were 0.07 (0.11), -0.08 (0.11) and -0.06 (0.11) for 50, 200 and 400 mg BI 671800 bid respectively, and -0.33 (0.12) for FP (one-sided p < 0.025 for FP). No significant imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.

Conclusion: Treatment with BI 671800 was associated with a significant improvement in FEV1 in controller-naive patients with poorly-controlled asthma. BI 671800 was well tolerated at total daily doses up to 800 mg for 6 weeks.

3085 Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid

Objective: To investigate the efficacy and safety of BI 671800 administered once daily in controller-naive patients with poorly-controlled asthma prescribed an inhaled corticosteroid.

Methods: Adults with asthma (FEV1 < 60% and ACQ >1.5) were enrolled in a randomized, double-blind, three period, incomplete cross-over study comparing BI 671800 400 mg (1, 2, 4 weeks). Changes from baseline in adjusted mean (SE) trough morning FEV1 (MDI) were -0.08 (0.11), -0.06 (0.11) and -0.33 (0.12) for FP (one-sided p < 0.025 for FP). No significant imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.

Conclusion: BI 671800 is an antagonist of the PGD2 receptor. CRTH2, PGD2 stimulates bronchoconstriction and allergic airway inflammation in animal models. Inhibition of CRTH2 may reduce airway inflamed cells, IL-4, -5, -13, production, serum IgE and airway hyper reactivity.

Objective: To investigate the efficacy and safety of BI 671800 versus placebo and fluticasone propionate (FP) in controller-naive patients with poorly-controlled asthma.

Methods: Adults with asthma (FEV1 < 60% and ACQ >1.5) were enrolled in a randomized, double-blind, parallel arm study comparing BI 671800 50, 200 or 400 mg bid with matching placebo bid or FP 110 μg bid for six weeks. The primary study outcome was change in trough FEV1.

Results: 385 patients were randomised (mean age 37–4 years, FEV1 72%, ACQ 2.9). Changes from baseline in adjusted mean (SE) trough morning FEV1% predicted versus placebo were 3.08% (1.65), 3.59% (1.60) and 3.98% (1.64) for 50, 200 and 400 mg BI 671800 respectively, and 8.61% (1.68) for FP (one-sided p = 0.02 for 200 and 400 mg bid and FP), achieving the primary efficacy outcome for the study. Change in ACQ mean (SE) scores versus placebo were 0.07 (0.11), -0.08 (0.11) and -0.06 (0.11) for 50, 200 and 400 mg BI 671800 bid respectively, and -0.33 (0.12) for FP (one-sided p < 0.025 for FP). No significant imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.

Conclusion: Treatment with BI 671800 was associated with a significant improvement in FEV1 in controller-naive patients with poorly-controlled asthma. BI 671800 was well tolerated at total daily doses up to 800 mg for 6 weeks.
3086 Effects of the novel toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma
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Abstract: Elevated serum IgE is associated with allergic asthma. Membrane IgE (sIgE) on the prime epitope, present in human IgE-switched memory B cells and plasmablasts. MEMP1972A, a therapeutic antibody specific for M1-prime that depletes M1-prime-expressing cells.

Methods: This randomized, double-blind, controlled study (NCT01196309) assessed the activity of MEMP1972A in adults with mild asthma after allergen inhalation challenge (AIC). Subjects (n=29) were randomized (1:1) to intravenous MEMP1972A (5 mg/kg) or placebo every 4 weeks for 12 weeks. The primary outcome was the area under the curve (AUC) of the late asthmatic response (LAR) at Wk 12. Secondary outcomes included early asthmatic response (EAR). Serum total IgE and allergen-specific IgE were measured to confirm mechanistic activity of MEMP1972A. Other exploratory biomarkers were measured eg sputum and blood eosinophils.

Results: MEMP1972A treatment was well tolerated. At Wk 12, MEMP1972A reduced the LAR AUC by 36% (90% CI -14.6, 69, p=0.21) and the EAR AUC by 26% (6, 43, p=0.046) vs placebo. AIC at screening and Wk 12 induced a >2-fold increase in allergen-specific IgE which was abrogated by MEMP1972A and more than >10-fold increase in sputum eosinophils, which was reduced by MEMP1972A at Wk 12. MEMP1972A reduced total IgE by ~20% at Wk 8, and blood eosinophils by ~45% at Wk 28 vs baseline.

Conclusions: Attenuation of EAR, LAR, serum IgE, pH, PEF, blood sputum and blood eosinophils following AIC is consistent with the mechanism of action of MEMP1972A. Depletion of the M1-prime-expressing B-cell lineage may be effective for the treatment of allergic asthma.
3090 Dynamic preferences for site of death among patients with advanced chronic organ failure
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Background: Being able to die at the preferred site is seen as a key principle of a good death. Aims of this study were to assess 1-year stability and determinants of preferences for site of death among patients with advanced COPD, Chronic Heart Failure (CHF), or Chronic Renal Failure (CRF) and to assess agreement between the actual site of death and the site patients indicated in advance as their preferred site.

Methods: 265 outpatients (105 COPD, 80 CHF; 80 CRF) were recruited. 206 patients (77.6%; 67.2 (13.1) years; 64.1% male) completed 1-year follow-up. Patients were visited at baseline, 4, 8, and 12 months to assess the preferred site of death. Patient characteristics were recorded. A bereavement interview was done with the close relatives of patients who died within 2 years after baseline (n=66, 24.9%) to assess actual site of death.

Results: At baseline, 106 patients (51.5%) preferred to die at home, 61 (29.6%) at the hospital, 21 (10.2%) at a care home or hospice and 18 (8.7%) did not know. Patients living with a partner were more likely to prefer to die at home (OR 3.21 (1.73-5.92)). During 1 year, 61.2% of the patients changed their preference for site of death. During the interview before their death, 34 patients (51.5%) preferred to die at home, 22 (33.3%) at the hospital; 8 (12.2%) at a care home or hospice and 2 (3.0%) did not know. 57.6% died at the hospital, 27.3% at home and 39.4% died at the preferred site (Kappa 0.07, p=0.42).

Conclusions: Although most patients preferred to die at home, the majority died in the hospital. Only 39% of the patients died in the preferred site. However, 61% of the patients changed their preference for site of death at least once during 1 year.

3091 Decrease of physical activity in patients with COPD in the course of the disease
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Methods: We measured total daily energy expenditure, the physical activity level (p.a.) and the number of activity days per week in 343 COPD patients during a median follow-up of 2.8 years (range, 1.8 - 3.5). Total daily energy expenditure was defined as the number of steps divided by resting metabolic rate, and steps per day by a multisensor armband over a period of 5 to 6 consecutive days in 26 patients with chronic bronchitis and 137 COPD patients (GOLD stage 1 - IV) at baseline and at follow-up. Results: During a median follow-up of 2.8 years (range, 1.8 - 3.5), total daily energy expenditure decreased from 2708 kcal (SD 590) to 2518 kcal (SD 536) resulting in an annual rate of decline of 68 kcal (p < 0.001). Physical activity level decreased from 1.57 (SD 0.28) to 1.48 (SD 0.25) resulting in an annual rate of decline of 0.03 (p < 0.001). Steps per day decreased from 6822 (SD 3786) to 5685 (SD 3546) resulting in an annual rate of decline of 418 steps (p < 0.001). The absolute decline of total daily energy expenditure, physical activity level, and steps per day was independent of baseline disease severity. The relative changes of all physical activity parameters were higher in patients with severe and very severe COPD.

Conclusion: Physical activity decreases across all severity stages of COPD in the course of the disease with relative changes being most prominent in severe stages.

Abstract 3092 – Table 1

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Change (95%CI)</th>
<th>Baseline</th>
<th>Change (95%CI)</th>
</tr>
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<tr>
<td>CRQ-dyspnea</td>
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<td>0.71*** (-0.46-0.96)</td>
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<tr>
<td>CRQ-fatigue</td>
<td>3.96</td>
<td>0.37*** (-0.17-0.59)</td>
<td>3.68</td>
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<tr>
<td>CRQ-emotion</td>
<td>4.87</td>
<td>0.31*** (-0.10-0.53)</td>
<td>4.85</td>
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<tr>
<td>CRQ-mastery</td>
<td>5.27</td>
<td>0.14 (-0.07-0.35)</td>
<td>5.20</td>
</tr>
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<td>ISWT (m)</td>
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<td>-12.77 (-0.90-26.44)</td>
<td>340.96</td>
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<tr>
<td>ESWT (s)</td>
<td>258.63</td>
<td>219.60** (140.86-298.33)</td>
<td>272.83</td>
</tr>
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<td>HADS-D</td>
<td>5.90</td>
<td>-0.65* (-1.15-0.19)</td>
<td>6.79</td>
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<tr>
<td>HADS-D</td>
<td>5.29</td>
<td>-0.50 (-1.04-0.04)</td>
<td>5.14</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001.

3092 A self-management programme of activity coping and education (SPACE) for COPD: 6 week results from a randomised controlled trial
Katy Wag1, Vicki Warrington1, Lindsay Apps1, Louise Sewell1, John Bankaran2, Mick Steiner1, Mike Morgan1, Sally Singh1,2, 1NIHR CLAHRC-LNR Pulmonary Rehabilitation Research Group, University Hospitals, Leicester, United Kingdom; 2Health Sciences, University of Leicester, United Kingdom; 3Health and Life Sciences, Coventry University, Coventry, United Kingdom

Introduction: SPACE for COPD is a self-management programme which individual patients follow independently with telephone support.

Objective: To test the effectiveness of SPACE on health related quality of life (HRQoL) and exercise capacity compared with usual GP care at 6 weeks.

Methods: 184 patients with COPD (101male; mean (SD) age 69(9.19) yrs; FEV1 1.45(0.56) l; BMI 27.3(6.52) were recruited from primary care and randomised to SPACE or usual care. Blinded measurements were taken at baseline and 6 weeks and included Chronic Respiratory Questionnaire-SR (CRQ-SF), hospital anxiety and depression scale (HADS).

Results: See Table 1.

Conclusion: SPACE is effective in improving HRQoL and exercise capacity, when compared with usual care. SPACE could be used to facilitate self-management of patients with COPD in primary care.

3093 Living with COPD: Psychological distress among family carers
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The impacts of Chronic Obstructive Pulmonary Disease (COPD) in terms of patients’ psychological distress have been well reported. However, COPD also poses several challenges to family carers, as they represent a primary source of support to patients. Yet, the burden of COPD in terms of family carers’ psychological distress remains relatively unexplored. This study aimed to assess the presence of anxiety and depression symptoms among family carers.

A cross-sectional study was conducted with 110 family carers of patients with COPD, in the central region of Portugal. A structured questionnaire based on ICF-checklist was used to collect socio-demographic and subjective health status data; Depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS). Descriptive statistics and χ2 tests were applied using PASW Statistics 18.0. Participants’ mean age was 59.9±12±33 years old and was predominantly female (n=78; 71%). The majority were spouses (n=75; 68.2%) and caring for more than 4 years (n=66; 60%). 67.3% of participants presented anxiety symptoms, 37.3% depression symptoms and 28.2% presented both. Subjective mental health was significantly associated with anxiety (p<0.001) and depression (p<0.001). Subjective physical health was significantly related with depression (p<0.001). No other statistically significant associations were found.

Caring for a patient with COPD can impact negatively on the psychological health of family carers. Similar results have been shown in the context of other chronic conditions, such as cancer, dementia or stroke. The results highlight the need of supportive interventions tailored to the particularities of DPOC caregiving in order to prevent burden among family carers.

3094 Reduced exertional dyspnea with supplemental oxygen in patients with COPD – Characteristics of responders and non-responders
Nina Fakvæde Caspergaard, Christine Gudin Karlsen, Anne Edvardsen, Sari Skulstad, Gulliksklinikken, Gulliksklinikken, Haskal, Norway

Introduction: Ambulatory oxygen is recommended for COPD patients who desaturate during activity, and who experience subjective effect of oxygen supplementation. COPD patients with no former oxygen treatment admitted for rehabilitation were referred to extended testing if oxygen saturation measured by pulse oximetry (SpO2) during 6-minute walk test (6MWT) fell below 88%.

Aim: Our study aimed at identifying characteristics that differed between patients who experienced subjective effect of oxygen during constant load treadmill test and those who did not.

Table 1
Methods: Lung function was measured and expressed in % reference values. Two 5 min constant load treadmill tests were performed at a speed just below 6MWT to mimic walking speed in daily activity. Arterial bloodgas samples were drawn before stop. Dyspnea was measured on Borg CR10 scale. Blinded and in random order, patients received oxygen supplement 6 L/min or placebo air administered continuously through nasal catheter.

Results: 27 of 39 patients rated their dyspnoea at least 1 Borg unit lower with oxygen than without. There were no differences in age (64 (8: 65 (6) p=0,56), FEV1 (35 (17); 32 (16) p=0,33), RV (193 (74), 171 (88) p=0,46), TLC (115 (40); 107 (49) p=0,66), DLOCOVA (38 (15); 37 (23) p=0,94), resting pO2 (8.9 (0,6); 8.8 (0,9) p=0,92), nadir pO2 with placebo (6,8 (0,4); 6,5 (0,8) p=0,19), nadir SpO2 during 6MWT (81(3); 78(5) p=0,10) or pO2 with oxygen (kPa) (10,4 (1,3); 10,9 (1,8), p=0,19) between patients with subjective effect and those without.

Conclusion: None of the registered variables were helpful in predicting subjective effect of ambulatory oxygen.

3095
A ten-year survey of long term oxygen treatment (LTOT) in severe COPD: Comparison of the survival during telemetric home monitoring vs standard care
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Paola Turco2, 3, Respiratory Unit, Ospedale Orlandi, Bassoleengo, VR, Italy; 4Centro Studi Nazionale di Farmacoeconomia e Farmacopediometria, CESFA, Verona, Italy; 5Respiratory Unit, Ospedale Mater Salus, Legnaro, VR, Italy.

Subjects’ survival, is a crucial outcome during long-term oxygen treatment (LTOT). The survival of a cohort of 886 patients suffering from very severe chronic obstructive respiratory disease (COPD) and admitted to long-term oxygen treatment (LTOT) at a home was investigated over the last ten years. Subjects were divided in two groups with matched for age, sex, lung function and daily oxygen use: group A, patients managed according to an usual protocol for home assistance, and group B, patients admitted to a telemetric daily monitoring. Statistics: Wilcoxon’s test was used in order to compare the survival and acute episodes of relapse, and p<0.05 was accepted.

Results: Mean survival had a significantly longer duration (2.5 fold) in subjects telemetrically controlled at home (1239.6 days ± 382.1 vs sd 482.6 days ± 273.9 sd, p=0.001), with a lower incidence of these subjects (17.3 vs 33.0%, and 11.3 ± 21.1% respectively, both p<0.01). When standardization for age, lung function, smoking habit, and comorbidities, females still showed a significantly longer survival when managed according to the telemetric protocol of home LTOT (1166.4 days ± 556 sd vs 1433.7 days ± 656,3 sd, p<0.01).

Conclusions: The telemetric management of home LTOT proves more effective than standard care in terms of patients’ overall survival. Even if further studies are needed, a different females’ psychological approach to this particular model of management and their better acceptance of procedures might presumably contribute to explain the difference observed in the main outcome.

347. Stem cells and progenitors in injury and repair

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LSC 2012 Abstract – Effects of stem cells of healthy or acute lung injury donors of recipient injury mice
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Background: The airways of the mammalian lung are lined with specialized epithelial cell types that are the target of airborne toxins and injury. Notch signaling plays an important role in the development of these cells, but its contributions to recruitment, expansion or differentiation of resident progenitor/stem cells in repair of injured lung remains unknown.

Aims & objective: To elucidate the role of Notch signaling in repair of injured airway epithelium.

Methods: We used targeted inactivation of, Notch1, via the epithelial-specific Gata6Cre transgenic line in the embryonic lung epithelium.

Results: Notch1(-/-) mice are viable with intact pulmonary epithelial cell fate determination/differentiation. However, Notch1 was found to be required for normal repair of the injured airway epithelium. Absence of Notch1 reduced the ability of cells distinguished by expression of PDGFRα, a marker of pulmonary neuroendocrine cells, which serve as a reservoir for regeneration of Clara cells.

Blgmecin treatment or influenza virus infection can induce severe damage in distal lung with the loss of large amounts of alveolar type II (AT2) and type I (AT1) cells. During the repair process, new AT2s and AT1s have to be produced to regenerate the damaged alveoli. A recent study showed that the newly generated AT2s were not derived from pre-existing AT2s after blgmecin treatment, indicating the existence of other progenitor cells for alveolar regeneration [1]. We have used a genetic lineage tracing system to follow Clara cells in mice. We show that large numbers of the newly generated AT2s and AT1s are derived from Clara cells after alveoli damage by blgmecin treatment or influenza virus infection. The intermediates between Clara cells and AT2s are SPc-expressing bronchiolar cells (or SEBCs). SEBCs are only observed in damaged area and initially positive for Clara cell marker Clara Cell Secretory Protein (CCSP) and gradually become CCSP negative. Anatomical analysis shows that SEBCs at the tips of bronchioles appear to dilate to regenerate alveolar epithelium in a process similar to that seen during the development of embryonic alveolar epithelium. These findings show that Clara cells are the progenitors to regenerate alveolar epithelium in response to severe lung damage.


3098
Secreted mediators from induced pluripotent stem cells (iPSc) attenuate fibrosis in blgmecin injured rat lung
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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease resulting from deregulated alveolar epithelial repair, after micro injuries. There are no promising treatments available hence; novel methods to regenerate the injured lungs are urgently required. We studied the role of secreted mediators from induced pluripotent stem cells (iPSc) in blgmecin injured rat lungs.

Methods: iPSc cells were generated from human foreskin fibroblasts by transfection of the transcription factors SOX2, OCT4, KL4, and c-MYC, after characterization by immunohistochemistry and RT PCR, the colonies were expanded and the conditioned media (CM) was collected (iPScCM). iPScCM was subjected to proteomics to analyze the contents. Adult male rats (F344) were instilled intratracheally (i.t) with blgmecin at day 7, days later were treated with iPScCM or control media (CM) and sacrificed 7 days after iPScCM or CM treatment.

Results: Proteomic analysis revealed presence of various interesting cytokines and growth factors in the iPScCM, which are involved in regeneration process; the total collagen content after iPScCM treatment was lower than CM group (753±56.12 ug/mg vs 4182±521.8 ug/mg of wet tissue) as measured by hydroxyproline assay. Furthermore, TGFβ1 mRNA levels were also reduced after iPScCM treatment (0.9±0.266 vs 2.4±0.9) (2-ΔΔCt).

Conclusion: Secreted mediators present in the iPScCM attenuate fibrosis in the blgmecin injured rat lungs and may offer a novel therapeutic option for pulmonary fibrosis.

3099
Notch signaling via hairy/enhancer of split-5 (Hes5) & paired-box containing gene 6 (Pax6) controls progenitor cell reservoir for repair of airway injury
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Background: The airways of the mammalian lung are lined with specialized epithelial cell types that are the target of airborne toxins or injury. Notch signaling plays an important role in the development of these cells, but its contributions to recruitment, expansion or differentiation of resident progenitor/stem cells in repair of injured airways remains unknown.

Aims & objective: To elucidate the role of Notch signaling in repair of injured airway epithelium.

Methods: We used targeted inactivation of, Notch1, via the epithelial-specific Gata6Cre transgenic line in the embryonic lung epithelium.

Results: Notch1(-/-) mice are viable with intact pulmonary epithelial cell fate determination/differentiation. However, Notch1 was found to be required for normal repair of the injured airway epithelium. Absence of Notch1 reduced the ability of cells distinguished by expression of PDGFRα, a marker of pulmonary neuroendocrine cells, which serve as a reservoir for regeneration of Clara cells.

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Hairy/Enhancer of Split-5 (Hes5) and a paired-box containing gene 6 (Pax6) were found to be downstream targets of Notch1. Both Hes5 and Pax6 expression were significantly increased in association with Clara cell regeneration in wild type lungs. Ablation of Notch1 reduced Hes5 and Pax6 and inhibited Clara cell regeneration significantly in association with Clara cell regeneration in wild type lungs. Ablation of Notch1 reduced Hes5 and Pax6 expression, and inhibited Clara cell regeneration. Thus, although dispensable in developmental ontogeny of airway epithelial cells, normal activity of Notch1 is required for repair of the airway epithelium. The signaling pathway by which Notch1 regulates the repair process also includes stimulation of Hes5 and Pax6 gene expression.

**Supported by NIH, NHLBI & The Hastings Foundation.**

**3100** Evidence of increased pluripotent cells in adult human lung tissue derived from fibrotic lungs compared to non-fibrotic control lungs

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**Introduction:** Tissue-specific multipotent stem cells have been identified in the human lung. However, their role in lung homeostasis or lung disease is not clear.

**Methods:** Primary human lung cells were cultured from fibrotic adult lung parenchyma (n=14) and from non-fibrotic control lungs (n=17). The characterization of different cell types was performed by immunofluorescence stainings.

**Results:** Undifferentiated primary cells grew from adult human lung parenchyma, showing neither a clear epithelial nor mesenchymal morphology/immunofluorescence typing (intermediate cells). When cultured in the respective appropriate media, intermediate cells transformed into mesenchymal cells (positive for fibronectin and smooth muscle actin) or into alveolar epithelial type II cells (positive for E-cadherin and surfactant protein-A). Pluripotency of intermediate cells was proven by positive stainings for Oct3/4 and NANOG. Successful inductive differentiation of adipogenic, osteogenic, myogenic, and chondrogenic differentiation was performed in intermediate cells. Finally, significantly more pluripotent cells were generated from fibrotic lung tissue (n=14) than from non-fibrotic control lungs (n=17).

**Conclusions:** Our data demonstrate that adult human lung contains pluripotent cells which are able to differentiate towards an epithelial as well as a mesenchymal cell type solely by changing their microenvironment. These pluripotent cells might have a pivotal function in lung homeostasis and tissue repair. The observed increased incidence of these cells in fibrotic lung tissue suggests a role in fibrogenesis.

**3101** Adrenaline stimulated mesenchymal stem cells modulate inflammation in lipopolysaccharide induced lung injury

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**Introduction:** Bone marrow derived mesenchymal stem cells (BMSCs) could modulate inflammation. Adrenergic receptor agonists could increase DNA synthesis and protect oxidative stress in mesenchymal stem cells. We investigated the potential role of adrenaline stimulated BMSCs on lipopolysaccharide (LPS) induced lung injury in vitro.

**Methods:** BMSCs from rats were cultured with adrenaline at 0–100 μM, followed by determination of CCK8. The optimal concentration was chosen for latter study. BMSCs and lung cells from normal or LPS injured rats were co-cultured in a Transwell system (4.5μm pore size) for 36h. The migrated BMSCs were stained by Giemsa. BMSCs and alveolar macrophages were co-cultured with LPS or adrenaline in Transwell (0.4μm pore size) for 6h. The supernatant was collected for cytokines (TNF-α, IL-1β, IL-6, IL-10, IL-13, angiopoietin-1, KGF and IL-11a) analysis by ELISA, and the mRNA expression levels in BMSCs were determined by PCR.

**Results:** Adrenaline at 10 μM promoted proliferation and migration of BMSCs towards injured lung. Adrenaline enhanced the inflammation modulation effects of BMSCs by decreasing TNF-α, IL-1β and IL-6, and increasing IL-10. Adrenaline could also increase angiopoietin-1 mRNA expression of BMSCs.

**Conclusions:** Adrenaline could help BMSCs modulate LPS induced lung injury in vitro, probably through promotion of proliferation, migration and angiopoietin-1 secretion.

**3102** LSC 2012 Abstract – Mesenchymal stromal cells identified in tissue from lung-transplanted patients


**Background:** Chronic rejection expressed as bronchiolitis obliterans (BO) is seen in 50% of lung-transplanted (LT) patients. BO is characterized by extra cellular matrix deposition, where the fibroblast is thought to be a key player. The fibroblast origin is at present not fully known. The fibrocyte is one of the potential origins, and our group has shown that fibrocytes are associated with remodelling in BO. In this study we focused on another origin the mesenchymal stromal cell (MSC).

**Objectives:** Our aims were to examine whether MSC are present in tissue from LT patients and to evaluate whether these cells displays characteristic MSC properties such as adherent clonal growth, multi-lineage potential and a characteristic surface marker profile.

**Methods:** We examined lung biopsy material from LT patients to identify MSCs. Immunofluorescence was used to stain for specific surface markers.

**Results:** MSCs were identified in lung biopsy material from LT patients and the single cell suspension was seeded in colony-forming unit-fibroblast (CFU-F) assays. Isolated MSC were differentiated towards adipocytes, osteoblasts and chondrocytes. Their surface markers was examined by flow cytometry.

**Conclusions:** Our study suggests that MSC are present in lung tissue from LT patients. These cells display colony growth, multipotential and a characteristic MSC surface marker profile.

**3103** LSC 2012 Abstract – TGF-β1 regulates the epithelial supportive capacity of mesenchymal stromal cells

Jonathan McQuater, Rosa McCarty, Ivan Bertocchi. Department of Pharmacology, University of Melbourne, Melbourne, United Kingdom

Despite recent advances in biomarker profiling, prospective isolation and clonogenic assay of putative lung stem cells their regenerative capacity remains ill-defined. On that account we have developed a clonogenic colony-forming assay that has enabled us to identify a population of multi-potent lung epithelial stem cells (EpCAM+CD49f+CD44+CD24−CD104+CD10−) that are able to self-renew and give rise to alveolar and Clara epithelial cell lineages. However, the intrinsic regenerative potential of stem cells is conditional upon their interaction with permissive and restrictive microenvironmental cues. On this note, we have shown that the proliferation and differentiation of lung epithelial stem cells in vitro is dependent on co-culture with endogenous lung mesenchymal stromal cells (EpCAMneg Sca1-1pos), or mesenchyme-derived growth factors including FGF-10 and HGF. On the flip side, we have shown that more differentiated mesenchymal stromal cells (FGE-110f0 SMApos) are unable to support epithelial colony formation. Importantly, we have shown that the capacity of mesenchymal stromal cells to support epithelial stem cells is regulated by TGF-β1 and can be reversed by blockade of SMAD2/3 phosphorylation downstream of TGF-β activation. This data suggests that TGF-β mediated mesenchymal differentiation in chronic lung diseases may obstruct epithelial regeneration.

**348. Act to change tobacco epidemics**

**3104** Stop smoking prevention in the BOLD study

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**Background:** Tobacco smoking is a risk factor for COPD. Stop smoking strategies are associated with slower lung function decline. We used the BOLD data to describe the use of stop smoking prevention across 20 sites.
smoking rate in 12-15 years old Parisian school is sensitive to political

Conclusions: Use of stop smoking prevention is associated with chronic respiratory disease and pack-years smoked, is higher in current smokers than in ex-smokers and in HICs than in LMICs. Understanding factors influencing use and optimising use in current-smokers and LMICs are important.

Smoking rate in 12-15 years old Parisian school is sensitive to political
decisions

Conclusions: Use of stop smoking prevention is associated with chronic respiratory disease and pack-years smoked, is higher in current smokers than in ex-smokers and in HICs than in LMICs. Understanding factors influencing use and optimising use in current-smokers and LMICs are important.

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Conclusions: Use of stop smoking prevention is associated with chronic respiratory disease and pack-years smoked, is higher in current smokers than in ex-smokers and in HICs than in LMICs. Understanding factors influencing use and optimising use in current-smokers and LMICs are important.
of the physicians had education about counselling regarding SHS in children. Of those without education, 49.2% wants to be educated.

Conclusion: Dutch physicians insufficiently discuss second-hand smoking in children and lack of time was the most frequent barrier. Child healthcare practices should make more efforts to increase parental awareness and actively contribute to the decrease of SHS in children.

3101

Gain in survival due to smoking cessation in the Italian population

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Introduction and aim: Smoking is the largest preventable cause of health impairment. An important and challenging task for health professionals is to communicate the health benefits associated with smoking cessation. A simple and effective way could be to compute, for each individual smoker, the number of life years which he/she may gain by quitting smoking. Aim of the study was to estimate gain in life years associated with smoking cessation by using Italian data.

Methods: We computed mortality tables [1] based on Italian data, specific for current and former smokers. Subsequently, the survival curves of former and current smokers were compared to estimate the number of life years gained with quitting smoking at various ages [2], by gender and number of cig. smoked per day.

Results: Based on the implemented statistical model, men and women smoking 10-19 cig. per day and quitting at age 30, 40, 50, or 60 years, gained about 7, 6, or 5, and 5, 4, 3, or 3 years of life, respectively. The gain in life years was higher for men and women smoking more cig. per day (9 years for > 20 cig.) and lower for light smokers (2 years for 1-9 cig.) and related to age of quitting.


3110

Factors influencing dropout of a smoking cessation consultation in patients treated with varenicline

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Introduction: Smoking cessation clinics have high dropout rates. Reasons are often not clear.

Aim: To determine factors influencing dropout of smoking cessation clinics in patients treated with varenicline.

Methods: Retrospective cohort of patients started on varenicline. Comparative analysis of patients who dropped out (group 1) or not (group 2) our clinic at 4, 12, 24 and 52 weeks according to demographics, attempts to quit smoking, previous diseases, motivation (Richmond) and dependence (Fagerstrom) assessed on first analysis of patients who dropped out (group 1) or not (group 2) our clinic at 4, 12, 24, and 52 weeks. At week 4 dropout was observed in older age (p = 0.018) and individuals with respiratory disease (p=0.045). There was negative relation between motivation and dropout at week 12 (p=0.05) and between dependence and dropout at week 24 (p=0.04). Smoking in the previous appointment increased dropout risk at 24 and 52 weeks (p=0.001 and p=0.001).

Conclusion: Younger individuals with no respiratory disease, less dependent and less motivated tend to dropout more. At week 24 and 52 those who continue smoking and do not adhere to varenicline quit more. Our results may help to identify individuals most likely to abandon programs and improve strategies to address them.

Method: We analyzed patients that were followed in our asthma unit in last 3 months. We totally recruited 141 patients (48 men (34.3%) and 93 women (66.7%); average age = 49.8±16.90 years old). We registered their smoking history and phase, control and crisis of asthma in the last year.

Results: 5 patients (3.5%) were in intermittent asthma, 18 (12.8%) mild persistent, 69 (48.9%) moderate persistent and finally 49 (34.8%) severe persistent. About control we observed 32 patients (22.7%) were well-controlled, 51(36.5%) were partially-controlled and 54 (41.1%) were not-controlled. The smoking history showed 18 patients (12.8%) were active smokers, 25 (17.7%) ex-smokers and 98 (69.5%) non-smokers. If we analyze the smokers ones, 9 (50%) were moderate-persistent asthmatics, 8 (44.4%) severe-persistent and only 1 patient (5.5%) was mild-persistent. Ex-smokers: 10 of them (40%) were severe-persistent, 9 (36%) moderate-persistent and 9 (20%) mild-persistent. About control of asthma, 11 smokers (61.1%) and 12 ex-smokers (48%) were not-controlled. 7 smokers (38.8%) and 9 ex-smokers (36%) were partially-controlled. Only 4 ex-smokers (16%) were well-controlled. Finally, 39 patients (27.7%) visited emergency units in the last year. 14 of them were smokers (35%) and 11 ex-smokers (28%). In the same way, 14 of total smokers (77%) needed emergency units care. So 11 ex-smokers (25%).

Conclusion: Tobacco can affect the asthma management. Smokers and ex-smokers have worse control of asthma than non-smoker people, and they use to have more severe asthma too.

349. Immunologic mechanisms in COPD and asthma

3112

The profile of dendritic cell and T cell response is related to the viral trigger in children with severe asthma exacerbation

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Viral infection are associated with asthma exacerbations (AE). Activation of dendritic cells (DC) plays a key role in the response to virus and drives the activation and polarization of T cells. Mobilization of Pattern Recognition Receptor (PRR)- Toll Like Receptor (TLR5) RNA helicases (RIG-I, MDA5) are involved. Our purpose was to analyze expression and function of the PRR in DC and to corroborate this with the presence of virus and the T cell response.

Methods: 54 allergic asthmatic children (6-15 y) included during hospitalization for severe AE. Virus identified on nasal secretions by RT-PCR. T cell response determined in blood and induced sputum at the inclusion and in the stable state, 8 weeks later. Mononuclear cells (MNC) stimulated with poly(IC) and with varespland and poly(I:C) and levels of IL-12, IFN-γ, IL-17A measured. Ex- pression of markers of maturation (CD80, CD86) and PRR studied in circulating DC and induced sputum at the inclusion and in the stable state.

Results: Virus were indentified in 60% (Rhinovirus: 82%). A Th1 and Th17 (IFN-γ, IL-17A) response was observed in the Airways and the blood from the infected patients (+V) during exacerbation whereas a Th2 (IL-4) response prevailed in non-infected patients (V-). The stimulation of MNC induced a Th2 and Th17 response for V+ at inclusion, but Th1 in V-. A defect in RNA helicases expression by blood DC was observed in V+ at inclusion, while the expression of the markers of maturation did not differ among both groups.

Conclusion: Viral infection modifies the T cell response during AE and is associated with a defect of RNA-helicase expression in DC. This could contribute to describe new mechanisms in the virus induced AE.

3113

Lung dendritic cells from chronic obstructive pulmonary disease patients induce type I T regulatory cells

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The high mortality rate and health care costs associated with Chronic Obstructive Pulmonary Disease (COPD) are due to a great extent to recurrent infections exacerbations. Impaired T cell immunity might explain this susceptibility to infections. Mature dendritic cells (DCs) are crucial players in the induction of T cell responses against infectious agents. By contrast, immature DCs induce tolerance by promoting the differentiation of regulatory T cells (Tregs). We have previously shown

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that lung DCs of COPD patients express low levels of co-stimulatory molecules, respond poorly to stimulation and display low ability to prime autologous lung T cells and allogeneic naive T cells. Importantly, naïve T cells primed with lung DCs from patients with COPD inhibit T cell proliferation. Here, we have characterized the gene and protein expression profile of these regulatory cells and investigated the mechanism of their suppressive function. Naïve CD4+ T cells primed with lung DCs from COPD patients showed increased gene expression for TGF-β, AHR and GATA3 (assessed by qRT-PCR) compared to T cells primed with lung DCs from smokers without COPD. Accordingly, flow cytometry analysis showed higher IL-10 and Foxp3 intracellular protein expression. These findings suggest that the induced regulatory cells are Tregs type 1. Type 1 Tregs suppress immune responses primarily through IL-10. Indeed, naïve T cells that had been primed with COPD lung DCs failed to inhibit T cell proliferation in the presence of blocking IL-10-10 receptor antibody. Our findings show that lung DCs from patients with COPD induce type 1 Tregs.

3114 Lung B cell-derived CXCL13 is critical for lymphoid follicle formation in chronic obstructive pulmonary disease (COPD). Eleni Litsiou1, Maria Semitekolou2, Ioannis Morianos 2, Aikaterini Tsoutsa 1, Konstantinos Potaris 1, Georgina Xanthou 2, Spyros Zaktakinos 1, Maria Tsoumakidou 5, Critical Care Medicine and Pulmonary Services, Evangelismos General Hospital, Athens, Greece; 2Cellular Immunology, Biomedical Research Foundation of the Academy of Athens, Greece; 3Pathology, Evangelismos General Hospital, Athens, Greece; 4Thoracic Surgery, Evangelismos General Hospital, Athens, Greece; 5Sotiria Chest Hospital, Athens, Greece

Lymphoid follicles (LFs) that have a similar organization to lymph nodes are found in small airways and alveoli in Chronic Obstructive Pulmonary Disease (COPD), but the mechanism of their development is unclear. During lymph node ontogeny, the initiating event to LF formation in COPD is B cell stimulation, leading to LT expression and CXCL13 production. CXCL13 positively feeds back LT, fostering LF formation in COPD-LFs. The BALB/c mice were treated with intranasal house dust mite (HDM) for 24 weeks. Finally, pulmonary Muc5ac mRNA expression was significantly increased upon 4 weeks of CS-exposure, but not upon 24 weeks. Accordingly, protein levels of Muc5ac were significantly elevated in BAL fluid of mice exposed to CS for 4 weeks, but not for 24 weeks. Finally, pulmonary Muc5ac mRNA expression was significantly increased upon both 4 and 24 weeks of CS-exposure, while we found no differences in the mRNA expression of Muc5b. These data demonstrate that 4 weeks of CS-exposure leads to increased expression of ADAM19 and enhanced shedding of neuregulin-1. Binding of neuregulin-1 to the epidermal growth factor receptor (EGFR) plays an ubiquitous role in the ontogeny of LT-expressing lymphoid tissue inducer cells induce lympho- phine production (mainly CXCL13) to LT-receptor-expressing stromal cells. Lymphokines attract haemopoietic cells leading to lymphoid organ development. We examined the role of the initiating event to LF formation from COPD patients with LFs (COPD-LF+), without LFs (COPD-LF-) and never-smokers. Lung CXCL13 was significantly increased in COPD-LF+ compared to COPD-LF- and never-smokers and positively correlated to surface area of LFs. Immunostaining showed CXCL13 expression in B cells of LFs. Flow cytometry indicated that among lung cells, B cells have the highest expression for LT receptors. Ex-vivo, lipopolysaccharide (LPS) and a LT-receptor agonist induced CXCL13 production to whole lung cell cultures have the highest expression for LT receptors. Enzyme-linked immunosorbent assay (ELISA) showed that the initiating event to LF formation in COPD is B cell stimulation, leading to LT expression and CXCL13 production. CXCL13 positively feeds back LT, amplifying its levels and attracting more B cells that organize themselves into LFs.

3115 Dendritic cells’ nerve interaction in allergic airway inflammation Duc Dong Le2,3,4, Sabine Rochlitzer 4, Ulrike Funck2, Hendrik Suhling2, M. de Vries, J. de Vries, M. van der Toorn, A.J.M. van Oosterhout, M.C. Nawijn. University Hospital, Groningen, Netherlands

Introduction: Dendritic cells (DC) play as antigen-presenting cells a decisive role within the allergic airway inflammation. The colocalisation of DC in sensory ganglia has not been explored so far. The aim of the present study is to evaluate possible interactions between DC in sensory ganglia concerning calcitonin gene-related peptides (CGRP)-expression during allergic airway inflammation. Methods: The BALB/c mice were treated with intranasal house dust mite (HDM) extract (32 μg/g) for 5 days a week within a total period of 7 weeks. The jugular-nodose ganglion complex was removed 24 hours after final allergen chal- lenge and histological slices were prepared. Immunohistochemistry was performed to determine the colocalisation of DC by MHC-II and CD11c and neurons by neuronal marker PGP 9.5. Results: Under physiological conditions dendritic cells are found in the vagal sensory ganglia of the mouse and that they were significantly increased during an allergic airway inflammation (DCs/neurons: control 23±8.7/6.1% vs. HDM 49.75±6.194%, p = 0.0083). Additionally, an increased number of CGRP positive neurons in vagal sensory airway ganglia during allergic airway inflammation was found (CGRP+/nerve terminal neurons: HDM 52.07±3.04%/vs. control 21.63±3.799%, p = 0.0001).

Conclusion: The finding of the presence of DC in the airway jugular-nodose gan- glion indicates a role of the DC in these ganglia under physiological conditions. The increased numbers of DC and CGRP-positive neurons in these ganglia suggest the involvement of the pathogenesis of allergic airway inflammation. However, the exact functions of DC and CGRP in allergic airway inflammation remain to be explored in future studies.

3116 LSC 2012 Abstract – The protective role of Pim1 in cigarette smoke induced damage of airway epithelium M. de Vries, R. Gras, L.E. den Boef, M. van der Toorn, A.J.M. van Oosterhout, M.C. Nawijn. Pathology and Medical Biology, Allergology and Pulmonary Disease, UMC, Groningen, Netherlands

Rationale: The main risk factor of developing COPD is exposure to cigarette smoke. CS exposure induces airway epithelial cell damage, release of DAMPs and an innate inflammatory response. We previously observed increased expression of Pim1 in vivo after sub-chronic CS exposure in mice. Pim1 is a serine/threonine kinase involved in cell growth and survival by preventing apoptosis induction through the mitochondrial pathway. We hypothesize that Pim1 plays a protective role in the airway epithelium after CS exposure by phosphorylating BAD and enhancing cell survival. Methods: Pim1 KO mice were exposed to CS twice a day for 4 days. Inflammatory cells and KC levels in BAL were determined. Beas-2b cells were treated with CS extract (CSE) for 4 hours with(out) Pim-inhibitor. Mitochondrial membrane potential (MMP) and apoptosis/necrosis induction were measured by flowcytometry. BAD phosphorylation was determined by Western Blotting. Results: CS exposure induces neutrophilic airway inflammation and increases KC levels in Pim1-KO mice, but not in WT controls. CSE induces a dose-dependent loss of BAD phosphorylation, loss of MMP and necrotic cell death in Beas-2b cells. All of these CSE-induced effects are aggravated by inhibition of Pim1. Conclusion: Pim1 protects airway epithelial cells from CS-induced damage and cell death by phosphorylating BAD and increasing the threshold for apoptosis. In vivo, this protective effect suffices to prevent CS-induced neutrophilic airway inflammation.

3117 LSC 2012 Abstract – Role of ADAM19 and neuregulin-1 in Muc5ac expression in lungs of cigarette smoke-exposed mice Lisa Dupont, Guy Joos, Guy Brusselle, Ken Bracke. Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

Mucus hypersecretion is an important feature of COPD, resulting in chronic cough and contributing to dyspnea by obstructing the airway lumen. Signalling through the epidermal growth factor receptor (EGFR) plays an ubiquitous role in the production of mucins. We hypothesise that A Disintegrin And Metalloprotease19 (ADAM19) stimulates mucin production by shedding of the EGFR-ligand neuregulin-1. C57BL6 mice were exposed to air or cigarette smoke (CS) for 4 or 2 weeks. IHC for ADAM19 on lung tissue sections showed intense staining in bronchial and vascular smooth muscle cells, as well as in endothelium, and a faint stain- ing in bronchial and alveolar epithelial cells. Quantitative PCR analysis of ADAM19 protein expression in the airway wall showed a significant increase upon 4 weeks of CS-exposure, but not upon 24 weeks. Accordingly, protein levels of neuregulin-1 were significantly elevated in BAL fluid of mice exposed to CS for 4 weeks, but not for 24 weeks. Finally, pulmonary Muc5ac mRNA expression was significantly increased upon both 4 and 24 weeks of CS-exposure, while we found no differences in the mRNA expression of Muc5b. These data demonstrate that 4 weeks of CS-exposure leads to increased expression of ADAM19 and enhanced shedding of neuregulin-1. Binding of neuregulin-1 to the EGFR may contribute to the increased expression of Muc5ac. However, especially upon chronic CS-exposure, other EGFR-ligands or alternative mechanisms may be involved in mucin production.
release and cell count of TH1 cells, these effects were enhanced in COPD. LPS effect on IL-2 negatively correlated with FeV1 [% pred.] and was abolished by CL895. In the presence of LPS, blocking MyD88/IRAK was more efficient in restoring IL-2 release in NS vs. COPD, whereas blocking TIRF/IKKc was more efficient in COPD, and miroxiforxacin (MXF) increased IL-2 release and cell count of TH1 cells. MXF effect on IL-2 was enhanced in COPD and correlated to the IL-2-inducing effect of p38MAPK inhibitor SB203580. All effects were p<0.05. LPS and MXF did not induce TH1 cell death.

TH1 response to bacterial infections is impaired in COPD due to a shift from MyD88/IRAK to TIRF/IKKc signalling, which enhances suppression of IL-2 and TH1 growth by LPS. MXF might reinforce IL-2 expression and TH1 growth by blocking p38MAPK signalling. Targeting TLR4 signalling combined with MXF might reduce exacerbation rates.

3119
LSC 2012 Abstract – FOXO transcription factors regulate innate immune mechanisms in respiratory epithelial cells during bacterial infection
Christoph Reisswenger, Frederik Seiler, Philipp Lepper, Robert Bals, Christian Herr. Department of Internal Medicine V, Saarland University Hospital, Homburg/Saar, Germany.

Bacterial pathogens are a leading cause of lung infections and contribute to acute exacerbations in patients with respiratory tract diseases. The innate immune system of the lung controls and prevents colonization of the respiratory tract with bacterial pathogens. Here, we show that FOXO transcription factors regulate innate immune mechanism of respiratory epithelial cells in response to bacterial pathogens such as Haemophilus influenzae and Pseudomonas aeruginosa. Infection with bacterial pathogens led to the activation of FOXO transcription factors in respiratory epithelial cells in vivo and in vitro. siRNA mediated knock down of FOXO3 in bronchial epithelial cells resulted in reduced expression of factors of the innate immune system such as antimicrobial peptides and factors involved in a proinflammatory response. In addition, FOXO3 plays a role in the internalization of bacterial pathogens. These data show that FOXO transcription factors are involved in the cellular response to bacterial stimuli and have a central role in regulating innate immune functions of respiratory epithelial cells.

350. Pulmonary manifestations of systemic diseases

3120
Ventilatory restrictive impairment in thalassemia patients: Gender differences and correlation with hypogonadism and iron overload
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Background and aim: Ventilatory restrictive (RES) impairment has been described in β-thalassemia, but no evidence exists on the causal mechanism. We investigated relationships among lung function, iron overload and clinical parameters in a homogeneous series of β-thalassemia major adult patients.

Methods: We studied 70 patients (males M/females F 44/35; age 34.5 ± 35 yrs) with β-thalassemia major on regular transfusion and iron chelation. Iron overload was assessed by serum ferritin, liver iron concentration (LIC) by SQUID susceptometry, cardiac iron by MRI T2*. Lung volumes, diffusion capacity, chelator drugs, hypogonadism (H), hypothyroidism and osteopenia were evaluated in stable hematologic conditions.

Results: 30/79 pt (38.5%) [21/44 (47.7%) M and 9/35 (25.7%) F] showed RES, 6 bronchial obstruction with no gender differences (3M:3F). In F LIC was higher 2249±903 vs 1497±553 mgFe/gliver dw; p<0.008 in RES vs normals and correlated with total lung capacity (r=0.40; p<0.03). No differences were present for hypothyroidism, osteopenia or 3 iron chelators. Among RES patients 575M and 88S/F were H. M males showed higher cardiac iron MRI T2* 29.6±12.7 vs 39.6±9.2 ms; p<0.03) but similar LIC in respect to non H, without correlation with total lung capacity. In F cardiac and hepatic iron levels were not different between H and non H.

Conclusions: RES is present in 1/3 of well compensated adult thalassemic (M/F 1:88). Iron (LIC) was higher in RES F vs normals and H males have higher MRI T2*. Different gender impact of H on lung and chest growth, severity and efficacy of replacement therapy can explain data but the involved mechanisms is still unclear.

3121
Coexistent granulomatosis with polyangiitis (Wegener’s) and Crohn disease: A clinicopathologic description of cases
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Background: Crohn disease (CD) may lead to various extraintestinal manifestations, including, rarely, respiratory tract involvement. When necrobiosis pulmonar y nodules are present, the differential diagnosis includes granulomatosis with polyangiitis (Wegener’s) (GPA). The respiratory tract manifestations of CD and GPA may mimic each other, complicating the diagnosis and suggesting the possible coexistence of these two conditions.

Aims: To describe the clinical, radiographic and histopathologic features of patients in whom CD and GPA coexist.

Methods: We reviewed the teaching files of the authors and searched the Mayo Clinic medical records for coexistent inflammatory bowel diseases and ANCA-associated vasculitides of the lungs. We reviewed in detail 97 patient charts, and excluded cases of ulcerative colitis and those in whom only one of the diagnoses was present or pathology slides were unavailable. Pulmonary and gastrointestinal biopsies were reviewed for the cases included in the study.

Results: Four cases were identified (2 women and 2 men, age range: 25-62). The diagnosis of CD preceded that of GPA in all cases. Protein-ANCA was positive in two cases, while in the other two PR3- and MPO-ANCA were both negative. Chest imaging showed pulmonary nodules in all cases. Pathology revealed features diagnostic of GPA in all cases with necrotizing granulomatous inflammation and segmental vasculitis. In addition, one case showed capillaritis.

Conclusion: Pulmonary nodules are more frequent in patients with CD, as the presence of granulomatous colitis in patients with GPA should prompt the inclusion in the differential diagnosis of a possible coexistence of CD and GPA.

3122
Arterial hypoxaemia in morbid obesity
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Introduction: Morbid obesity (MO) can be associated with arterial hypoxaemia, mostly to a highly prevalent obstructive sleep apnoea (OSA).

Objective: To determine the prevalence of hypoxaemia in patients with MO before and one year after bariatric surgery (BS) and its correlation with OSA.

Methods: We included 230 patients (44% M, 56% female; BMI, 46.7±2 kg/m2; and, waist-to-hip-ratio, 0.96±0.08). OSA was defined as an apnoea/hypopnoea index (AHI) ≥10.

Results: Before BS, all patients (ERV, 33.4±22%) had spirometry and DLCO within reference values, with normal PaO2 (83±12 mmHg) and PaCO2 (36±3 mmHg) values. One hundred and fifty four (70%) patients had OSA (48%, severe OSA [AHI ≥30]), 66 (43%) with hypoxaemia (PaO2, 70.6±7 mmHg). Patients with OSA had lower PaO2 and higher PaCO2 than those without OSA (p<0.05 each). Thirty out of 230 patients (13%) without OSA had hypoxaemia (PaO2, 74±4 mmHg), whose PVC, FEV1, VC, IC, ERV and DLCO were lower than those in normoxaemic patients (p<0.01 each). Overall PaO2 was correlated with waist-to-hip-ratio (r=0.30, p<0.05). Before BS, age, sex, PVC, ERV and waist-to-hip-ratio were the independent factors associated with hypoxaemia (r2=0.28, p<0.05) (multiple regression analysis). After BS, patients had a 76±18% of excess weight loss with overall improvement in lung function (p=0.01 each) while OSA ameliorated in 65% of them. Post-BS ERV (115±37%) and PaO2 (93±10 mmHg) improvements (p<0.01 each) were associated (r=0.22, p<0.05).

Conclusions: Hypoxaemia continues to be a common finding in MO, mostly in patients with OSA. However, hypoxaemia can also be present without OSA, possibly related to central obesity.

Supported by FIS PI080311, CIBERES, Almirall and Esteve.

3123
Hypoxic challenge assessments in patients with obesity hypoventilation syndrome
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Background: With worldwide increase in obesity and air travel, more obese people are likely to travel by air in future. No prospective studies have investigated the degree of arterial hypoxaemia during a hypoxic challenge test (HCT) in patients with obesity hypoventilation syndrome (OHS).

Objectives: To investigate the likelihood of a positive HCT in patients with OHS
who are not hypoxicemic at sea level and any possible predictors of desaturation during HCT.

Methods: Ten patients with OHS treated with long term nocturnal non invasive ventilation (NIV) were recruited. Clinically unstable patients and those with COPD were excluded. HCT was part of a detailed assessment and consisted of breathing 15% oxygen via a Douglas bag for 20 minutes.

Results: Mean age 57.4 years (±12.4) and mean BMI 32.8 (±13.3). Seven out of ten had a positive HCT (PaO2 < 6.6 kPa or SpO2 < 85%). Arterial blood gas was attempted in all but could not be taken in two patients. Mean PaO2 before and during HCT were 10.4 kPa (±0.4) and 6.2 kPa (±0.5) respectively. Mean PaCO2 before and during HCT was 5.5 kPa (± 0.8) and 3.5 kPa (±0.8) respectively. Baseline PaCO2 correlated negatively with PaO2 and SpO2 during HCT (r = -0.823, p=0.012 and r = -0.795, p=0.018 respectively). BMI, baseline PaO2 and SpO2, distance walked and minimum SpO2 during BSAT were not significantly correlated with the PaO2 or SpO2 during HCT.

Conclusion: Seventy percent of these patients had a positive HCT despite adequate control of their ventilatory failure. Baseline PaCO2 but not the PaO2 or SpO2 was predictive of a positive HCT. Although these results need to be confirmed in larger studies, we suggest assessment of these patients including a HCT before air travel.

3124 Pulmonary involvement in patients with Marfan syndrome
Isa Ceretti, Angelo Corsico, Bianca Tirone, Federica Albicini, Amelia Grosso, ErncaGini, Andrea Mazzetta, Eti Maria Giulia Di Vincenzo, Roberto Dore, Eleonora Arbustini, Maurizio Lunetti. Foundation IRCCS “San Matteo” Hospital, University of Pavia, Italy

Pulmonary involvement is not generally considered a main feature of Marfan syndrome, particularly in the early days of this disorder caused by mutations of the extracellular matrix protein fibrillin1 particularly affecting vascular, skeletal and ocular systems. However, thanks to the substantial progress in treatments, life expectation of these patients has been dramatically improved in the last 20 years determining changes in different organ systems. The number of patients with a degree of underlying pulmonary pathology may be higher than expected. Clinical history, chest CT, spirometry, lung volumes, and diffusion capacity have been assessed in 64 patients of our national referral center (mean age 32±14 years; M 45%). None of the patients reported chronic respiratory symptoms and only 5% had smokers. Fourteen per cent reported a previous pneumothorax and 2 of them underwent surgery. Three reported bullae and 1 underwent bullectomy. Eleven per cent had radiological signs of emphysema and 32% apical blebs. Twenty-three per cent had aortic thoracic surgery. Forty-five per cent had moderate to severe rib cage abnormalities; 4 of them underwent repeated surgical corrections. Only 37% of our patients showed a restrictive pattern and 19% an obstructive pattern or an isolated diffusion impairment or an isolated hyperinflation. All patients with previous pneumothorax showed an obstructive pattern and diffusion impairment. In conclusion, in the absence of respiratory symptoms, pulmonary abnormalities should be actively detected and monitored and particular attention should be paid to prevent pneumothorax. Our results support the importance of lung volume determination and, when needed, chest CT in Marfan patients.

3125 Lung function abnormalities in patients with heart failure and preserved ejection fraction
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Introduction: Heart failure with preserved ejection fraction (HFPEF) accounts for 40-50% heart failure patients. The aim of this study was to evaluate the prevalence, type and severity of lung function abnormalities among patients with HFPEF.

Methods: In this prospective, descriptive study we included consecutive outpatients with new onset of HFPEF according to the European Society of Cardiology criteria. All underwent a clinical evaluation, chest X-ray, electrocardiogram, echocardiography, brain natriuretic peptide determination, forced spirometry, lung volumes by body plethysmography, single-breath carbon monoxide diffusing capacity (DLCO) corrected for alveolar volume and arterial blood gases.

Results: We included 193 outpatients (68% females), mean age 77 years. Mean body mass index 29.8 kg/m2. 85% had arterial hypertension. 25.4% former smokers (5% women). 19% had hypoxemia (mild 63.3%, moderate 26.6%, severe 10%).

Conclusions: Patients with HFPEF show a high prevalence of lung function abnormalities. Most are underdiagnosed and may contribute to their symptoms. Their pathophysiology is likely multifactorial (smoking, obesity, age, heart function) but requires further research.

3126 Patients with tissue hypoxia with unknown origin
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Background: Dyspnea is common complication in respiratory disease and is mainly caused by hypoxemia due to lung diseases, cardiac diseases or neurologic diseases. Patients with dyspnea without hypoxemia, hypercapnia and clear abnormal chest X-ray findings considered to be a difficult diagnostic problems. We have found a group of some patients who complain dyspnea without hypoxemia (normal SpO2 and PaO2) have high venous oxygen level (PvO2). The aim of this study was to investigate the clinical characteristics of patients who have high PvO2 and normal SpO2.

Methods: Eight patients have dyspnea with high PaO2 with normal SpO2 were enrolled in this study. Patients with any other lung diseases or systemic diseases, abnormal chest X-ray finding or elevation of inflammatory markers were also excluded. Arterial and venous blood gas analysis was performed after 10 minutes bed rest. Tissue oxygen levels (PtO2) was calculated using following equation; PtO2 = PaO2 - PaO2 - PvO2. Serum lactate and pyruvate level were measured by enzyme assay.

Results: PaO2 in patients enrolled (67±12.4 mmHg) was higher than normal range (24-40 mmHg) and PaO2 in patients enrolled was lower (22±17.3 mmHg, normal range: 40-70 mmHg) than normal range. Serum lactate (21.6±7.9 mg/dl) and pyruvate (2.1±0.9 mg/dl) were also elevated compared to normal range.

Discussion and conclusion: The group of patients seem to have dyspnea due to tissue hypoxia. The tissue hypoxia probably raises pyruvate and lactate levels due to activation of anaerobic glycolysis. PtO2 measurement and assessment of tissue hypoxia is need for the patients with dyspnea without hypoxemia. It would be also necessary to explore the cause of tissue hypoxia in the patients.

3127 Lung cancer as a comorbidity in idiopathic pulmonary fibrosis (IPF)
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Introduction: IPF is associated with an increased risk for lung cancer. This might be explained by a contribution of IPF to lung cancer (LC) development or a role of LC in IPF development and/or by shared pathomechanisms causing both IPF and LC. However, data on incidence and reports on treatment related complications are limited.

Methods: In a retrospective monocenter analysis, patients (pts) who were diagnosed between 1/2004-12/2011 with IPF according to the current ATS/ERS guideline were reviewed for the diagnosis of LC.

Results: Of 229 IPF pts, 28 had IPF with LC (12%): 92% male, median age 67 years, median 39.5 pack years, median VC 82% pred., TLC 81% pred, TLCO-SB 35% pred. 75% had NSCLC with stages IA (5%), IB (10%), IIIA (29%), IIIB 35%. Of 229 IPF pts, 28 had IPF with LC (12%): 92% male, median age 67 years, median 39.5 pack years, median VC 82% pred., TLC 81% pred, TLCO-SB 35% pred. 75% had NSCLC with stages IA (5%), IB (10%), IIIA (29%), IIIB 35% pred. 75% had NSCLC with stages IA (5%), IB (10%), IIIA (29%), IIIB 35% pred. 75% had NSCLC with stages IA (5%), IB (10%), IIIA (29%), IIIB 35% pred.

Discussion: LC is a frequent comorbidity in IPF where an interdisciplinary evaluation of therapeutic options is mandatory. However, treatment related complications, especially after surgery are high. Prognosis of operable patients with IPF and LC might be decreased compared to patients either suffering from IPF or with LC alone.

351. Epidemiology and care research of lung cancer

P318 KBP-2010-CPHG: Characteristics and management of 6,083 new cases of non-small-cell lung cancer (NSCLC)
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355s
Lung cancer in Berlin – Significant changes in age structure, gender ratio and histologic subtypes from 2000 to 2008

Torsten Blum1, Stephan Eggeling2, Christian Gogoll3, Christian Grab4, Christian Grohé5, Christel Lauer1, Gunda Leschber1, Jens Neudecker6, Wulf Pankow2, Bernd Schicke1, Paul Schneider1, Nicolas Schoenfeld2, Christian Witt5, Anita Jagota7, Lungenklinik Heckerborn, HELIOS Klinikum Emil von Behring, Berlin, Germany; 8Klinik fuer Pneumologie/Klinik fuer Thoraxchirurgie, Vivantes Klinikum Neukolln, Berlin, Germany; 9MVZ, St. Hedwig Krankenhaus, Berlin, Germany; 10Klinik fuer Pneumologie, Gemeinschaftskrankenhaus Havelsehoefe, Berlin, Germany; 11Klinik fuer Pneumologie/Klinik fuer Thoraxchirurgie, Evangelische Langenklklinik, Berlin, Germany; 12Klinik fuer Pneumologie/Klinik fuer Thoraxchirurgie, Choruit, Berlin, Germany; 13Projektgruppe Lungencarcinom, Tumorzentrum Berlin, Germany; 14Klinik fuer Thoraxchirurgie, DRK Klinik Berlin Mitte, Berlin, Germany

Background: The Tumourzentrum Berlin (TZB) analyses the clinical data of lung cancer pts. in Berlin in order to improve patient care by means of joint quality assurance.


Methods: In this retrospective case study, the pooled data of the TZB of pts. with newly diagnosed lung cancer during 2000 and 2008 were analyzed. Pts. were divided into three 3-year groups (G1: 2000-2, G2: 2003-5 and G3: 2006-8).

Results: The total cohort comprised 14,302 pts. (G1: 4,284 pts, G2: 5,049 pts and G3: 4,969 pts). The increase in pt. numbers in G2 and G3 is explained primarily by an absolute increase in pts. aged ≥ 70 yrs., but there was no trend for an increase of younger pts (Figure 1).

Methods: King’s College Hospital, London, UK, has a multiethnic, deprived hospital 2000-2009.

Results: 7,610 patients were enrolled in 119 centres. 6,083 patients (86.3%) had a NSCLC. The main characteristics of NSCLC patients were: mean age, 65.4±11.4 years; 24.4% female; 11.9% non-smokers, 40.5% ex-smokers, 47.6% current smokers; 69.8% performance status 0 and 1. The main characteristics of the tumour were: 53.5% of adenocarcinoma, 31.0% of squamous-cell carcinoma, and 12.9% of large cell carcinoma; 18.1% stage IA to IB, 14.0% stage IIA, 9.5% stage IIIB and 58.3% stage IV. First-line treatments were: curative surgery, 19.0%; radiotherapy alone, 18.7%; combined radio-chemotherapy, 26.1%; and chemotherapy, 61.8%.

Conclusions: In 10 years, characteristics of NSCLC patients changed with a significantly increase (p<0.001) of women, non-smokers, adenocarcinoma histology, and stage IV at diagnosis.

P3129

Proportion of adenocarcinomas of the lung rise from 22 to 42% in a London hospital 2000-2009

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1Department of Respiratory Medicine, King’s College Hospital, Denmark Hill, London, United Kingdom; 2Department of Medical Oncology, King’s College Hospital, Denmark Hill, London, United Kingdom; 3Department of Histopathology, King’s College Hospital, Denmark Hill, London, United Kingdom

Background: The proportion of lung cancers that are adenocarcinomas (ACs) is reported to be increasing in Europe. In 2000-2008 the proportion of UK lung cancers typed as AC was 26%. 1 Incidence of lung cancer in females has recently been reported to be increasing in Europe. In 2006-2008 the proportion of UK lung cancer in females was in line with UK data and is not significantly different from the latest UK female incidence.

Methods: King’s College Hospital, London, UK, has a multiethnic, deprived population of 250,000. Since 1999, all lung cancers have been discussed at a multi-disciplinary (MDT) meeting and recorded on a database. Data for histologically confirmed cases of primary lung cancer diagnosed over the period 2000-2008 were analyzed. Pts. were divided into three 3-year groups (G1: 2000-2, G2: 2003-5 and G3: 2006-8).

Results: The total cohort comprised 14,302 pts. (G1: 4,284 pts, G2: 5,049 pts and G3: 4,969 pts). The increase in pt. numbers in G2 and G3 is explained primarily by an absolute increase in pts. aged ≥ 70 yrs., but there was no trend for an increase of younger pts (Figure 1).

Table 1. Lung cancer cases 2000-9

<table>
<thead>
<tr>
<th>Epoch</th>
<th>Lung Cancer</th>
<th>Female</th>
<th>Adenocarcinoma</th>
<th>Squamous Cell Carcinoma</th>
</tr>
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<tbody>
<tr>
<td>2000-1</td>
<td>227</td>
<td>69 (30)</td>
<td>49 (22)</td>
<td>96 (43)</td>
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<tr>
<td>2002-3</td>
<td>222</td>
<td>79 (36)</td>
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<td>235</td>
<td>91 (39)</td>
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<td>2006-7</td>
<td>264</td>
<td>100 (38)</td>
<td>90 (34)</td>
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<tr>
<td>2008-9</td>
<td>252</td>
<td>98 (39)</td>
<td>105 (42)</td>
<td>79 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>1200</td>
<td>437</td>
<td>375</td>
<td>437</td>
</tr>
<tr>
<td>Chi square for trend*</td>
<td>3.7</td>
<td>25.4</td>
<td>8.46</td>
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<tr>
<td>P value</td>
<td>0.053</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

*1 degree of freedom.

Conclusion: The trend for increasing proportion of ACs (and decreasing SCCs) was highly significant; the proportion of ACs in our cohort since 2006 is greater than the latest UK figure and numbers of ACs do not appear to have stabilised. 1 The proportion of female cases is in line with UK data and is not significantly changing.


Figure 1

The proportion of pts. with adenocarcinomas has increased over time for all age groups (Figure 2).

Figure 2

Conclusions: The data of the TZB documented significant epidemiologic changes in pts. with lung cancer over time. In contrast to other regions in the world,
there was no increase of younger pts. inspite of a growing proportion of pts. with adenocarcinoma.

P3131 Features of lung cancer in young people: Report of 14 cases
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Introduction: Lung cancer is one of the most common cancers in all ages. Little is known about clinical factors associated with the development of lung cancer in young patients. That is why mistakes are often made in radiological diagnosis of lung cancer in young people.

Method: In this report were included 14 patients admitted in our institute between 2003 and 2012, 8 males/6 females with the mean age of 29 years. Eight patients were non-smokers, 6 patients were smokers (10-65 pack-years). The patients were initially diagnosed with different lung diseases: asthma (2), pneumonia (7), tuberculosis (5). All patients were evaluated with chest X-ray, CT-scan, bronchoscopy.

Results: Patients presented at the doctor for several symptoms: dyspepsia, fatigue, cough in all cases, fever (2), wheezing (2). Ten patients had inflammatory syndrome. The radiological aspects were: lung tumor (11), multiple nodules (2), and atelectasis (1). All patients had negative exams for My. Tuberculosis. The mean delay of diagnosis was 3.5 months. Cancer was confirmed on histological examinations: bronchial biopsy (12), tumor removed during surgery (1), necropsy (1). The type of carcinoma was adenocarcinoma (6), epidermoid (7), macrocellular (1). Six patients died during initial hospitalization, 8 cases were operated and received postoperative chemotherapy. Conclusion: Lung cancer is unfortunately not the first diagnosis taken into account in young people with respiratory problems. The young patient’s condition deteriorates rapidly and the diagnosis of cancer is made when disease is already in an advanced stage. Diagnosis is often delayed and patients might lose the opportunity of curative treatment.

P3132 A retrospective study of lung cancer in young women Hafsia Zaibi, Hager ben Abdellakhfar, Leila Fekih, Dorra Greb, Ines Akrout, Hela Hachime, Soraya Fenniche, Dalenda Belhabib, Mohamed Lamine Megdiche. IBN NAFIS, Abderrahmane Mami Hospital, Ariana, Tunisia

Introduction: Less advanced disease staging at presentation, better performance status and better survival figures have been noticed in younger (<50 years) lung cancer women W1 as compared to older (>50 years) patients with the disease W2.

Aim: To compare clino-pathological features of lung cancer in young and elderly women and to determine any existing difference between the two groups.

Patients and methods: It’s a retrospective study, including 44 women admitted in our department with lung cancer.

Results: There were 15 young women with a mean age of 41 years (20-50 years) and 29 elderly patients with a mean age of 64 years (51-85 years). 26% of first group were current smoker. 26% of W1 had family history of lung cancer vs 3% of W2 (p=0.02). Comorbidities were seen in 5 cases of W1 and in 45% of W2 (p <0.002). Diagnosis delay was 3 months in W1 and 4.4 months in W2 (p=0.04). 94% of younger women had favourable performance status (PS) ≤1. They were more likely to have small cells carcinoma (20% vs 9%), without significant differences in adenocarcinoma rate (46% vs 43%). 20% of W1 had stage I disease at presentation vs 3% in W2 (p=0.05). Younger had more frequently surgical treatment 33% vs 6% (p=0.04). Mean survival time were better in W1 (3 years vs 1.4 years, p=0.03).

Conclusion: Majority of these patients presented with early stage disease. 26% had positive family history suggesting a possible genetic factor. Favourable performance status resulted in higher resection rate and active treatment, which lead to better survival.

P3133 Pathological profile of lung cancer in Tunisia Abdelhamid Ben Amar, Ilhem Tangui, Wajdi Ketata, Sameh Msaad, Abdelkader Ayoub. Pneumology Department, Hedi Chaker Hospital, Sfax, Tunisia

Introduction: Primary lung cancer represents a major public health problem. Its incidence is increasing worldwide and between one in Tunisia.

Aim: The aim of this work is to study the pathological profile of lung cancer in our department.

Methods: A retrospective study on 200 patients treated between 2005 and 2010 for a primary lung cancer.

Results: The average age of our patients was 60 years and the sex ratio was 10. Histological and seventy eight cases of diagnosed patients were smokers or former smokers. Only one woman was smoking and only 14 among the 181 men were non-smokers. The tobacco intoxication average was 48.9 PA. The non-small-cell lung cancer (NSCLC) has represented the majority of primary lung cancer in our study with 165 cases (82.5%) against 35 cases (17.5%) of small-cell lung cancer (SCLC). Only one woman presented a small-cell carcinoma. The study of the distribution of histological types in the NSCLC showed a predominance of adenocarcinoma (47.5% of cases) followed by a lesser incidence of squamous cell carcinoma (28.5% of cases) and large cell carcinoma (3% of cases). The gender analysis has objectified the same frequency profile in the women and men. The adenocarcinoma and squamous cell carcinoma (63% against 21% of adenocarcinoma of squamous cell carcinoma). Other rare histologic types that were found in our study are: large cell carcinoma, one case of adenosquamous carcinoma and one case of pleomorphic carcinoma.

Conclusion: The histological distribution of primary lung cancer shows an increased frequency of adenocarcinoma, which was more frequent than squamous cell carcinoma (47.5% vs 28.5%) while the latter was clearly predominant in 1994 (42.8% versus 15, 3%).
Aamir Khakwani
critical.

survivors can be attributed to similar aetiologies, genetics and the effects of treat-

(n=4). NSCLC cases showed a relatively equal distribution of early (n=8) and

abdomen, brain) for diagnosis and staging. Most histological types of CPPS were

somatic at diagnosis (n=17). All patients performed chest X-ray and CT (chest,

Table Abstract P3135 – Table

P3136
Second primary lung cancer in clinical emergency hospital of Constanta – A prospective study
Doina Tofolean

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Background: More people are living with a diagnosis of cancer than ever before. One of the consequences of surviving cancer is the increased likelihood of being diagnosed with a second primary cancer.

Aim: To determine the frequency of secondary primary lung cancer (SPLC) in clinical practice.

Material and method: A total of 176 patients was diagnosed with lung cancer, between January 2001 and January 2011 in 1st Internal Medical Department of Clinical Emergency Hospital of Constanta; 22 patients (12.50%) were already diagnosed with other cancers. Positive diagnosis of SPLC included chest X-ray, spiral CT, bronchoscopy, EUS+FNAB, CEUS.

Results: Most patients diagnosed with SPLC were initially diagnosed with Hodgkin’s disease (n=4), head and neck cancer (n=3). Gender distribution showed male predominance (n=16). Most patients (n=14) were heavy smokers (>25 Pack Years; P<0.0001). Most patients were symptomatic at diagnosis (n=17). All patients performed chest X-ray and CT (chest, abdomen, brain) for diagnosis and staging. Most histological types of CPPS were NSCLC (n=18; P<0.0001). All cases of SPLC were diagnosed in advanced stages (n=24). NSCLC cases showed a relatively equal distribution of early (n=8) and advanced stages (n=10).

Conclusions: The excess risk of developing a second malignancy among cancer survivors can be attributed to similar aetiologies, genetics and the effects of treatment. As the number of cancer survivors continues to grow, the importance of ongoing medical supervision and screening to detect second primary cancers at an earlier stage and thereby improve the effectiveness of treatment will remain critical.

P3137
The histological confirmation rate of lung cancer in the UK using the NLCA database
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Background: The optimal histological confirmation rate (HCR) for lung cancer is unknown. However, in the UK, an arbitrary figure of 75% has been recommended by the National Lung Cancer Audit (NLCA) as a benchmark. The aim of this study was to quantify the effect of patient features on the likelihood of having a histological diagnosis of lung cancer.

Methods: Individuals with a diagnosis of lung cancer were selected from the NLCA database from between 01/01/2004 and 31/12/2010. Percentage and odd ratios with 95% confidence interval were calculated to assess the proportion of patients having histology.

Results: Our study included a total of 127,099 individuals with NSCLC. HCR for NSCLC in the NLCA was found to be 66.8%. This however was increasing from 62.2% in 2007 to 72.3% in 2010. The histology in patients aged <65, PS of 0/1 and Charlson Index (CI) of 0 was 89.5%, while 56.8% in patients with the same age and CI but PS of 4. This reduced to 30% in patients with age >75 years and CI of 0 and PS of 4. Increasing age and worsening PS were also associated with a reduced odds ratio, whilst stage and CI had little effect on the likelihood of having proven histology. Individuals from least affluent areas were 23% less likely (adj OR 0.77, 95% CI 0.74 to 0.81, p<0.001) to have histology than patients from most affluent areas.

Conclusion: HCR is crucial in determining the appropriate treatment plan for every patient, especially with the advent of targeted therapies. Our results also show that there is a difference in the histological rate in the sub groups of patients. Therefore achieving 75% HCR in the total population is unreasonable and it should focus on different attainable HCR in sub group of patients.

P3138
Organization and results of the EGFR mutation Spanish quality control program

Material and method: A total of 235 patients, diagnosed with lung cancer by histological and/or cytological bronchoscopic findings(2009-2011), we conducted a correlation between demographic and medical data at the time of diagnosis with the type of histological confirmation of malignancy. In Greece, even though the incidence of lung cancer continues to grow, smoking is confirmed to have the strongest correlation with all lung cancer types. The mean age of first diagnosis is lower than expected from studies conducted in the US.

Introduction: Lung cancer remains in Europe the second most frequent type of malignancy. In Greece, even though the incidence of lung cancer continues to grow, there is not enough epidemiological data. Our aim was to conduct a retrospective epidemiological study using the large pool of data from our Bronchoscopic Unit.

Methods: In a total of 235 patients, diagnosed with lung cancer by histological and/or cytological bronchoscopic findings(2009-2011), we conducted a correlation between demographic and medical data at the time of diagnosis with the type of lung cancer.

Results: The mean age of first diagnosis was between 60-70 years (33%) and the male to female ratio was 3.8:1. There was no significant difference between the three most common histological types (ADCL 24%, SqCLC 21%, SCLC 22%). In the third round 31 spanish centres (25 hospitals, two medicine schools and four private laboratories) sent the complete results. Three mutated (one L858R and two different Del19) and one wild-type adenocarcinomas were selected. No false positive results were reported. There were 11 non-informative and 13 false-negative cases among the 124 analysed. Most of the false-negative results were obtained in centres that used Sanger sequencing in the L858R case where the percentage of neoplastic cells was small.

There is a need to stablish an organized quality control program for molecular testing in lung cancer patients. Pathology societies could be the organizers making routine laboratories perform these tests according to best practices.

P3139
Epidemiological data and correlation with bronchoscopic findings in first diagnosis of lung cancer in the last 3 years in a tertiary Greek hospital
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Department of Pulmonary Medicine, Evangelismos Hospital, Athens, Greece.

Introduction: Lung cancer remains in Europe the second most frequent type of malignancy. In Greece, even though the incidence of lung cancer continues to grow, there is not enough epidemiological data. Our aim was to conduct a retrospective epidemiological study using the large pool of data from our Bronchoscopic Unit.

Methods: In a total of 235 patients, diagnosed with lung cancer by histological and/or cytological bronchoscopic findings(2009-2011), we conducted a correlation between demographic and medical data at the time of diagnosis with the type of lung cancer.

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There is a need to stablish an organized quality control program for molecular testing in lung cancer patients. Pathology societies could be the organizers making routine laboratories perform these tests according to best practices.
P3140
Meeting the referral criteria to the rapid access lung cancer clinic: A 10-year audit
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Introduction: Although targeting patients with agreed criteria (where the risk of cancer is high) under the “two week wait” rule to fast-track lung cancer clinic allows an efficient and timely diagnosis, the referral of other patients to such services will potentially waste valuable healthcare resources. To look at this further we studied the trends in referral to our dedicated rapid access lung cancer clinic since its inception in 2001.

Methods: We audited referrals in 2001, 2009 and 2011, looking for their compliance with the nationally agreed referral criteria, and their subsequent placement and outcome.

Results: There was an increase in referrals that did not meet the agreed criteria with time.

Of those that did not meet the agreed criteria, in 2001: 10 were returned to the referrer, 18 redirected to a general chest clinic, and 3 were already under specialist care (2009: 15, 51, and 17; 2011: 44, 108, and 12 respectively).

Subsequently 9 (3%) were diagnosed with lung cancer (8 at follow-up and only 1 referrer, 18 redirected to a general chest clinic, and 3 were already under specialist treatment).

Conclusion: These results show that a significant and increasing proportion of referrals are made outside the agreed national criteria and may have been more appropriately referred elsewhere. We are seeking to educate our colleagues to ensure that these scarce and expensive healthcare resources are best used for this unfortunate patient population.

P3141
Timely diagnosis and therapy for suspected lung cancer patients in a 2 day rapid outpatient diagnostic program with integrated FGD-PET and diagnostic CT
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Introduction: Delays in the diagnosis of lung cancer are under debate and may affect outcome. The objectives of this study were to compare delays in a rapid outpatient diagnostic program (RODP) for suspected lung cancer patients with those described in literature and guideline recommendations, to investigate the effects of referral route and symptoms on delays, and to establish whether delays affected stage and outcome.

Methods: We performed a retrospective chart study of all patients with suspected lung cancer, referred to our RODP of our tertiary care university clinic between 1999 and 2009. Patient characteristics, tumor stage and different delays were analyzed.

Results: Of 565 patients with available data, 290 were diagnosed with lung cancer, 48 with another type of malignancy, and 111 patients with a non-malignant lesion. In 112 patients no immediate definite diagnosis was obtained, and in 82 of these the proposed follow-up strategy confirmed a benign outcome. The median first disease delay was 60 days, patient delay - 25±30 days. 39% of patients were previously treated for other malignancy.

Conclusion: In our patient population a surgical procedure is performed in 37.7% of patients with lung cancer. This is higher than the surgical rate of 16.9% according to the audit criteria.

P3142
The use of surgical services in the management of suspected lung cancers
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Introduction: The National Lung Cancer Audit Report 2011 identified an average surgical rate of 14% in England and Wales. This focuses on potentially curative surgery with the exception of mesothelioma and so does not encompass the full breadth of surgical intervention undergone by our patients. This study aimed to describe this spectrum for our patient population in a secondary care setting.

Method: The electronic patient record system was searched for all patients discussed at multidisciplinary meetings in 2010. Data was gathered from letters, operation notes and meeting minutes on the system.

Results: 1172 cases were discussed of which 212 (18%) had confirmed lung cancer. In these, 74 (37.7%) procedures were performed. 1.4% of patients had two procedures. 80.6% had a lobectomy, 4.7% a wedge resection or segmentectomy, 14.6% a VATS drainage of effusion, biopsy and/or pleurodesis (4.2% for mesothelioma) and 5.2% other procedures. For 2.4% there was no diagnosis.

After surgery, histology revealed NSCLC in 52.7%, mesothelioma in 13.5%, SCLC in 2.7%, carcinoid in 1.4% and no malignancy in 6.8%. In 5.4%, a differential diagnosis was given, and in 17.6% there was no data.

All referred patients were discussed at multidisciplinary meetings in 2010. Data was gathered from letters, operation notes and meeting minutes on the system. The delay of diagnostics worsens prognosis of disease.

The purpose: To define factors, associated with a delay of lung cancer diagnostics.

Materials and methods: An analysis of waiting times for 31 patients with lung cancer was undertaken. Males 65%, villagers 61%, mean age 55±14 yrs. Clinical, radiological, laboratory data of all admitted patients were collected. The period from the disease manifestation up to making a hospital diagnosis was 106±68 days, patient delay - 25±30 days. 39% of patients were previously treated of an assumed pneumonia before hospitalization in TB hospital. All patients have been hospitalized with wrong diagnosis “pulmonary TB”, a principal cause - misinterpretation of chest radiogram.

Results: 48% of patients up to making a hospital diagnosis received antituberculous treatment. 55% of patients - smokers.

Conclusion: The results would allow to optimize the diagnostic approaches to such a patients.

P3143
Lung cancer patients in TB hospital: Factors associated with diagnostic delay
Zhanaa Laushkina 1, Pavil Filimonov 2, Elena Pustikarava 2. Pulmonary TB Department, Novosibirsk Research TB Institute, Novosibirsk, Russian Federation

The delay of diagnostics worsens prognosis of disease.

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Materials and methods: An analysis of waiting times for 31 patients with lung cancer was undertaken. Males 65%, villagers 61%, mean age 55±14 yrs. Clinical, radiological, laboratory data of all admitted patients were collected. The period from the disease manifestation up to making a hospital diagnosis was 106±68 days, patient delay - 25±30 days. 39% of patients were previously treated of an assumed pneumonia before hospitalization in TB hospital. All patients have been hospitalized with wrong diagnosis “pulmonary TB”, a principal cause - misinterpretation of chest radiogram. 48% of patients up to making a hospital diagnosis received antituberculous treatment. 55% of patients - smokers.

Results: Factors associated with increase of diagnostic delay: acute disease beginning (OR 0,34, p=0,03), absent of hematological changes (OR 0,23, p=0,01), nonspecific microbial growth in sputum (OR 0,1, p=0,003). Factors, associated with decrease of a diagnostic delay – old age (OR 2,7, p=0,034), low body weight (OR 2,4, p=0,038), lost of appetite (OR 3,7, p=0,006), dyspnea (OR 3,4, p=0,002), leukocytosis (2,5, p=0,03), ESR acceleration (3,3, p=0,007), lymphopenia (2,5, p=0,043), eosinophilia (3,3, p=0,011), spherical opacity patterns on chest radiogram (5,9, p=0,000), pleural exudates (9,1, p=0,000), presence of atypical cells in sputum (OR 46, p=0,000), biopsy performed (OR 10,5, p=0,000).

Conclusion: The results would allow to optimize the diagnostic approaches to such a patients.

P3144
Risk factors for early mortality in lung cancer
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Aim: To analyze risk factors for mortality due to lung cancer before 1st and 3rd month after diagnosis.

Methods: Revision of all the patients with lung cancer diagnosis in 2 years. Analysis of: demographic variables, smoking status, histological subtype, staging, ECOG, blood analysis, treatments, cause of death. Univariate and multivariable analysis ( Cox regression).

Results: 270 cases, characteristics shown in table 1. In table 2, multivariate analysis. AUC of 0,952 in the 1st month, 0,874 for the 3rd. Among 41 patients who died before the 1st month, 9 (22%) received palliative treatment (6 Radiotherapy [RT], 3 Chemotherapy [QIT]). As death causes: infectious complications in 8 cases (3 QT), respiratory insufficiency 16 cases, rest: tumoral progression and general sepsis.

Conclusions: High percentage of patients die before the 1st month (15%) and 3rd month (29%) after diagnosis. ECOG >2 points, the most impacting factor for early mortality.Other factors: IV TNM stage, low haemoglobin, adenocarcinoma or small-cell histological subtype (1st month mortality) and a high CA125 level
**Conclusions:** Smoking cigarettes is the principal risk factor for causation of LC. Preventive control of smoking appears to be an urgent priority in lung cancer prevention.

Objective: to determine the existence of the eventual causal associations among the cigarette smoking and development and distribution of the lung cancer.

Methods: The investigation was an analytical type of case-control study. It elaborated 185 patients diseased of LC, and the same number of persons without malignant disease (control group-CG). Risk analyses were done using unconditional logistic regression, which provides results in the form of crude odds ratio.

Results: The odds ratios and their 95% confidence intervals (CI) were computed. In the group of patients, there were 67% of current smokers (CS), 23.8% of ex-smokers (ES) and only 9.2% of never smokers (NS), compared to 40.5% of controls (n=1383) 1.4 18.7 79.8

Similar results were observed in the Italian population regarding the T allele frequency in SSC and SSc-ILD in the French population: 10% and 11.1%, respectively.

Background: Combined pulmonary fibrosis and emphysema (CPFE) is characterized by upper lobe emphysema associated with lower lobe fibrosis.

Methods: We retrospectively evaluated 102 consecutive patients who were diagnosed with pulmonary fibrosis after bronchoalveolar lavage (BAL). Cytokine levels and differential cell counts in BAL fluid, pulmonary function, CT scores, and levels of serum markers were compared between patients with emphysema and those without.

Results: Among the 102 patients (14 females, mean age, 68 y/o), 38 showed upper lobe emphysema on CT. In BAL fluid, the levels of ENA-78/CXCL5 and IL-8/CXCL8 were significantly higher in patients with emphysema than in those without. The levels of MCP-1/CCL2, MIP-1a/CCL3, TNF-α, TGF-β1, and neutrophil elastase did not differ between the two patient groups. In patients with emphysema, whereas %VC was greater, FEVI/FVC and %DLCO/VA were lower than in those without emphysema. The composite physiologic index and serum levels of KL-6 and SP-D, markers of interstitial lung disease, were not different between the groups. Levels of CXCL5 and CXCL8 were associated with the...
proportion or absolute number of neutrophils in BAL fluid. In addition, CXCL8 levels were correlated inversely with %VC and %DLCO/VA and positively with the flow of low attenuation on CT.

Conclusion: Elevated CXCL chemokine levels in the airspace might contribute to the emphysematous change in patients with pulmonary fibrosis, which may be associated with the development of CPFE.

P3147
Gene expression profiles of idiopathic interstitial pneumonias: Identification of disease-specific diagnostic markers and molecular therapeutic targets
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Introduction: Idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) are characterized by alveolar epithelial damage and inflammatory responses that lead to fibroblast proliferation and, ultimately, to loss of normal pulmonary architecture and function. Differential diagnosis between IPF and NSIP may be difficult. The molecular mechanisms underlying idiopathic interstitial pneumonias (IPFs) remain unclear.

Aims: This study aimed to elucidate the mechanisms underlying IPFs and identify disease-specific diagnostic markers and molecular therapeutic targets.

Methods: The study included 12 patients with IPFs (IPF; 7 patients; NSIP, 5 patients). RNA was extracted from frozen lung specimens from the study population and was profiled using Illumina Human WG-V 3 BeadChip. Gene ontology functional annotations were investigated in the genes upregulated in IPFs.

Results: Evaluation of 48,000 transcripts in the expression profiles helped identify 1354 transcripts that were commonly upregulated in lung tissues from IPF patients compared to those from normal control subjects. The transcriptional profiles of IPF and NSIP were unexpectedly similar. Lungs with IPF were characterized by increased expression of transcripts associated with cell cycle, cell-to-cell interaction, and p53 signaling pathways, such as MDM2, RB1, RAD21, CFTPR and BAX.

Conclusion: The current data provide valuable information on the molecular mechanism underlying pulmonary fibrosis in IPF patients. Additionally, several potentially promising and novel diagnostic biomarkers as well as therapeutic targets have been identified for IPFs.

P3148
The JAK3 Inhibitor CP-690550 is a potent anti-fibrosis agent in a murine model of pulmonary fibrosis induced by bleomycin
Beixian Zhou, Yingping Fu, Yansheng Wang, Jun Xu. The State Key Lab of Respiratory Disease, Guangzhou Medical University, Guangzhou, China

Rationale: We previously suggested that JAK3, a cytoplasmic tyrosine kinase involved in receptor signaling for cytokines, is a molecular determinant in exacerbated innate immune inflammation. A selective JAK3 inhibitor can alleviate immunopathologic injury. Does it have a potential for treating the lung fibrosis associated with autoimmunity? In the present study, CP-690550, a novel inhibitor of JAK3, was subjected to examination of its effects on lung fibrosis in a murine model of Bleomycin (BLM)-induced pulmonary inflammation.

Methods: JAK3 activity, cytoxia, lung histology and collage deposition were evaluated in mice treated with BLM and CP-690550.

Results: CP-690550 significantly reduced the lung fibrosis and collagen deposition as compared to mice treated with BLM (p < 0.01). Histologically, CP-690550 treatment induced significant reduction in collagen deposition as compared to BLM-treated mice (p < 0.01). Flow cytometry for typing bronchoalveolar lavage fluid revealed a significant reduction in the number of CD3+CD8+ and NKT+ cells in the BLM-challenged mice than control, but no significant changes were detected in the mice treated with CP-690550 compared to BLM-treated mice.

Conclusion: We have previously shown that BLM-derived T cells secrete HGF, regarded as a potent anti-fibrotic cytokine, antagonist of TGFβ, and the promising tool for experimental therapies in lung fibrosis. However, our preliminary results concerning HGF expression in ILD lower airways were not convergent.

Methods: HGF concentration in BAL fluid from pulmonary sarcoidosis (PS), idiopathic pulmonary fibrosis (IPF), extrinsic allergic alveolitis, nonspecific interstitial pneumonia (NSIP), BOOP and eosinophilic pneumonia (n=48, 20, 7, 13, 7, 6 resp.) was assessed by ELISA method. BAL cells were analyzed for intracellular HGF by flow cytometry.

Results: HGF concentration was significantly increased in IPF nonsmokers (317±13.56 pg/ml vs 148±17 in controls, p<0.02, median±SEM). IPF smokers (215±12 vs 141±10, p>0.001) and smokers with advanced PS, t-test, and nonsmokers with increased HGF levels in NSIP and BOOP was observed. HGF concentration was strongly negatively correlated with pulmonary function (VC% pred) and positively, inter alia, with BAL neutrophil and eosinophil relative count as well as with TGFβ levels. Systemic steroid therapy resulted in decline of HGF expression in respective IPF, NSIP and PS subgroups.

Conclusion: Our data seem to disagree with the previously suggested HGF strong anti-fibrotic activity. Its high expression was paradoxically observed in ILD patients with severe lung fibrosis SIIL, our observations might reflect the up-regulated TGFβ enhanced expression aimed at sustaining lung homeostasis.

P3150
Autoimmunity profile in patients with combined pulmonary fibrosis and emphysema (CPFE)
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Background: The combination of pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome, encompassing a distinct radiologic, revealing both upper lobe emphysema and lower lobe fibrosis, as well as lung function profile, with apparently preserved lung volumes contrasting with disproportionately impaired gas exchange. It has also been recently described in the context of connective tissue diseases. Our primary aim was to investigate the autoimmunity profile of patients with CPFE.

Patients and methods: Thirty nine patients, mean age of 66.5 years, 37 men, all smokers, with CPFE based on radiologic and functional criteria (mean FVC: 68.5% pred, FEV1/FVC: 78.2, DLCO: 34.9%pred) were recruited on a retrospective and prospective basis. All patients underwent a thorough investigation of their immunologic profile.

Results: Fourteen patients (36%) had positive anti-nuclear antibodies (ANA). Patients with positive ANA presented with elevated CD20 levels in lung biopsy specimens suggestive of elevated B cell activity. In addition, 6 patients (15%) presented with positive antineutrophil cytoplasm antibodies (ANCA) against myeloperoxidase (MPO) indicative of microscopic polyangiitis. Among the latter three developed respiratory and renal insufficiency and were successfully treated with cyclophosphamide and methylprednisolone whereas the remaining three were switched to azathioprine maintenance treatment.

Conclusions: A significant proportion of patients with CPFE may present with underlying auto-immune disorder which may be recalcitrant. Early identification of these patients using a panel of auto-antibodies may lead to more targeted and potentially effective therapeutic applications.

P3151
Frequencies and dynamics of peripheral immune cell subsets in idiopathic pulmonary fibrosis: Preliminary results and clinical implications
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Involvement of the immune response in the pathogenesis of idiopathic pulmonary fibrosis (IPF) is not well clarified. Emerging T cell subsets including IL-17 secreting T helper cells (TH17) and regulatory T lymphocytes (Treg) expressing TGF-beta may exert antiinflammatory actions. Distribution and phenotype characteristics of peripheral immune cells along with TH17/Treg dynamics were investigated by multi-parametric flow cytometry in 13 IPF patients (mean age 63 yrs; 13 men) and 10 age- and sex-matched healthy subjects. Propensity for CD20+ B cells and of CD20+ T cells and of B (CD20+) lymphocytes were similar in the two groups. Frequencies of NKT (CD3+CD56+) and NK cells (CD3 CD56+CD16+) were reduced in IPF (p<0.001 for NK cells), the 24% of the latter co-expressing CD16 and CD52a (versus 4.2±3.3; p<0.001). IPF patients displayed higher Treg proportions (CD4+CD25highFoxP3+ (0.71±4.0 vs 0.3±1.3; p<0.05). No differences in the distribution of highly suppressive Treg (CD127-+) were found. Upon stimulation, Treg expression of TGF-beta was similar in the two groups. Conversely, frequencies of IL-17-expressing CD4+ cells were significantly lower in IPF (0.92±0.56 vs 0.21±0.11; p<0.001). This finding was associated with an increased IL-17/IL-17 ratio in IPF (2.8±1.5 vs 0.38±0.2; p<0.001). This study first provides evidence in IPF of a peripheral Treg/TH17 functional imbalance along
Silent microaspiration in idiopathic pulmonary fibrosis: The role of videolaryngoscopy

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A strong association between gastroesophageal reflux (GER) and idiopathic pulmonary fibrosis (IPF) has been reported. A significant proportion of patients may have signs of microaspiration and still remain asymptomatic. Videolaryngoscopy can be a useful tool to detect silent microaspiration, which to date has never been investigated in IPF. The aim of the study was to assess signs of micro-aspiration by videolaryngoscopy in patients with IPF and to relate them with clinical findings. We recruited 20 IPF patients (mean age 52 ± 7 yrs). We investigated the presence/absence of GER symptoms and performed videolaryngoscopy to evaluate abnormal laryngeal findings considered indirect signs of micro-aspiration. Three out of twenty patients (15%) had classic GER symptoms, while 17 (85%) did not report any kind of GER symptoms. Among asymptomatic patients, 5 (25%) had indirect signs of microaspiration at videolaryngoscopy while the remaining twelve had no such signs. Of interest, IPF patients with laryngeal abnormalities at videolaryngoscopy showed a lower FVC% at the diagnosis compared to patients without such abnormalities [46% (45-82) vs 75% (72-87); p=0.03]. Conversely, no differences in age, smoking history and BMI were found between the two groups of patients. In conclusion our study shows that videolaryngoscopy may be a useful diagnostic tool to detect silent microaspiration in patients with IPF even in the absence of GER symptoms. These findings may have important therapeutic implications.

Elevated serum LOXL2 levels are associated with rapid disease progression in idiopathic pulmonary fibrosis (IPF)

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Background: LOXL2, expressed in fibrotic lung, plays a crucial role in matrix remodeling and fibrogenesis. We hypothesized that elevated serum LOXL2 levels are associated with rapid IPF disease progression.

Methods: Serum samples were collected prior to treatment randomization at selected U.S. clinical trial sites for TARTEMS-IPF. LOXL2 levels were measured using proprietary anti-human-LOXL2 antibodies. Progression free survival (PFS) lung function decline, respiratory hospitalizations (RH) and death served as the primary endpoint.

Results: Subjects with (n=69) and without (n=423) serum samples had similar baseline IPF severity. Among subjects with detectable LOXL2 (n=67), the median LOXL2 level was 31.5 pg/mL. Of interest, 14/5-752.4 pg/mL. Although subjects randomly assigned to receive ambrisentan (n=49) had more severe IPF and higher LOXL2 levels than placebo treated subjects (mean 902.8 pg/mL ± 3172 vs 294 pg/mL ± 288, p=0.026), LOXL2 levels and IPF severity did not correlate. In multivariate analyses that included treatment assignment, 6-minute walk distance and compositive physiologic index, high LOXL2 lev (≥800 pg/mL) in comparison to low LOXL2 levels (<800 pg/mL), were associated with increased risk for disease progression (hazard ratio [HR] 4.95, 95% confidence interval [CI] 1.52-16.18, p=0.008), lung function decline (HR 7.36, 95% CI 1.16-46.74, p=0.034), and RHs (HR 4.85, 95% CI 1.09-21.88, p=0.039).

Conclusion: High baseline serum LOXL2 levels are associated with rapid IPF progression and may reflect disease activity, not severity. Due to potential confounding effects of ambrisentan, these results need to be replicated in other IPF populations.

Hyaluronan synthetase-2 over expression has impact on the evolution and on the prognosis of idiopathic pulmonary fibrosis patients

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Background: The idiopathic pulmonary fibrosis (IPF) is a terminal illness characterized by unremitting extracellular matrix (ECM) deposition. In this regard, the myofibroblasts and the ECM components such as hyaluronan (HA) have an important role in the fibrosis. We analyzed the expression of HAS1 (HA synthase 1), HAS2, HAS3 and hyaluronic acid receptor (CD44) by epithelial and myofibroblasts cells in patients with IPF and we correlated with a survival.

Methods: HAS-1, HAS2, HAS3 and CD44 epithelial and myofibroblasts expression were evaluated in 27 surgical lung biopsies from patients with IPF in minimal and severe fibrosis by the point-counting technique. Impact of these markers was tested on pulmonary functional tests and follow-up until death from IPF.

Results: HAS2 and CD44 expression were significantly increased and directly associated with severe fibrosis. Myofibroblast HAS2 activity was indirectly associated to DLO/VA (p=0.584; p<0.05). Kaplan Maier curves determined a higher risk of death for patient with high HAS2 (>6.83%) expression than in low expression (Log Rank p<0.05).

Conclusion: The increased HAS-2 activity in epithelial and myofibroblasts cells have impact in the remodeling process and the survival evolution, suggesting that strategies aimed at preventing the effect of this ECM component may have a greater impact in patient’s outcome.

Perceptions, experiences and information needs of patients with idiopathic pulmonary fibrosis (IPF): A qualitative study

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Background: Idiopathic Pulmonary Fibrosis (IPF) is a rapidly progressive lung disease, with median survival of 2-4 years from diagnosis with symptoms that impact on quality of life. There has been little work to date which explores the experiences of these patients, or their family carers, in-depth.

Aim: To understand the experiences, perceptions and information needs of patients with IPF.

Methods: Qualitative study, involving in-depth, audio-recorded, semi-structured interviews, supported by a topic guide (developed from review of the literature and input from patients and clinicians). Seventeen patients with moderate to advanced IPF referred to a tertiary respiratory centre in north-west England, and six of their family carers, were interviewed. Data were analysed using Framework Analysis ( Ritchie and Spencer 1994).

Conclusions: Patients with IPF have many unmet information and support needs. There is an urgent need for improved recognition of these needs, as well as increased availability and accessibility of services.

The correlation of pulmonary function tests and exercise testing with high resolution computed tomography in patients with idiopathic interstitial pneumonias in a tertiary care hospital in south India

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Background: Idiopathic interstitial pneumonias (IIP) are a heterogeneous group of diffuse parenchymal lung diseases (DPLD). Although open lung biopsy is the gold standard for its diagnosis, HRCT(High Resolution Computed Tomography) is gradually replacing the former. Repeating HRCT for follow up is costly and involves radiation exposure. Among pulmonary function tests(PFT) and exercise testing, it is unclear which parameter would correlate best with HRCT.

Aim: To find out the correlation of pulmonary function tests and exercise testing with HRCT in patients with IIP.

Methods: Consecutive patients who were diagnosed as IIP were included. PFT and exercise testing parameters were noted. HRCT was scored based on an alveolar...
score, an interstitial score and a total score. Correlation of each of the parameters with HRCT scores were analyzed.

**Results:** A total of 94 patients [85 had Idiopathic Pulmonary Fibrosis(IPF)] were included to obtain a sample size of 105. Forced Vital Capacity, Total Lung Capacity and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) among PFT parameters and Distance Saturation Product and lowest saturation among exercise testing parameters had significant correlation with the total HRCT score. Among these DLCO corrected was the most correlating with a negative r value of 0.565.

**Conclusion:** In patients with idiopathic interstitial pneumonia, pulmonary function tests and exercise testing had good correlation with HRCT. DLCO corrected was the most correlating parameter.

**P3157**

**Osteoporosis treatment effectiveness in patients with idiopathic pulmonary fibrosis (IPF)**

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**Aim:** To assess effectiveness of osteoporosis treatment by Calcium, Vitamin D3 (VD3), Bisphosphonates (BPN), Calcitomin (CTN) in patients with IPF.

**Subjects:** 95 Caucasian patients with IPF, 18 male, 77 female, 55.4±10.9 y.o., treated with glucocorticoids.

**Materials, methods:** Bone Mineral Density was measured by DEXA: Patients were categorized according to T-criterion value. 19 patients (1st group) had T-criterion >-1.5 SD. In this group only Calcium and VD3 were recommended. 24 patients (2nd group) had T-criterion value from -1.5 SD to -2.0 SD. In this group Calcium, VD3 and BPN were prescribed. 20 patients (3rd group) had T-criterion value from -2.0 SD to -2.5 SD. In these cases Calcium, VD3 and CTN were prescribed. 32 persons (4th group) had T-criterion lower than -2.5 SD. These patients received Calcium, VD3, CTN, BPN.

**Results:** Results were assessed in a year. The main criteria were: T-criterion change (ΔT), fractures incidence, presence of bone pain (BP). In the 1st group ΔT was -0.07 SD, 10.5% patients had manifestation of BP. In the 2nd group ΔT was -0.25 SD; one hip fracture occurred; the number of patients with BP decreased from 66.7% to 25.0% (p<0.01). In the 3rd group ΔT was +0.04 SD, no fractures were registered, the number of patients with BP increased from 20.0% to 30.0%. In the 4th group ΔT was +0.11 SD; no fractures were registered, the number of patients with BP decreased from 25.0% to 6.3% (p<0.01).

**Conclusion:** Combination of Calcium and VD3 with antiresorptive agents (both CTN and BPN) is an essential way to prevent and treat osteoporosis in patients with IPF. CTN has an advantage due to its analgesic effect in osteoporotic patients with bone pain.

**P3158**

**Post-marketing surveillance of pirfenidone for idiopathic pulmonary fibrosis in Japan: Interval analysis of 973 patients**

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**Background:** Pirfenidone (Pirespa®), anti-fibrotic agent, was approved for the treatment of idiopathic pulmonary fibrosis (IPF) in Japan in 2008. We conducted a post-marketing surveillance enrolling all patients with IPF who were administered pirfenidone from Dec 2008 to Oct 2009 to gain understanding, in the clinical setting, of the safety and efficacy of pirfenidone in the treatment of IPF.

**Methods:** The safety was evaluated by comparing the incidence of adverse drug reactions with that reported in Phase II and III trials. The efficacy was evaluated on the change in vital capacity (VC).

**Results:** For this interim analysis, 973 cases were evaluable for safety (male 78.2%, age 69.5±8.4 y.). At baseline, 407 cases (41.8%) were ranked as severity grade IV in Japan (PaO2 at rest <60 Torr) or (PaO2 at rest <70 Torr and 6MWT SpO2 <90%). The incidence of adverse drug reactions was 67.0%. The major adverse drug reactions were decreased appetite (28.6%) and photosensitivity reaction (15.0%). The data on VC were available from 453 cases and the analyses revealed that VC had an increase from 66.7% to 25.0% (p<0.001). In the 3rd group ΔT was +0.11 SD; no fractures were registered, the number of patients with BP decreased from 25.0% to 6.3% (p<0.01).

**Conclusion:** The efficacy of pirfenidone was confirmed by the interim analysis.

**P3159**

**The long-term safety of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF)**

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**Background:** Pirfenidone (Pirespa®), anti-fibrotic agent, was approved for the treatment of idiopathic pulmonary fibrosis (IPF) in 2008. We conducted a post-marketing surveillance enrolling all patients with IPF who were administered pirfenidone from Dec 2008 to Oct 2009 to gain understanding, in the clinical setting, of the safety and efficacy of pirfenidone in the treatment of IPF.

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**Conclusion:** The efficacy of pirfenidone was confirmed by the interim analysis.

**P3160**

**Predictors of effects and adverse effects of pirfenidone on idiopathic pulmonary fibrosis**

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**Background:** Pirfenidone (Pirespa®), anti-fibrotic agent, was approved for the treatment of idiopathic pulmonary fibrosis (IPF) in Japan in 2008. We conducted a post-marketing surveillance enrolling all patients with IPF who were administered pirfenidone from Dec 2008 to Oct 2009 to gain understanding, in the clinical setting, of the safety and efficacy of pirfenidone in the treatment of IPF.

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**Conclusion:** The efficacy of pirfenidone was confirmed by the interim analysis.

**P3161**

**Introduction:** Idiopathic pulmonary fibrosis (IPF) is a poor prognostic fibrotic lung disease with unknown etiologies. Pirfenidone (PFD) was recently reported to decrease the rate of decline in vital capacity and it is anticipated that PFD improves prognosis of IPF patients.

**Aim:** We prospectively examined clinical findings of IPF to predict the effects and adverse effects of PFD.
P3161
Anti-fibrotic effects of nintedanib (BIBF 1120) in primary human lung fibroblasts derived from idiopathic pulmonary fibrosis
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis. One year treatment with the receptor tyrosine kinase inhibitor nintedanib (BIBF 1120) specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) was associated with a 68.4% reduction in the rate of decline in forced vital capacity in patients with IPF versus placebo, which approached statistical significance.

Aim: To determine the in vitro effect of nintedanib on primary human lung fibroblasts.

Methods: Primary human lung fibroblasts were isolated and propagated from lung parenchyma derived from patients with IPF (n=14). After treatment with nintedanib (0.0001 – 1 μM) enzymatic activity for matrix metalloproteinases (MMP) was assessed in aliquots of the culture medium by gelatin zymography. Gene expression of MMP was measured by quantitative real time PCR. Collagen secretion and deposition was quantitated by the Sircol assay, and cell proliferation was assessed by mechanical cell counting.

Results: Nintedanib significantly inhibited secretion and deposition of collagen by IPF fibroblasts in a dose-dependent manner. Nintedanib significantly increased MMP-2 gene expression and dose dependently stimulated MMP-2 enzymatic activity. The pro-proliferative effect induced by PDGF (10 ng/ml) was completely reversed by nintedanib.

Conclusion: Our data demonstrate a significant anti-fibrotic effect of nintedanib in primary human lung IPF fibroblasts. This work is supported by a non-conditional grant by Boehringer Ingelheim GmbH.

P3162
Management of idiopathic pulmonary fibrosis in France: A survey of 1,456 pulmonologists
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It has been suggested that prostacyclin improves patients with pulmonary hypertension through direct myocardioc effects. In an experimental model of acute right ventricular (RV) failure, we previously reported that prostacyclin did not present with significant inotropic effects, but that there might have been a trend as assessed from improved RV-arterial coupling (Kerbala et al. ARJCCM 2007).

Therefore, we further explored the pathobiology of acute RV failure with or without prostacyclin infusion. Dogs were randomized to a sham-(n=8) or to a 90-min pulmonary artery constriction (PAC)-operation (n=15). In 7 dogs with persistent RV failure, prostacyclin was infused 30 min after banding release. After euthanasia, RV tissue was sampled for pathological evaluation. 90-min PAC increased RV gene expressions of interleukin (IL)1β, monocyte chemotactrant protein (MCP)1, IL6, VCA1M1, and decreased expression of IL10. No changes in RV gene expressions of IL1α, macrophage inflammatory protein (MIP)1 and ICAM1 were observed after PAC. Protein expressions of IL1β and IL6 were observed in the failing RV, while IL10 protein expression was decreased. Pro-inflammatory IL6/IL10 and pro-apoptotic Bax/Bcl2 ratios were increased in the failing RV. Increased diffuse macrophage recruitment was observed within the failing RV. Prostacyclin depleted RV gene expressions of IL10, MCP1, MIP1α, VCA1M1 and increased IL10 expression. Prostacyclin decreased RV gene expressions of IL6/IL10 and Bax/Bcl2 ratios, and IL1β protein expression compared to PAC group.

Acute load-induced persistent RV failure appears to be related to an activation of inflammatory processes which seems to be limited by prostacyclin.
Conclusions: Pulmonary hypertension (PH) is a progressive and fatal disease. The gold standard for diagnosing PH and estimating prognosis is the invasive method of right heart catheterization. To date no biomarker is available to prove or exclude the diagnosis of PH.

Aims and objectives: The aim of this study is to identify and validate new biomarkers for PH.

Methods: Plasma from the pulmonary artery banding (PAB) and the monocrotaline (MCT) rat model, and corresponding sham and control animals (n=9), was used for 2D-gel electrophoresis (2D-GE) and MALDI-TOF-MS analysis. Further, plasma changes of interesting candidates were confirmed by ELISA. Human study population consists of patients with idiopathic pulmonary arterial hypertension (n=40), PH associated with collagen vascular disease (n=45), pulmonary venous hypertension (n=44), chronic thromboembolic PH (n=45), and non-PH controls (n=34).

Results: The spot density analysis of 2D-GE and identification by MALDI-TOF-MS revealed 7 proteins significantly changed in PAB vs. sham, and 15 proteins in MCT vs. control group. Complement component 4 (C4) and complement inhibitory factor H (CFH) were upregulated in PAB and MCT. ApoE was changed 15-fold in MCT plasma, but not in PAB. The analysis of human samples revealed no significant difference in mean plasma ApoE between the patient groups (119.4±10.3, 147.6±11.6, 116.8±9.9, 110.2±8.3 μg/ml) and controls (135.3±14 μg/ml).

Conclusions: Despite published data on the role of ApoE in PH and the significant changes in rats, ApoE seems not suitable as biomarker for PH in humans. Other candidates identified by mass spectrometry will be evaluated for their potential as biomarker.
that fibrocytes may cooperate with endothelial progenitors to induce angiogene-
sis. We successfully isolated fibrocytes from blood of IPF patients. The characteriza-
tion of fibrocytes used flow cytometry, real time q-PCR and confocal analysis. We investigated the interaction between fibrocytes and cord blood derived endothel-
ial colony forming cells (ECFC) angiogenic potential in vitro and in vivo in a preclinical model of vascularization.

We showed for the first time the formation of functional microvascular beds in im-
munodeficient mice when human ECFC and fibrocytes isolated from IPF patients were coinoculated in matrigel plugs. Evaluation of implants after 2 weeks revealed an extensive network of blood vessels containing erythrocytes. Secreted media from fibrocytes enhances SDF-1/CXCR4 pathway in ECFC in vitro. Blocking CXCR4 in vivo in implants significantly inhibited blood vessel formation. Finally, we confirmed the relevance of these data by showing that vessels close to fibrotic areas in biopsy specimens from IPF patients expressed high levels of CXCR4, in contrast to control lungs. Circulating fibrocytes might be involved in vascular remodelling process observed in patients with fibrotic disease and should represent a useful biomarker for fibrosis progression.

P3170

miR-16 modulates human pulmonary artery smooth muscle cell phenotype

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Introduction: Pulmonary artery hypertension (PAH) is progressive fatal disease characterized by excessive proliferation of human pulmonary artery smooth muscle cells (hPASMC) and formation of small pulmonary arteries, leading to severe pulmonary hypertension and right ventricular failure.

Objective: Serotonin mediates hPASMCs proliferation through serotonin trans-
porter (5HT). Recently micro RNAs have been identified to be involved in patho-
genetics of miR-16 targets SERT and Cyclin D1. Our previous results show that miR-16 is down regulated in hypoxic PAH mice. We hypothesize that overexpression of miR-16 can alter PAH phenotype. In the present study, we investigated the phenotypic consequences of overexpression of miR-16 in hPASMCs in vitro.

Methods: hPASMCs were commercially obtained and cultured according to manufacturer instructions. Cells were transfected with plasmid containing miR16 and over-expressed SERT or CyclinD1. Cells were treated with increasing concentrations of serotonin (3H-thymidine) and apoptosis (Hoechst nuclear staining; DNA fragmentation ELISA) assays were performed.

Conclusions: miR-16 overexpression down regulates SERT and CyclinD1 levels. Most importantly miR-16 modulates hPASMC phenotype which is a major hallmark in PAH, implicating a potential therapeutic role in PAH.

This work was supported by R01HL105932NH, AHA/10SDG260987.

P3171

Macrophage migration inhibitory factor (MIF) promoter polymorphisms are associated with favorable hemodynamic indices in systemic sclerosis-associated pulmonary arterial hypertension

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Rationale: Inflammatory mediators are increasingly associated with pathogen-
esis in pulmonary arterial hypertension (PAH). We have previously observed a 3.7-fold increase in serum levels of the pro-inflammatory macrophage migration inhibitory factor (MIF) in PAH patients. MIF promoter polymorphisms (-173C, -794CATT5-8) have been associated with disease susceptibility or phenotype in sev-
eral inflammatory syndromes. We hypothesized that MIF promoter polymorphisms may influence PAH development or severity.

Methods: Genomic DNA was isolated from 117 European-American PAH pa-
tients, including idiopathic (PAH; N=30) and systemic sclerosis-associated PAH (SSc-PAH; N = 82), healthy European-American controls (N=264), and SSc pa-
tients without PAH (N=343). Allele and genotype frequencies for the MIF -173C
single nucleotide polymorphism and the -794CATT5-8 variable nucleotide tandem repeat were compared between PAH patients and controls, and were compared with initial hemodynamic indices and survival in PAH patients.

Results: We found no significant difference in the frequencies of either MIF pro-
mitter polymorphism between controls and PAH patients. SSc-PAH patients with the MIF -173C polymorphism had higher cardiac output (P=0.04), cardiac index (P=0.003), and stroke volume index (P=0.01) at diagnosis. Neither polymorphism predicted survival in PAH patients.

Conclusion: The MIF -173C polymorphism may improve initial hemodynamic

ics in SSc-PAH. However, MIF promoter polymorphisms do not predict PAH susceptibility or survival. These results suggest that MIF may function as a disease-modifying gene in SSc-PAH.

P3172

Dexamethasone induces anti-remodelling effects in rat pulmonary arterial smooth muscle cells

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Introduction: Dexamethasone (dex) reverses PAH and pulmonary vascular remod-
eling in established rat monocrotaline (MCT)-induced PAH, we tested contributing mechanisms in pulmonary arterial smooth muscle cells (PASMC). Nuclear local-
ization of the p65 subunit of NF-kappaB was used as a marker of inflammation in MCT-exposed rats.

Methods: PASMC from control and MCT 6-week old male Wistar rats were treated with increasing dex concentrations. Proliferation (3H-thymidine) and apop-
tosis (Hoechst nuclear staining; DNA fragmentation ELISA) assays were performed.

Results: Dex reduced proliferation of PASMC at all concentrations with a maximal effect seen at 10-7M (3H-thymidine counts/minute 84997±6802 to 1993±3135, p<0.0001). Dex increased serum starvation-induced PASMC apoptosis as deter-
mined by Hoechst staining and DNA fragmentation in a time- and concentration-
dependent manner, reaching a plateau at 72hrs with 10-7M dex (0.40±0.17 to 1.29±0.54, p<0.001). In rat lung, caspase immunostaining was increased in the PASMC layer in dex-treated MCT rats vs. MCT-alone controls (0.40±0.4% vs. 58.3±1.00%, p<0.0001). Finally, nuclear p65 was reduced in PASMC and endothelial cells in MCT-treated rats at all doses studied.

Conclusion: Dexamethasone reduces proliferation and augments apoptosis in rat

PASMC in vitro, and reduces activation of NF-kB within vascular cells. These results, at least in part, may explain the reversal of PAH by dex seen in the rat MCT-PAH model.

P3173

Exogenous BMPR2 modulates TGF-β signalling in human small airway epithelium and smooth muscle cells

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Introduction: Idiopathic Pulmonary Arterial Hypertension (IPAH) is a fatal dis-
ease characterized by reduced BMPR2 and increased TGF-β expression. 

Aims and objectives: To investigate the effects of upregulation of BMPR2 on TGF-β signalling in human small airway epithelial cells (hSAEC) and pulmonary artery smooth muscle cells (hPASMC)

Methods: The BMPR2 gene was delivered to both hSAEC and hPASMC using a plasmid construct or Adenovirus vector, then TGF-β signalling events assessed.

Results: In hSAEC, TGF-β upregulated P3-8MAPK phosphorylation and vimentin but downregulated pancytokeratin, consistent with epithelial to mesenchymal trans-
ition (EMT). In preliminary studies, prior transduction to upregulate BMPR2, ameliorated the TGF-β-induced increase in vimentin. In hPASMC, TGF-β did not affect P3-8MAPK, but led to a substantial increase in phosphorylated ERK 42/44 and Smad2, and reduced phosphorylation of Smad3/5/8. These effects were largely prevented by BMPR2 transduction.

Conclusions: To date, these findings suggest that BMPR2 gene delivery reduces TGF-β-induced epithelial to mesenchymal transition and TGF-β signalling in smooth muscle cells.

Supported by: Australian NHMRC.

P3174

Increased right ventricular cardiomyocyte stiffness in patients with pulmonary arterial hypertension

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Introduction: This study aims to determine whether changes in right ventricular
(RV) cardiomyocyte contractile apparatus are involved in RV failure secondary to pulmonary arterial hypertension (PAH).

**Methods:** Maximal force and passive stiffness were determined in membrane-permeabilized RV cardiomyocytes isolated from RV tissue obtained after heart-lung transplantation of PAH-patients and non-failing donors. Maximal force was measured at maximal Ca2+-activation, while cardiomyocyte passive stiffness in relaxing solution (low Ca2+ concentration).

- The role of β-Adrenergic receptor signaling on cardiomyocyte passive stiffness was mimicked by determining passive stiffness after PKA incubation.

**Results:**

- No significant differences were found in cardiomyocyte maximal force in PAH patients and controls.
- Passive stiffness was significantly increased at all sarcomere lengths in PAH patients compared to donors.
- PKA incubation partially restored RV cardiomyocyte passive tension in PAH patients to donor values.

**Conclusions:** Our study demonstrates increased RV cardiomyocytes passive stiffness in PAH patients, partially restored by PKA incubation. This finding suggests that reduced β-adrenergic receptor signaling plays an important role in the development of RV diastolic stiffness in PAH patients.

P3177

**The role of bromodomain-containing protein 4 in the constitutive activation of nuclear factor-kappa B in endothelial cells from patients with pulmonary arterial hypertension**

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**Background:** Pulmonary arterial hypertension (PAH) is characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. Pulmonary endothelial cells (P-ECs) are well known as producers of cytokines and chemokines essential in the recruitment of inflammatory cells to the lungs, and a constitutive activation of the nuclear factor-kappa B (NF-κB) signaling pathway in P-ECs has been recently described in PAH. RelA lysine-310 acetylation of NF-κB generates a specific docking sites for bromodomain-containing protein 4 (Brd4). We hypothesise that Brd4 through an NF-κB-dependent mechanism contributes to the hypoproliferative and proinflammatory phenotype in P-ECs in patients with PAH.

**Aim:** The aim of the study was to evaluate the in vitro effect of Brd4 inhibition using the selective inhibitor JQ1 on proliferation and apoptosis in P-ECs.

**Methods and results:** The effect of JQ1 on P-ECs proliferation was established by assessing the incorporation of BrdU. We found a strong anti-proliferative effect of JQ1 in P-ECs (Fig. 1A). We also demonstrated that JQ1 induces caspase-3 activity in P-ECs resulting in increased apoptosis (Fig. 1B).

**Conclusion:** Selective Brd4 inhibitors, such as JQ1, may represent novel therapeutic agents for the treatment of PAH. Further work is necessary to explore this hypothesis.

P3176

**Upstream mediators of p53 in cigarette smoke induced endothelial apoptosis**

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**Background:** Pulmonary endothelial cell (EC) apoptosis is an early determinant of lung destruction in emphysema. We set out to characterize the upstream molecular mediators responsible for p53 dependent cigarette smoke (CS) induced EC apoptosis and rationalize them as potential therapeutic targets. p38 mitogen activated protein kinase (MAPK) has been shown to be activated in alveolar walls in patients with COPD. We have observed that XOR activation is necessary for CS-induced EC apoptosis. XOR activation by mechanical stress or hypoxia is through p38 MAPK dependent pathways. We hypothesize that p38 MAPK activation and its upregulation of XOR activity are necessary upstream events in p53 dependent CS-induced EC apoptosis.

**Methods:** Pulmonary microvascular endothelial cells (PMVEC) were exposed to cigarette smoke extract (CSE) for 4 and 24 hours. Molecular and pharmacologic approaches were used to manipulate p38 MAPK, XOR, and p53 expression. End-points included Western blotting and quantification of EC apoptosis as well as XOR enzymatic activity using the pterin fluorimetric assay (Beckman et al., 1989). Results: Exposure to CSE increases p38 MAPK activity, XOR activity, and p53 expression in our PMVEC. When EC were pretreated with inhibitors for p38 MAPK, XOR, or p53, they were protected from CSE-induced apoptosis. Inhibition of p38 MAPK blocked CSE-induced XOR activation. Suppression of the mitochondrial function of p53 with pifithrin-μ blocks CS-induced apoptosis. Conclusions: CS exposure induces increased apoptosis in PMVEC that is dependent on p33 expression and XOR activation. Inhibition of p38 MAPK prevents upregulation of XOR activation and p53 expression, protecting cells from CS-induced apoptosis.

**Methods and results:** The combined therapy of HGF and G-CSF for pulmonary hypertension in rats

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**Introduction:** Despite advances in therapy of PAH, the treatment and prognosis remain poor.

**Objectives:** This study was to investigate whether expression of HGF through the transplantation of genetically modified MSCs combined with G-CSF could offer therapeutic benefit.

**Methods:** Three weeks after monocrotaline, SD rats were randomly divided into PAH (n=10), MSCs (transplantation of 5×10^6 MSCs transfected with an empty adenovirus vector, n=10), HGF (transplantation of 5×10^6 MSCs transfected with Ad-HGF, n=10), G-CSF group (100 μg/kg daily for 5 days, n=10) and HGF+G-CSF group (transplantation of 5×10^6 MSCs transfected with Ad-HGF and G-CSF, 100 μg/kg daily for 5 days, n=10). Three weeks later, hemodynamic, histomorphological, endothelial and angiogenesis function were detected, involving serum levels of TGF-β, ET-1 and protein level of VCAM-1 and MMP-9.

**Results:** Compared with HGF, G-CSF and PAH group, HGF and G-CSF group have significantly less right ventricular hypertrophy, PASP and mPAP (p<0.05). Histologically, vascular smooth muscle cell proliferation and extra cellular matrix were also significantly decreased (p<0.05). The vascular density of...
HGF+G-CSF group is higher than control group ($P < 0.05$). The TGF-β and ET-1 concentration in the plasma of pulmonary hypertension rats showed markedly decreased in HGF group and HGF+G-CSF group ($P < 0.05$). Furthermore, HGF induced gene and protein expression of VCA-M1 and HGF treatment together with G-CSF synergistically stimulated MMP-9 expression.

**Conclusion:** Transplanted HGF-MSCs combined with G-CSF could offer synergistic therapeutic benefits for the treatment of pulmonary hypertension. This study illustrates mechanisms underlying the synergistic effect of G-CSF and HGF combination.

**P3179**
A critical role for p130cas in the progression of pulmonary hypertension in humans and rodents

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Pulmonary arterial hypertension (PAH) is a progressive and fatal disease characterized by pulmonary arterial muscularization due to excessive pulmonary vascular cell proliferation and migration, a phenotype dependent upon growth factors and activation of receptor tyrosine kinases (RTKs). p130cas is an adaptor protein involved in several cellular signaling pathways that control cell migration, proliferation and survival. We hypothesized that in experimental and idiopathic PAH p130cas signaling is over-activated, thereby facilitating the intracellular transmission of signal induced by fibroblast growth factor (FGF), epidermal growth factor (EGF), and platelet derived growth factor (PDGF). In ipAH patients, levels of p130cas protein are higher in the serum, in walls of distal pulmonary arteries, in cultured smooth muscle (PA-SMCs) and pulmonary endothelial cells (P-ECs) than controls. These abnormalities in the p130cas signaling were also found to be in evidence for convergence and amplification of the growth-stimulating effect of EGF, FGF2 and PDGF signaling pathways via p130cas signaling pathway. Finally, we found that daily treatment with each of the EGF-R inhibitor gefitinib, the FGF-R inhibitor dovitinib and the PDGF-R inhibitor imatinib started 2 weeks after a subcutaneous monocrotaline injection substantially attenuate the abnormal increase in p130cas and ERK1/2 activation and regress established PH. Our findings demonstrate that p130cas signaling plays a critical role in ipAH by modulating pulmonary vascular cell migration, proliferation and by acting as an amplifier of RTKs downstream signals.

**P3180**
Surgery for obstructive sleep apnea: Sleep endoscopy determinants of outcome

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Although drug-induced sleep endoscopy (DISE) is often employed in order to determine the site of obstruction in patients with obstructive sleep apnea (OSA) who will undergo upper airway surgery, it remains unknown whether its findings are associated with surgical outcome. This study tested the hypothesis that DISE variables can predict the outcome of upper airway surgery. Forty-nine OSA patients (41 men; mean apnea-hypopnea index (AHI) 30.9±18.5 events/h) underwent firstly DISE, secondly upper airway surgery, and thirdly follow-up polysomnography to assess surgical outcome. Twenty-three patients (47%) were responders and twenty-nine non-responders (53%). Non-responders had a higher occurrence of complete or partial circumferential collapse at velum, and of complete antero-posterior collapse at tongue base or epiglottis, in comparison with responders. Multivariate logistic regression analysis revealed that, among baseline clinical characteristics and DISE findings, the presence of complete circumferential collapse at velum, and of complete antero-posterior collapse at tongue base were the only independent predictors of upper airway surgery failure. Patterns of collapse on DISE associated with failure. A. complete circumferential collapse at velum; B. complete antero-posterior collapse at tongue base; C. complete antero-posterior collapse at epiglottis. In conclusion, DISE findings are predictors of upper airway surgery outcome in OSA.

Conclusions: It can be concluded that in a healthy population, the BMI has no influence on the position dependent collapsibility of the airway. This means that collapse of the UA in healthy subjects is mostly defined by the natural collapsibility of the subject’s airway.

**P3181**
BMI is not the driving factor in position dependent upper airway collapsibility in healthy subjects

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**Introduction:** In obstructive sleep apnea (OSA) patients, the minimal cross-sectional area (CSA) of their upper airway (UA) correlates well with the severity of their pathology. However, since there is a correlation between body mass index (BMI) and severity of OSA in a population of OSA patients, it is not known if the minimal CSA is defined by the natural collapsibility of the UA or by the mass of the surrounding tissue. The objective of this study is to evaluate the influence of BMI on the position dependent changes in UA geometry assessed by CT imaging.

**Materials and methods:** A total of 20 normal subjects who had BMI $<$ 25, 6 had a BMI between 25 and 30 and 7 had a BMI $>$ 30 were included. 15 valid CBCT scans could be analyzed as the rotating gantry of the CBCT touched the shoulders of some subjects with a BMI $>$ 30, causing motion artifacts. The supine UA CT scans were performed using the GE VCT LightSpeed scanner and the upright CBCT scans were performed using the ISi-CAT scanner.

**Results:** BMI was not a predictor for difference between the minimal CSA in a supine and upright posture (R=0.05, p=0.86) as seen in the figure.

**Conclusions:** BMI is not the driving factor in position dependent upper airway collapsibility in healthy subjects.
and can be an important screening tool as well as an important part of pre-test physical examination. However, its role in predicting severity of OSA remains doubtful and needs further study.

**P3184**

**Validation of respiratory inductive plethysmography in people with obesity hypoventilation syndrome**

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The excessive chest and abdominal adiposity present in obesity hypoventilation syndrome (OHS) may reduce the accuracy of respiratory inductive plethysmography (RIP). The aim of the study was to validate RIP measures of ventilation in OHS against a clinical standard (spirometry). Measures of tidal volume (VT), minute ventilation (VE) and respiratory rate (RR) were obtained simultaneously from RIP (LifeShirt™) and a spirometer during two 40-minute air/supplemental O2 breathing tests. 16 paired samples were obtained per subject. Using the Bland Altman method, bias was expressed as spirometer-RIP mean difference (MD), and as a percentage. Differences between groups were assessed with independent samples t-tests. 162 viable paired samples were obtained from 13 subjects with OHS and 107 paired samples were obtained from 13 age- and gender-matched controls. Error of RIP measures was larger in subjects with OHS: VT: MD=3mL (1%), LOA=-216 to 222mL (±36%) compared with controls, MD=5mL (1%), LOA=-160 to 169mL (±20%); VE: MD=0.2L/min (2%), LOA=-4.1 to 4.4L/min (±36%) in subjects with OHS compared with MD=0.1L/min (1%), LOA=1.4 to 1.5L/min (±20%) for controls; and RR: MD=0.2br/min (2%), LOA=5 to 5br/min (±27%) in subjects with OHS compared with MD=0.1br/min (1%), LOA=1 to 1br/min (±12%) for controls. Between group differences were only statistically significant for RR (p<0.05). VT %error correlated strongly with body mass index (t=b=0.53, p<0.01) and waist circumference (t=b=0.61, p<0.01). In conclusion, the accuracy of RIP is reduced in people with OHS, limiting its capacity for detecting small changes in ventilation.

**P3185**

**Validation of raised serum bicarbonate for diagnosis of obesity hypoventilation syndrome**

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**Introduction:** The need for early detection of Obesity Hypoventilation Syndrome (OHS) is clear because delay in the diagnosis and treatment is associated with significant morbidity and mortality.

**Objective:** To validate previously reported raised serum bicarbonate of 27 mmol/l for the diagnosis of OHS in obese patients attending sleep clinic.

**Methods:** A retrospective analysis of prospectively collected sleep clinic data on consecutive obese patients referred to sleep clinic from January 2009 to January 2011 in the North Middlesex University Hospital was performed. Subjects with suspected sleep disorders were evaluated according to our clinic protocol and capillary blood gases were measured in obese subjects (BMI=30 kg/m²).

**Results:** 525 consecutive patients (mean age 51±14.127, 65.71% males, mean BMI 34.59±8.1) were evaluated. A total of 344 (65.52%) were obese (mean age 52.29±12.4, 63.66% males) of which 128 (37.2%) were morbidly obese (BMI>40 kg/m²), 275 (50.5%) were morbidly obese patients were found to have OSAHS (AHI>20, %O2<90) and 272 (51.52%) were morbidly obese patients with OHS. AHI<15 was found in 162 subjects and AHI>20 was found in 163 subjects. Error was expressed as limits of agreement (LOA) and as a percentage. Differences between groups were assessed with independent samples t-tests. 162 viable paired samples were obtained from 13 subjects with OHS and 107 paired samples were obtained from 13 age- and gender-matched controls. Error of RIP measures was larger in subjects with OHS: VT: MD=3mL (1%), LOA=-216 to 222mL (±36%) compared with controls, MD=5mL (1%), LOA=-160 to 169mL (±20%); VE: MD=0.2L/min (2%), LOA=-4.1 to 4.4L/min (±36%) in subjects with OHS compared with MD=0.1L/min (1%), LOA=1.4 to 1.5L/min (±20%) for controls; and RR: MD=0.2br/min (2%), LOA=5 to 5br/min (±27%) in subjects with OHS compared with MD=0.1br/min (1%), LOA=1 to 1br/min (±12%) for controls. Between group differences were only statistically significant for RR (p<0.05). VT %error correlated strongly with body mass index (t=b=0.53, p<0.01) and waist circumference (t=b=0.61, p<0.01). In conclusion, the accuracy of RIP is reduced in people with OHS, limiting its capacity for detecting small changes in ventilation.

**P3186**

**Effects of supplemental O2 on PCO2 and ventilation in people with obesity hypoventilation syndrome**

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Breathing 100% O2 increases PCO2 in some people with obesity hypoventilation syndrome (OHS). It is not known how lower concentrations of O2 affect people

**569s**
with OHS. This study investigated the effect of clinically relevant O2 concentrations on PCO2, pH and minute ventilation (Ve) in stable OHS patients pre and post treatment with positive airway pressure (PAP), and in controls. In a double-blind randomised crossover study, 14 subjects with OHS and 14 age- and gender-matched controls breathed inspired O2 fractions (FiO2) of 0.28 and 0.5, each for 20min, separated by a 45min washout. The OHS group were retested after 3 months of nocturnal PAP. Arterialised-venous PCO2, and pH, and Ve were measured every 5min. Data were analysed with repeated measures ANOVA. In OHS pre-PAP, small rises in PCO2 of 2.0±1.7mmHg, 3.7±3.2mmHg (both p<0.01) occurred after 20min of breathing FiO2 0.28 and 0.5, respectively, with no significant difference between concentrations. pH fell accordingly, with FiO2 0.5 inducing mild acidemia (7.34±0.030, p<0.01). Ve fell below the room air baseline for both FiO2 0.28 (5±11%, p<0.01) and FiO2 0.5 (7±20%, p<0.01). The controls' responses differed significantly from the OHS group (p<0.01). PCO2 and pH did not change significantly with either FiO2 and mild hyperventilation occurred (Ve +1.3±1.9%, FiO2 0.28, +12±1.7%, FiO2 0.5). In OHS, O2-induced PCO2 rises tended to be smaller after PAP (1.2±2.3mmHg, FiO2 0.28, and 0.9±1.7mmHg, FiO2 0.5). Commonly used concentrations of O2 caused hyperventilation, small PCO2 rises and mild acidemia in stable OHS. When providing supplemental O2 for people with stable OHS, close monitoring and targeting of O2 saturations is recommended.

P3187 Multiscale entropy analysis of RR time series obtained from polysomnographic recordings in wide age spectrum group
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Costs and complication of polysomnography lead to attempts to develop cheaper and simpler methods. The analysis of heart rate's dynamics is biased by several physiological factors. The aim of this study was to check influence of age on multiscale entropy (MSE) of RR time series.

64 patients undergoing routine diagnostic in sleep lab were recruited (36 male, 28 female, age 1.5-63 yrs mean: 25.2±20 yrs, RDI: 0.4-9 1/h mean:1.5 1/h). The full night PSG (ASSM 2007) were performed. The R-R intervals were detected in recorded ECG signal (250Hz), and the multiscale entropy (Goldberg’s MSE) was calculated (m=2, r=0.15, scale = 1–20).

We found high correlation between entropy in SE(1) and age (Fig. 1) in adults, however in the children group (age<15) there was no such relation.

After removing subjects younger than 15yrs the correlation increase (R=0.58, p<0.001). Using MSE we found significant differences between the lowest and highest quartiles (Fig. 2)

We conclude that entropy is biased by age in adults and the lack of such relation in young group needs further investigations.

P3188 Effect of nasal CPAP therapy on functional respiratory parameters and cardiopulmonary exercise test in obstructive sleep apnea syndrome
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Aim: Nasal CPAP treatment is an effective treatment modality for patients with OAS. It can improve physical and mental functions by reducing daytime hyper-somnolence, arousal index and sleep fragmented. The purpose of this study was to evaluate whether pulmonary functions, exercise limitation confirmed with CPET and quality of life can be improved after eight weeks of nCPAP treatment.

Method: We evaluated our case group with physical examination, SF-36 health survey, body composition analysis before and after nCPAP treatment for 8 weeks. Spirometric flow rates, PImax, PEmax, lung volumes and exercise capacities with CPET were measured.

Results: 31 of 40 patients (4 female, 27 male) completed the study. The mean age was 53.4±1.46, 51.6±1.6 of cases had comorbidities and the smoking history rate was 54.8. All of them had exercise limitation before treatment. After treatment there were increases in PImax-PEmax (p<0.05), VO2 peak (p<0.001), Load max (p<0.001), maximal heart rates (p<0.001), all SF-36 scores except pain (p<0.05) and a decrease in systolic blood pressure (p<0.005). We didn’t see any changes in body compositions, spirometric flow rates except FEV1 and lung volumes.

Conclusion: OSAS may lead to exercise limitation. nCPAP treatment is effective in reducing exercise limitation, can help to control blood pressure and improves respiratory muscle strength. nCPAP can also improve the quality of life scores in OSA patients without any comorbidities or with comorbidities under control. Our findings may suggest that these results are the improvements of patients’ cardiac function, daytime somnolence and fitness.

P3189 End expiratory lung volume as a predictor of obstructive sleep apnea severity
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Background: One of the contributing factors to upper airway collapses in obstructive sleep apnea (OSA) is reduced end expiratory lung volume (EELV) (Kapur, V.H. et al. Respiratory Care 2010;55). There is evidence for correlation of apnea hypopnea index (AHI) with EELV in supine position during sleep (Owens, R. W. App Physiol 2010;108:445-51). In respiratory function testing however, EELV is routinely measured in sitting position and during wake (EELVaw).

Aims and objectives: To establish the relationship between EELVaw and OSA. We hypothesized that EELVaw may affect the severity of OSA.

Methods: In an observational study the relationship between EELVaw and OSA in 59 adult patients of Orhis Medical Centre, Sittard (The Netherlands) was assessed using a regression analysis. EELVaw was evaluated by helium dilution technique, and severity of OSA by apnea hypopnea index (AHI) based on polysomnography measurements. In addition EELVaw was compared to other predictors of OSA; Epworth sleepiness score (ESS), Mallampati score, body mass index (BMI), and neck- and abdominal circumference, by means of a multiple regression analysis.

Results: EELVaw was a predictor of AHI, R=0.392 (p<0.003). Multiple regression analysis demonstrated that abdominal circumference explained 15.5% of variance of AHI, and together with EELVaw, 23.4% of the variance of AHI was explained. Other predictors were not significant.

Conclusions: EELVaw contributes to the severity of OSA and might therefore be useful to differentiate between high and low risk patients for OSA in screening and diagnostics settings. Abdominal circumference also appeared to predict severity of OSA and had even more impact on AHI compared to EELVaw.

P3190 Inflammatory processes and effects of continuous positive airway pressure (CPAP) in overlap syndrome
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Aim: We aimed to compare serum levels of the inflammatory mediators of C-Reactive Protein (CRP), Tumor Necrosis Factor-α (TNF-α) and Asymmetric-Dimethyl-Arginine (ADMA) in Chronic Obstructive Pulmonary Disease (COPD), Obstructive Sleep Apnea Syndrome (OSAS) and their coexistence called Overlap Syndrome (OVS). Also, we planned to investigate the changes of these mediators with the treatment of continuous positive airway pressure (CPAP) in OSAS and OVS patients.

Methods: CRP, TNF-α, ADMA levels were analyzed by ELISA method with the blood samples taken from patients with COPD (N=25), OVS (N=25) and moderate-severe stage OSAS (N=25) in the morning after polysomnography application and second blood samples taken from OSAS and OVS patients who underwent regular CPAP treatment throughout 3-6 weeks.

Results: In comparison of three groups prior to CPAP treatment, ADMA levels in OSAS group were significantly lower than in COPD group (p=0.009), but
OSA is often associated with obesity and metabolic syndrome. The aim of this study was to assess prevalence of hyperuricaemia in OSA patients and relations between elevated plasma uric acid (UA) and OSA severity, obesity and cardiovascular diseases. We studied 1144 OSA pts: AHI = 39.7±21.7, BMI = 34.2±6.4 kg/m², mean SAO₂ = 90.8±5.7%, T90 = 26.6±28.9%, Epworth score = 11.3±3.5. Points. Hyperuricaemia [males: UA > 7 mg/dl (2005-2007) and > 8.5 mg/dl (since 2008), females: UA > 5.7 mg/dl (2005-2007) and > 6.2 mg/dl (since 2008)] was found in 354 pts (30.9% (different laboratory methods)). Comparison of subjects with hyperuricaemia and normouricaemia is shown in table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal UA (n=790; 69.1%)</th>
<th>Increased UA (n=354; 30.9%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.5±10.4</td>
<td>56.2±10.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31±1.6</td>
<td>36±1.6</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>AHI (ah)</td>
<td>38±2.1</td>
<td>42±2.1</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>T90 (%)</td>
<td>22±6.7</td>
<td>35±8.4</td>
<td>p&lt;0.004</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>61 (45.9%)</td>
<td>299 (84.5%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>158 (129%)</td>
<td>99 (28%)</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>69 (8.7%)</td>
<td>59 (16.7%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>154 (19.5%)</td>
<td>93 (26.9%)</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Logistic regression analysis revealed that arterial hypertension, obesity (BMI > 30 vs < 30 kg/m²), and T90 > 30% were independent predictors of hyperuricaemia (OR=1.76; 95%CI – 1.23-2.51; p=0.002, OR=2.47; 95%CI – 1.67-3.65; p<0.001 and OR=1.79; 95%CI – 1.34-2.40; p<0.001, respectively) after adjusting for NT-proBNP, diabetes, heart failure, coronary artery disease, COPD and stroke.

Conclusions: Hyperuricaemia was frequent in OSA patients. Main predictors of hyperuricaemia were obesity, overnight desaturation time - T90> 30% and arterial hypertension.

P3193
Cardiovascular diseases are responsible for increased plasma NT-proBNP level in obstructive sleep apnoea (OSA) patients
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Increased plasma NT-proBNP concentration in OSA subjects was associated with severe obstructive sleep apnoea syndrome (OSAS) and OSAS severity, obesity, overnight desaturation time - T90>30% and arterial hypertension. Moreover, increased NT-proBNP was found in OSA patients with hyperuricaemia and normouricaemia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elevated NT-proBNP (%)</th>
<th>Normal NT-proBNP (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.2±8.8</td>
<td>54.1±10.1</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.7±2.7</td>
<td>14.6±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (ah)</td>
<td>37.9±20.1</td>
<td>40.2±22.1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SAO₂ (%)</td>
<td>90.5±7.3</td>
<td>91±7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>128 (47.6%)</td>
<td>134 (15.8%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>59.2 (19.3%)</td>
<td>37.4 (13.0%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>86.2 (29.2%)</td>
<td>44.1 (12.0%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>249 (87.4%)</td>
<td>549 (69.8%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>17.5 (5.8%)</td>
<td>26 (7.1%)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>52.7 (17.7%)</td>
<td>90 (15.6%)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Logistic regression analysis revealed that heart failure (OR=4.4; 95%CI – 4.09-4.74; p<0.0001), atrial fibrillation (OR=4.22; 95%CI – 3.89-4.58; p<0.0001), coronary artery disease (OR=2.29; 95%CI – 2.16-2.43; p<0.0001), arterial hypertension (OR=1.87; 95%CI – 1.75-2.0; p<0.0001) and COPD (OR=3.77; 95%CI – 1.27-4.77; p=0.0001) were independent predictors of increased NT-proBNP after adjusting for BMI, diabetes, hyperuricaemia and stroke.

Conclusions: Increased plasma NT-proBNP concentration in OSA subjects was mainly related to cardiovascular diseases.
Conclusions: We found a dose-response relationship between the severity of sleep apnea during the night in women and the levels of BNP in the morning.

P3195
The relationship between uric acid levels and mean plateau volume and metabolic syndrome in males with obstructive sleep apnea syndrome
Ahmet Akkaya, Onder Ozturk, Uluğ Bük Khayri, Mustafa Saygin

Aim: The aim of our study was to investigate the post-treatment changes in the level of UA and the relationship between serum uric acid (UA) levels and mean plateau volume (MPV) and metabolic syndrome in males with obstructive sleep apnea syndrome (OSAS).

Material and methods: Seventy nine men who had performed a single night polysomnography (PSG) (mean AHI=42.59±2.79 events/hour), were included to the study. Demographics characteristics, serum uric acid levels, MPV and PSG results were recorded. We divided patients in two groups according to centiles of UA levels: 1st with hyperuricaemia - UA > 6.86 mg/dL and 2nd with normouricaemia - UA < 6.86 mg/dL.

Results: There was a statistically positive correlation between UA (0.03±0.13 mg/dL) and AHI (p=0.037), BMI (p=0.013), waist circumference (p.<0.002), desaturation % (p=0.047). Subjects with hyperuricaemia had higher AHI, BMI, (p.<0.05), waist circumference (p.<0.01), neck circumference, oxygen saturation index (ODI). UA desaturation % and triglyceride. The duration of REM decreased and Stage 1 and 3 increased. The UA and MPV were found higher in patients with MS and OSAS and UA levels decreased after CPAP treatments. However, OHI and AHI were included to the model to estimate AHI at stresse regression analysis (R square 58%, p.<0.001).

Conclusion: This study showed that obesity was the determinant of hyperuricaemia and high levels of UA was found with MS and OSAS. The levels were decreased after CPAP therapy. An also, it is thought that high levels UA and MPV are associated with cardiovascular complications in OSAS.

P3196
Adaptive servo ventilation in the treatment of central sleep apnea related to ischemic stroke
Anne-Kathrin Brill, Regula Rosit, Matthias Guggert, Sebastian Robert Ott

Respiratory and Sleep Medicine, University Hospital (Inselspital) and University of Bern, Switzerland

Background: Adaptive Servo Ventilation (ASV) is a well-established treatment of central sleep apnea (CSA) related to chronic heart failure (CHF). So far, only few studies evaluated effectiveness and complications of ASV in patients with CSA of other etiologies. Therefore, we analyzed ASV in CSA following ischemic stroke.

Methods: Retrospective analysis of ASV treatment in stroke patients with CSA between 2005 and 2011. Patients with acute stroke (<1 month) or diagnosis of CHF were excluded. Demographic, clinical (including Epworth sleepiness scale; ESS), polygraphic/polysomnographic, ventilator setting and compliance data were collected.

Results: Fifteen out of 123 patients treated with ASV suffered from CSA or complex sleep apnea related to ischemic stroke (median time from stroke 11 month). 13/15 patients were pretreated with positive pressure ventilation without clinical success (CPAP 11/15; BiPAP 2/15). Indication for ASV was complex sleep apnea in 6 patients, CSA/Cheyne-Stokes-Breathing in 5 patients, and mixed sleep apnea in 4 patients. At follow up after 66.3±42.0 days, mean daily use of ASV was 5.4±2.4 h per night. ASV significantly improved AHI (46.7±24.3 to 8.5±12.0 h, p=0.001). ESS was reduced from 8.7±5.7 to 5.6±2.5 (p=0.08).

Conclusion: Our data clearly suggests that ASV is a well-tolerated and clinically effective treatment in patients suffering from CSA related to ischemic stroke. Prospective randomized trials are warranted to establish ASV in the treatment of stroke related central sleep apnea.

P3197
Relationship between NT-proBNP level, echocardiographic parameters and cardiovascular diseases in patients with obstructive sleep apnea (OSA)
Anna Czyzak-Gradkowska, Anna-Kathrin Brill

Respiratory and Sleep Medicine, University Hospital (Inselspital) and University of Bern, Switzerland

Brain natriuretic peptide (BNP) is a hormone secreted by the ventricles in response to heart overload. The aim of this study was to assess prevalence of elevated NT-proBNP (inactive form of BNP) level in OSA patients and its relations to echocardiographic parameters and OSA-associated cardiovascular complications.

We studied 87 OSA pts, mean AHI was 42.3±24.1 age - 57.5±10.6 yrs, mean plasma NT-proBNP level was 198.5±357.3 pg/ml. Elevated NT-proBNP concentration was found in 34 pts with OSA. Comparison of OSA pts with normal and elevated NT-proBNP level is shown in a table below.

Elevated NT-proBNP level was found in 39.8% OSA subjects. Logistic regression analysis revealed that elevated NT-proBNP level (>125pg/ml) did not correlate with studied echocardiographic parameters in OSA pts (p>0.05). NT-proBNP level negatively correlated with AHI (r=-0.25, p=0.02). Elevated NT-proBNP concentration indicated at increased risk of coronary artery disease (OR = 12.94, 95%CI = 2.4-68.5, p<0.01).

Conclusions: Increased plasma concentration of NT-proBNP was not related to echocardiographic parameters, but it was associated with occurrence of CAD in OSA subjects.

355. “Predicting the future”: the impact of reference values on a range of respiratory parameters

P3198
All-age multi-ethnic reference values for spirometry: The Global lung function initiative (GLI)
Janet Stocks, Sanja Stanjevic, Tim Cole, Xavier Baur, Graham Hall, Bruce Calver, Philip Quanjer

Centers for Respiratory Unit, UCL, Institute of Child Health, London, United Kingdom; #Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada; 2MRC Centre of Epidemiology for Child Health, UCL, Institute of Child Health, London, United Kingdom; 3Universitätsklinikum Hamburg-Eppendorf, Hamburg - Pneumologie; 4Arthromedizin and Maritime Medizin, Hamburg, Germany; 5Telethon Institute for Child Health Research, University of Western Australia, Perth, WA, Australia; 6Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, United States; 7Department of Pulmonary Diseases and Department of Pediatries, Erasmus Medical Centre, Erasmus University, Rotterdam, Netherlands

Background: The GLI (an ERS Task Force) was established to develop the first global reference equations for spirometry. These are the result of unprecedented international cooperation and are endorsed by six international respiratory societies, including the ERS.

Methods: Data from 74,187 healthy non-smokers aged 3-95 years were used to derive reference equations using modern statistical methods, including development of age dependent lower limits of normal.

Results: All-age reference equations are now available for Caucasians, African Americans, South East Asians (south of the Huaihe River and Qinling Mountains), and South East Asians (north of the Huaihe River and Qinling Mountains). For individuals not represented by these four groups a composite equation is provided. Since the observed ethnic differences were proportional to Caucasians, for groups not represented, samples of healthy subjects, composed of at least 300 individuals, studied according to international standards (Quanjer et al ERJ 2011, 37; 658-664) and with height and age measured accurately to one decimal place.

Conclusion: The GLI 2012 reference equations are a major step forward and provide a robust reference standard to streamline interpretation of spirometry across all-ages worldwide. Widespread use of the GLI equations will, however, depend on timely implementation by manufacturers of spirometric devices.

P3199
A comparative study of FVC, FEV1, and TLC in non-smoking Saudi students at Eastern Province, Saudi Arabia with Caucasian reference values
Noor AL-Khathlan, Stephanie Enright, Mohammed Amr El-Noueama

Child Health, London, United Kingdom; 2Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada

Introduction: It is well-known that pulmonary function testing (PFT) values vary with height, age, gender, and ethnicity. The influence of ethnic variation on PFT values from the Caucasian population. We aimed to compare Saudi measured values, including the ERS.

Methods: Data from 74,187 healthy non-smokers aged 3-95 years were used to derive reference equations using modern statistical methods, including development of age dependent lower limits of normal.

Results: All-age reference equations are now available for Caucasians, African Americans, South East Asians (south of the Huaihe River and Qinling Mountains), and South East Asians (north of the Huaihe River and Qinling Mountains). For individuals not represented by these four groups a composite equation is provided. Since the observed ethnic differences were proportional to Caucasians, for groups not represented, samples of healthy subjects, composed of at least 300 individuals, studied according to international standards (Quanjer et al ERJ 2011, 37; 658-664) and with height and age measured accurately to one decimal place (Quanjer et al ERJ 2012, PM:22183491), can be used to validate the GLI and/or create an appropriate adjustment factor (www.lungfunction.org).

Conclusion: The GLI 2012 reference equations are a major step forward and provide a robust reference standard to streamline interpretation of spirometry across all-ages worldwide. Widespread use of the GLI equations will, however, depend on timely implementation by manufacturers of spirometric devices.
for forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and total lung capacity (TLC), with Caucasian RV.

Methods: Healthy non-smoker university students were recruited to perform spirometry and plethysmography. Measurements were obtained according to ATS/ERS recommendations, standardized for height and age and compared with Caucasian RV.

Results: We studied 128 subjects, 16 of which were excluded for technical reasons. Significant difference (p<0.01) was found between the measured values in Saudis (52 males and 60 females) and Caucasian RV. The means for the measured values of FVC, FEV1 and TLC for Saudis were found to be lower than the means of RV for Caucasians by about 10%, 5% and 8% respectively for males and 16%, 12% and 5% respectively for females.

Discussion: Matching the reference and patient populations when selecting RV for PFT is significant. The observed differences we found between Saudis' PF and Caucasian RV can be deemed of great importance and maybe explained in terms of environmental and life-style factors. However, larger study is required to confirm these findings.

References:

P3200
Reference values for spirometry in healthy subjects 17 to 25 years
Ivánia Gonçalves 1,2, Barbara Tavares 1,2, Sandra Gomes 1,2, Traco Jacinto 1,3,4,5,6
1Cardiopneumologia, Escola Superior de Tecnologia da Saúde do Porto; 2Vila Nova de Gaia, Portugal; 3Cardiologia, Consultório de Cardiologia Dr. Ribeiro Santos; 4Masa, Portugal; 5Cardiologia, Hospital de São Martinho, Porto, Portugal; 6CENTISSE - Centro de Investigação em Tecnologias e Sistemas de Informação em Saúde, Universidade do Porto, Portugal; 7Departamento de Ciências da Informação e da Decisão em Saúde, Faculdade de Medicina da Universidade do Porto, Portugal;

Background: Spirometry is the most common method to evaluate pulmonary function. The European Respiratory Society recommends the development of new reference equations, in order to upgrade and improve the existing ones.

Aim: Develop reference equations to calculate reference values adjusted to a healthy population of college students.

Methods: A total of 49 healthy female individuals with ages ranging 17 to 25 years old were enrolled in the present study. A standardized respiratory and allergy symptoms questionnaire was applied and spirometry was performed in the selected individuals. FEV1, FVC and FEV1/FVC were used as dependent variables in simple and multivariate linear regression models.

Results: Height is the variable that best explains variation of FEV1 (r² = 0.36; p < 0.001) and FVC (r² = 0.44; p < 0.001), while weight is the variable that best explains FEV1/FVC (r² = 0.15; p = 0.006). Knudson’s equations were the most different from this model, while Quanjer’s were the closest.

Conclusions: There are no spirometry alterations in patients with morbid obesity with no history of cardiovascular, skeletal, neuromuscular or respiratory diseases. There are no difference between sexes.

P3201
Spirometry measurements in the morbid obesity
Khalid Abu Shamg 1, Maria Hernandez 1, Amaia Iridoy 1, Susana Clemos 1, 1Pneumología; 2Spain Pneumology, 3Internal Medicine, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain

Background: The obesity is a particular case of thoracic respiratory function restriction. Obstructive Apnea Syndrome and hypoventilation have been described in relationship to the morbid obesity (MO).

Objective: To evaluate the alterations presented in spirometric measurements concerning the healthy subject with morbid obesity.

Methods: Spirometry and flow-volume curve were performed in 44 patients suffering of MO studied in our Department. Of 44 cases, 8 were male (18.2%) with a mean age of 37.4±8.8 years and 36 women (81.8%) with a mean age of 39.9±11.1 years.

Table 1. Physical attributes

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 8.8</td>
<td>39.9 ± 11.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>135.5 ± 8.7</td>
<td>122.6 ± 18.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.8 ± 4.8</td>
<td>157.5 ± 7.0</td>
</tr>
<tr>
<td>BMI*</td>
<td>46 ± 4.3</td>
<td>49.7 ± 7.5</td>
</tr>
</tbody>
</table>

*Body Mass Index.

Table 2. Spirometry results

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>FEV1 (% pred.)</td>
<td>86.7 ± 22.9</td>
<td>88 ± 17.5</td>
</tr>
<tr>
<td>FVC (% pred.)</td>
<td>88.2 ± 20.9</td>
<td>89.8 ± 17.7</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>87.3 ± 16.4</td>
<td>84.4 ± 6.3</td>
</tr>
<tr>
<td>REF (% pred.)</td>
<td>72.1 ± 22.7</td>
<td>85.5 ± 20.5</td>
</tr>
<tr>
<td>FEV1 (% pred.)</td>
<td>86.2 ± 36.4</td>
<td>80.3 ± 28.3</td>
</tr>
</tbody>
</table>

Conclusions: There are no spirometry alterations in patients with morbid obesity with no history of cardiovascular, skeletal, neuromuscular or respiratory diseases. There are no difference between sexes.

P3202
Comparison of different predicted and lower limit of normal (LLN) values in ventilation disorders detection
Marina Kamegev 1, Artem Tsitkovich 1, Alina Bylkova 1, Vasily Tretfovsky 1, 1Lung Function Laboratory, Institute of Pulmonology Pavlov's State Medical University, St. Petersburg, Russian Federation; 2Information Technologies in Education, Institute for Informatics and Automation of RAS, St. Petersburg, Russian Federation; 3Department of Physics, Mathematics and Informatics, Pavlov's State Medical University, St. Petersburg, Russian Federation; 4Department of Hospital Therapy, Pavlov's State Medical University, St. Petersburg, Russian Federation

Methods: To estimate the agreement of Russian equations (Klement), ECCS and NhanesIII spirometry evaluating systems in determining the types of ventilation abnormalities by predicted and LLN (5th percentile) values.

Materials and methods: The study enrolled 7,779 Caucasians examined in pulmonary clinics of St.Petersburg's Pavlov's State Medical University in 2005-2011: 3,584 males (mean age 47.40±0.25, mean height 175.44±0.18) and 4,195 females (mean age 49.66±0.20, mean height 162.29±0.10). The cases that can not be classified as norm, obstruction or restriction, were accumulated in the “mixed” group.

Conclusion: The best agreement was obtained by ECCS and Klement systems both in predicted values and LLN. NhanesIII significantly differs from both Klement and ECCS in LLN for all groups. In predicted values these three systems agreed in obstruction but still generally disagree in norm and restriction.

P3203
The effect of body composition on pulmonary function
Jung Eun Park 1, Jin Hong Chung 2, Kyeong Cheol Shin 1, Kwan Ho Lee 1, 1Internal Medicine, Yeungnam University College of Medicine, Daejeon, Korea; 2Internal Medicine, Yeungnam University College of Medicine, Daejeon, Korea

Background: The pulmonary function test (PFT) is the most basic test methods to diagnose lung disease. The purpose of this study was to research correlation of the body mass index (BMI), the fat percentage of the body mass (Fat%), the muscle mass, the fat-free mass (FFM) and the fat-free mass index (FFMI), waist-hip ratio (WHR) on the forced expiratory volume curve.

Abstract P3202 – Table 1

<table>
<thead>
<tr>
<th></th>
<th>Klement (1)</th>
<th>ECCS (2)</th>
<th>NIHANES III (3)</th>
<th>Cohen’s Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>1-3</td>
<td>1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norm FEV1/FVC</td>
<td>≥0.7</td>
<td>FVC ≥80%Pred, FVC ≥LLN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 &gt;80%Pred</td>
<td>2978 (0.38)</td>
<td>3146 (0.40)</td>
<td>2383 (0.31)</td>
<td>0.85 (0.83-0.87)</td>
</tr>
<tr>
<td>FEV1 ≥LLN</td>
<td>3568 (0.46)</td>
<td>3415 (0.44)</td>
<td>2301 (0.30)</td>
<td>0.86 (0.85-0.88)</td>
</tr>
<tr>
<td>Obstruction: FEV1/FVC &lt;0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 &gt;80%Pred</td>
<td>2765 (0.36)</td>
<td>2710 (0.35)</td>
<td>2855 (0.37)</td>
<td>0.87 (0.84-0.90)</td>
</tr>
<tr>
<td>FEV1 &lt;LLN</td>
<td>2906 (0.32)</td>
<td>2508 (0.32)</td>
<td>2836 (0.36)</td>
<td>0.91 (0.90-0.93)</td>
</tr>
<tr>
<td>Restriction: FEV1/FVC ≥0.7</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>FVC &lt;80%Pred</td>
<td>1247 (0.16)</td>
<td>1089 (0.14)</td>
<td>2035 (0.26)</td>
<td>0.83 (0.83-0.87)</td>
</tr>
<tr>
<td>FVC &lt;LLN</td>
<td>784 (0.10)</td>
<td>921 (0.12)</td>
<td>2160 (0.28)</td>
<td>0.87 (0.85-0.89)</td>
</tr>
<tr>
<td>Mixed</td>
<td>789 (0.10)</td>
<td>834 (0.11)</td>
<td>506 (0.06)</td>
<td></td>
</tr>
<tr>
<td>LLN</td>
<td>903 (0.12)</td>
<td>935 (0.12)</td>
<td>482 (0.06)</td>
<td></td>
</tr>
</tbody>
</table>
Methods: Between March and April 2009, a total of 291 subjects were enrolled. 152 men and 139 female (mean age: 46.3±9.92) were measured the FVC, FEV1, FEF25-75, from the forced expiratory volume curve by the spirometry and the body composition Calopero, with the bioelectrical impedance method. From the correlation and multiple linear regression between body composition and pulmonary function were used executed.

Result: BMI and Fat% had no correlation with FVC, FEV1, in male, but FMFI is positively correlation. In contrast, BMI and Fat% had correlation with FVC, FEV1, in female, but FMFI had no correlation. Both male and female, FVC and FEV1, had not significant correlation with WHR (male FVC r=0.237, FEV1, r=0.36; p-value <0.05) (female FVC r=0.175, FEV1, r=0.213; p-value <0.05).

In a multiple linear regression of considering body composition at total sex group, FVC was explained FMM, BMI, FMFI in order (R²=0.579, 0.657, 0.663), FEV1 was explained only Fat% (R²=0.011). FH25-75 was explained mean muscle mass. FMFI (R²=0.126, 0.138, 0.148).

Conclusion: The BMI, Fat%, muscle mass, FMFI, WHR have significant correlation with pulmonary function but (coefficient of determination) were not high enough for explaining lung function.

P3206
Impact of a pulmonary laboratory quality control oversight on continual improvement
Carl Mottram, Susan Blonsunique, Karin Kjek, Jeremy Road. Pulmonary Function Quality Control Program, Diagnostic Accreditation Program, Vancouver, BC, Canada

Introduction: The purpose of this study was to evaluate the impact of a quality control (QC) oversight program on compliance with QC, biological coefficient of variation (CV) targets, and test performance improvements.

Methods: The Diagnostic Accreditation Program (DAP) of British Columbia is responsible for accrediting 27 pulmonary function (PF) laboratories representing 45 testing systems throughout the Canadian province. In 2008 DAP elevated the required elements of their quality assurance program to be more consistent with the current ATS-ERS recommendations for QC testing. This included increasing the frequency of the biological testing and adding a diffusing capacity mechanical QCM model. DAP also changed the data review model to include assessment by an external consultant with a feedback report process to the sites. We compared the data through 2011 to assess the impact of the feedback process. Data were categorized into major and minor subsets for compliance, BioQC targets, and test performance based on an assessment of overall impact of the deficiency on lab performance (e.g. BioQC DLCO CV target < 5%, a CV >5-10 categorized as major; CV >10% a major deficiency).

Results:

<table>
<thead>
<tr>
<th>Category of Deficiency</th>
<th>Submission Cycle 05</th>
<th>Submission Cycle 10 (2011)</th>
<th>% Improvement</th>
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</thead>
<tbody>
<tr>
<td>Compliance Major</td>
<td>26</td>
<td>3</td>
<td>88%</td>
</tr>
<tr>
<td>Compliance Minor</td>
<td>20</td>
<td>20</td>
<td>0%</td>
</tr>
<tr>
<td>BioQC Major</td>
<td>8</td>
<td>2</td>
<td>75%</td>
</tr>
<tr>
<td>BioQC Minor</td>
<td>23</td>
<td>23</td>
<td>0%</td>
</tr>
<tr>
<td>Test performance</td>
<td>10</td>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>37</td>
<td>61.8±0.05</td>
</tr>
</tbody>
</table>

Discussion: There was a significant improvement in all three areas of the monitoring program with a total improvement of 61% (p<0.05). Using a formal external oversight process which includes written feedback appears to improve the overall outcome of this regulated quality assurance program.

P3207
Validation of spirometer calibration syringes
Blenning Madison, Lung Function Laboratory, Allergy and Lung Clinic Helsingør, Helsingør, Capital Region, Denmark

The calibration syringe is probably the most important instrument in pulmonary function laboratories, yet no validation results have been published.

Methods: We weighed a 3 L calibration syringe before and after emptying it of water and determined the corresponding volume of gas by using a modified rolling seal spirometer.

Results: The volume of a spirometer calibration syringe could be verified with an accuracy of ±15 ml. All syringes larger than one litre had volumes within the label claimed volume ±0.5%.

<table>
<thead>
<tr>
<th>Syringe Manufacturer claimed, verified deviation ml (pct.)</th>
<th>Volume</th>
<th>Volume</th>
<th>Volume</th>
<th>Syringe duty cycle</th>
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</thead>
<tbody>
<tr>
<td>Hans Rudolph</td>
<td>2.989</td>
<td>2.988</td>
<td>1.003</td>
<td>2008–2011</td>
</tr>
<tr>
<td>Hans Rudolph</td>
<td>2.496</td>
<td>2.496</td>
<td>4.02</td>
<td>Never</td>
</tr>
<tr>
<td>Hans Rudolph</td>
<td>3.000</td>
<td>2.987</td>
<td>13.04</td>
<td>Never</td>
</tr>
<tr>
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<td>2.988</td>
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<td>2.994</td>
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<tr>
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</tr>
<tr>
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<td>16.16</td>
<td>1998–2011 Routine</td>
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<tr>
<td>Ferraris</td>
<td>1.000</td>
<td>2.979</td>
<td>21.07</td>
<td>1998–2011 Routine</td>
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</table>

Conclusion: Spirometer calibration syringes have a stable stroke volumes. The maximal interval between syringe validations should perhaps be extended beyond the 1-year period required by current standards. Use of two syringes would allow one syringe exceeding the maximal permissible error to be detected earlier.
The comparison study on the effects of high versus low flux membrane on pulmonary function tests in hemodialysis patients

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Background: Several studies have been carried out to evaluate the effects of dialysis on pulmonary function tests (PFT). Dialysis procedure may reduce volumes and capacities of the lung or cause hypoxia; however, based on our knowledge, there was no previous study on evaluation of effects of membrane type (high flux vs. low flux) on PFT in these patients. The aim of this study was the evaluation of this relationship.

Materials and methods: In a cross-sectional study, 43 hemodialysis patients without pulmonary disease were enrolled. In these patients dialysis was conducted by low and high flux membranes and before and after of procedure, spirometry were done and the results were evaluated by t-test and chi square.

Results: Mean age of the patients was 56.34 years. Twenty three women (53.5%) and 20 men (46.5%) were enrolled. Patients' body weight after dialysis were decreased significantly compared to before dialysis. Type of membrane (high flux vs. low flux) had not significant effect in PFT results of the patients (P>0.05).

Conclusion: Since high flux membranes are more expensive than low flux membranes and there was no significant difference in the results of spirometry of patients, it could not be offered of high flux membrane for this purpose.

P3210

Pulmonary volumetric analyses based on three-dimensional computed tomography (3D-CT) potentiated the application in the daily clinical practice.

Hiroshi Muto1, Sayaki Hiraoka1, Kako Mota1, Musamichi Koyanagi1, Kenichi Yokoyama1, Yoshinosuke Fukuchi1, Toshiaki Nitatori1, Hajime Goto1, Sayuki Hiraoka1, Keiko Mota1, Masamichi Koyanagi1.

Background: Three-dimensional computed tomography (3D-CT) potentiates the application in the daily clinical practice.

Methods: Forty four patients (30 COPD, 12 lung cancer, 2 miscellaneous) were enrolled in this study. Lung volumes (LV), as well as the low attenuation volume (LAV), were measured based on 3D-CT both at end inspiratory volume (EIV) and end expiratory volume (EEV) and compared with the physiological data of ordinary pulmonary function tests.

Results & discussion: Lung volumes determined using reconstituted 3D-CT images at end inspiratory volume (EIV), those at end expiratory volume (EEV), and their difference (EIV – EEV), were significantly associated with TLC (p<0.0001), RV (p<0.0001), VC (p=0.0028), respectively. Furthermore, the percentage of the LAV to LV at EIV (LAV/LV%) was associated with the changes in the various results of pulmonary function tests, including FEV1, %FVC, RV/LV, VC. Both FEV1 and %FEV1 were associated with LAIExp and LVEp, in participants whose LAV were larger than 10mL. These results suggested that 3D-CT, taken at both EIV and EEV, provides the data not only on lung volumes in the static state, but also dynamic information. Furthermore, there is a significant association between the FEV1 and the difference between the normal attenuation volumes (NAV) of the 3D-CT at EIV and those at EEV (p<0.001). This suggested that not only LAV but also NAV contributed to the airflow limitation, represented by FEV1 reduction.

Conclusion: 3D-CT reveals not only the physiological properties, but also provides some insights into the mechanism of respiration.

P3211

Estimation of chest-wall mechanics by laser self mixing interferometer

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Background: Several studies demonstrated that the chest wall (CW) may be split into at least two compartments (rib cage and abdomen) characterized by spatial distribution inhomogeneities in CW mechanics. Up to now, it has been assessed by means of complex technique such as Optoelectronic Plethysmography (OEP). We have developed a CW scanning system (CWSW) based on self-mixing laser interferometers that allows measuring relative displacement contactless with high spatial resolution (<1 μm) in an economical and easy to use way.

Methods: Five healthy subjects, in supine position, were analyzed while submitted to a sinusoidal pressure forcing at the mouth with components at 5, 11 and 19 Hz.

Results: Displacement of several points on their CW has been measured with the CWSW and phase shift among these points and the pressure stimulus was estimated by spectral analysis.

Conclusion: The impedance averaged maps in the figure below show high spatial inhomogeneities, in particular one may appreciate that at 5 Hz it is possible to identify the region of the rib cage, where the pressure stimulus moves fast, and the abdomen where the pressure wave is slowed down by the high inertive component.

P3212

Specificity and sensitivity of the methacholine challenge test for the diagnosis of asthma in athletes

Alexander Chemkov, Tatyana Pashkova, Malika Mustaphina, Svetlana Chikina, Tatiana Molostova, Zaurbek Aisanov. Functional Diagnostic, Research Pulmonology Institute, Moscow, Russian Federation

The report of recurrent symptoms of bronchial obstruction as chest tightness, wheeze and cough provoked by exercise is a prerequisite for the diagnosis of asthma or exercise-induced bronchospasm (EIB) in athletes. The report of symptoms should be verified by the demonstration of reversibility of airflow obstruction, EIB or other methods of diagnosing either indirect or direct bronchial hyperreactivity (BHR). The purpose of this study was to examine specificity and sensitivity of the methacholine challenge test (MCT) for the diagnosis of asthma in athletes.

Twenty seven athletes (16 M/11 F, mean age 22.0±4.3 yrs) with respiratory
symptoms were studied. Lung function with assessment of reversibility to salbutamol (n=27) and challenge tests with methacholine (n=25) were performed. The specificity and sensitivity of the MCT were evaluated.

**Subjects and methods:** Patients with respiratory symptoms raising suspicion of asthma and patients with partially controlled asthma underwent methacholine challenge (MC) using ATS Guidelines (1999). The test was considered negative for a PC20 >16 mg/mL and borderline for 8-16 mg/mL. Bronchial hyper-reactivity was considered severe for PC20 <0.125 mg/mL.

Pre-test probability of bronchial hyper-reactivity was recorded by the pulmonologist using visual analog scale (VAS) based on history, clinical findings and previous spirometry results; the scores ranged from 0 (no hyper-reactivity) to 10 (doubtful hyper-reactivity).

**Results:** 50 patients were evaluated. VAS scores and PC20 values differed significantly in the two groups:
- In the 26 patients with known asthma VAS scores were 5.1-10 (mean 7.6). MC showed moderate or severe bronchial hyper-reactivity in all subjects, with PC20 0.03-2 mg/mL (mean 0.56).
- In the 24 patients with suspicion of asthma VAS scores were 0.9-9 (mean 4.8). MC was negative in 13, borderline in 2 patients and showed bronchial hyper-reactivity in 9 (severe in 1, moderate in 5, mild in 3 patients; mean PC20 5.3).

A strong correlation was seen between VAS pre-test scores and PC20 values in the suspicion of asthma group (r=0.832, p<0.000) and a weak correlation in the known asthma group (r=0.389, p=0.049).

**Conclusions:** Pre-test clinical probability of bronchial hyper-reactivity recorded by the pulmonologist on visual analog scale correlated well with the PC20 values at methacholine challenge in patients with suspicion of asthma. However using mMRC to determine symptoms & GOLD stage for risk produced a significantly different distribution (A=20.3%; B=24.7%; C=5.0% and D=50.0%: p<0.001).

Data using mMRC score & exacerbation frequency was similar to that using GOLD stage and different to that using CAT with exacerbation frequency (p<0.0001).

**Conclusions:** Using either mMRC or CAT scores to determine symptoms results in a significant difference in the proportion of patients being categorised into the risk categories which will affect risk assessment and hence therapeutic choice. Longitudinal follow up and monitoring will enable the best method and threshold to be determined for patient management.
Conclusions: Both definitions, had longer time to sleep onset, lower sleep quality, more awake nighttime symptoms were more breathless (BDI domains, focal scores p < 0.0001 for all, both definitions). A significantly higher percentage of patients with nighttime symptoms reported sleep disturbance on SGRQ vs those without (p<0.0001 both definitions). Patients with nighttime symptoms were more breathless (BDI domains, focal scores p<0.002, both definitions), had longer time to sleep onset, lower sleep quality, more awakenings, difficulty falling back to sleep, less total sleep, and were less rested in the AM6778. Both definitions were those with some symptoms.

Conclusions: COPD nighttime symptoms are associated with impaired health status, breathlessness, and poor sleep. Clinicians should consider COPD nighttime symptoms when prescribing treatment.

P3219
Nighttime symptoms and reduced quality of life among COPD patients
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Aims: To assess the rate of decline of FEV1 over time in patients with GOLD stage 3-4 COPD and compare the rate of decline in non-smokers and smokers.

Methods: The primary outcome was the rate of decline of FEV1/year in current smokers versus non-smokers; secondary outcomes included the rate of decline in FEV1 at different stages of airflow obstruction. In a retrospective case series, we included patients with a primary diagnosis of COPD, GOLD stage 3–4 under regular review with 3 years spirometry data performed in the respiratory clinic using standard methods. The sample was divided into non-smokers, persistent smokers, and intermittent quitters.

Results: Data was available for 95 patients range 3-23 years. The rate of decline in smokers was significantly higher than non-smokers. The mean (SD) decline in FEV1 (ml/yr) was faster in earlier stages in GOLD2 53.2 (16.7); GOLD3 32.0 (29.7) and GOLD4 5.9 (7.2). In the overall sample the line of best fit of FEV1 over time was exponential. The rates of decline (mean (SD)) in non-smokers GOLD3 was 33.9 (35.3) and GOLD4 17.3 (51.3) and for smokers GOLD3 = 42.7 (34.5) and GOLD4 = 25.3 (NA).

Rate of decline in FEV1 in ml/year

<table>
<thead>
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<th>Number</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>25</td>
<td>99.1</td>
</tr>
<tr>
<td>Intermittent quitters</td>
<td>25</td>
<td>61.1</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>45</td>
<td>37.8</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>58.0</td>
</tr>
</tbody>
</table>

Conclusion: Even in late stages the decline in FEV1 is faster in smokers than intermittent quitters who declined faster than non-smokers. Unlike the Fletcher Peto diagram we found that the decline in FEV1 was faster in earlier than later stages. The benefits of quitting diminish as the disease progresses. To minimise lung damage it is essential identify people in early stages and for them to stop smoking immediately.

P2319
Comparison of quality of life scores with modified Medical Research Council (mMRC) dyspnoea scale using data from the European health-related quality of life study
Paul Jones1,2, Lukasz Adamek3, Gilbert Nadeau3, Norbert Banki3, 1Clinical Science, St. George’s University, London, United Kingdom; 2Respiratory Centre of Excellence, GlaxoSmithKline, Uxbridge, United Kingdom; 3Biostatistics and Epidemiology, GlaxoSmithKline, Munich, Germany.

The 2011 Global Initiative for chronic obstructive lung disease (GOLD) guidelines recommend a combined assessment for measuring the impact of COPD which considers current symptoms and future exacerbation risk. Two symptom cut-points are proposed using the COPD Assessment Test (CAT) score ≥ 10 and modified Medical Research Council (mMRC) dyspnoea score ≥ 2. There are currently no published data comparing CAT scores by different mMRC grades.

This analysis examined health status scores for CAT, St George’s Respiratory Questionnaire (SGRQ) and short form health survey (SF-12) Physical Component (PC) split by mMRC grade in a primary care population using data from the Health-Related Quality of Life in European COPD Study.

Data from 1817 patients (mean [SD] FEV1, 1.06 [0.6]; age 64.9 [9.6] years; males 72%) were used. The CAT, SGRQ and SF-12 PC scores are tabulated.

The mMRC showed a clear relationship with scores from the comprehensive generic and disease-specific measures. mMRC Grade 1 was associated with very significant levels of health status impairment. Even the patients with mMRC Grade 0 had modestly elevated CAT and SGRQ scores, which means that mMRC Grade 0 does not mean the absence of symptoms.

P3220
The effect of reducing breath holding time to assess diffusion capacity
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The single breath method to measure diffusion capacity requires a subject to inspire a gas mixture followed by a 10–2 second breath hold. However, dyspnoea may preclude measurement in patients with advanced pulmonary disease. We sought to determine if breath hold time reduction had a significant effect on measured DLCO values.

Forced spirometry and CO-diffusion by the single breath method were performed in duplicate with breath-holding for 10–2 seconds, 8.1±2 seconds and 6±2 seconds in 30 controls (FEV1, 107±2.04% predicted), 30 severe COPD patients (FEV1, 37.2±6.92% predicted), and 30 patients with interstitial lung disease (ILD) (FEV1, 69.5±17.61% predicted). There was no significant difference between DLCO(SB) and DLCO(VA) measured at 10, 8 and 6 seconds in the control (p=0.4431) and ILD groups (p=0.5915). However, there was a significant difference between DLCO(SB) (p=0.0003) and DLCO(VA) (p=0.0183) measured at 10, 8 and 6 seconds in the COPD group.

In the presence of severe airway obstruction the DLCO decreases with breath hold time reduction. However, in healthy controls and patients with ILD, there was no significant change in the DLCO when breath hold time is reduced from 10 to 6 seconds. This could allow for a reduction in breath hold time when measuring the DLCO in patients with advanced ILD who are unable to breathe hold for 10 seconds.

P3221
Reference values for respiratory system resistance in adults
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The degree of airway disease is usually determined in spirometry using mane-
vers that require quite some effort, i.e. FEV1 and FVC. Bodyplethysmography can assess airway obstruction during tidal breathing by determination of airway resistance. Reference values for resistance are, however, scarce. Within the embaphema versus airway disease (Eva) study we therefore have determined airway resistance in a population of 261 apparently healthy Caucasian subjects aged 45 to 75 with 163 males and 98 females. These were ex-smokers for more than a year or never smokers (27%) with no evidence of acute or chronic lung disease. We determined total resistance (Rt), inspiratory resistance (Ri), expiratory resistance (Rex) and specific resistance (Sr). Rex for the entire group was 0.22±0.11 kPaxsec/L (95 Percentile = 0.45) for males it was 0.20±0.12 kPaxsec/L and for females it was 0.26±0.12 kPaxsec/L. Rin for the entire group was 0.16±0.07 kPaxsec/L (95 Percentile = 0.29) for males it was 0.15±0.07 kPaxsec/L and for females it was 0.18±0.08 kPaxsec/L. Rin for the entire group was 0.19±0.09 kPaxsec/L (95 Percentile = 0.34).

The resistance values for the females as compared to males were significantly higher for all 4 types of parameters (p<0.001 each). As expected resistance parameters Rin and Rex showed a strong inverse correlation with FEV1 (mls). There was no impact of age or packyears. The data obtained can form the basis for the evaluation of airway resistance in obstructive lung diseases like COPD.

Supported by EU FP7 project #200506.

P3222
The longitudinal determinants of decline in COPD and asthma-COPD overlap in an Australian population
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1Priority Research Centre for Asthma and Respiratory, the Faculty of Health, The University of Newcastle, NSW, Australia; 2Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia; 3Woolcock Institute of Medical Research, The University of Sydney, Glebe, NSW, Australia

Longitudinal examination of the characteristics of COPD and asthma-COPD overlap will improve our understanding of these conditions and help identify the role of systemic inflammation (SI). We hypothesised that overlap and SI are associated with the greatest decline in FEV1, and health status.

Aim: To determine the association between the decline of FEV1, and other clinical outcomes over time.

Methods: A prospective cohort study with 4 year follow up. Participants with COPD and asthma-COPD overlap, underwent an assessment of spirometry, health status, and biomarkers of CRP and sputum cell counts at baseline and 4 years. Results: 84 (84%) of the original cohort were contactable, 41(41%) were re-assessed, and there were 15 deaths. The mean (SD) age at follow up was 72.2 (6.8) years. COPD and overlap diagnosis was 57.5% and 42.5% respectively. The mean difference in 2 years between the SI and MDW was 0.39 (0.77). 6MWD decreased by 42 (44.4) meters, Rin was a 2.2 (11.4) unit decrement in SGRQ. Changes did not differ by diagnosis. Those with SI (CRP >3 mg/L) at baseline had the greatest decline in SGRQ (diff 5.7 (2.4) versus -2.2 (2.5); p=0.03), but there was no difference in FEV1 decline. Mean (SD) baseline FEV1% pred (41.12.3) V 59.5 (18.0); p=0.0007, 6MWD (319 (100) V 440 (97); p=0.0001) and SGRQ (55 (16) V 42 (17); p=0.0009) was worse in the group that died compared to survivors.

Conclusions: Overlap asthma-COPD is not associated with increased functional decline. SI is associated with declining health status, suggesting a need to target treatment to low grade SI. Overall there was only slight health status and functional decline over 4 years, however the 15% that died had the greatest baseline impairment.

P3223
Association between COPD and other co-morbid conditions: Results from a 1-day, point-prevalence study in 2,04,912 patients from 860 cities and towns in India
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1Respiratory Research, Chest Research Foundation, Pune, Maharashtra, India; 2Respiratory, Cipla Ltd, Mumbai, Maharashtra, India

COPD is known to be associated with various systemic manifestations. We aimed to study the association between COPD and cardiovascular disease, diabetes, and anaemia in a cohort of patients from 22 states and 5 union territories in India.

Methodology: 13,225 general practitioners (GPs) and general physicians (Gen Ps) from 860 cities and towns were randomly selected and invited to participate in this 1-day point-prevalence, cross-sectional study. On 1st February 2011 all participating doctors captured details of age, gender, presenting symptoms and diagnosis of all patients who visited them. Clean data was transferred into the EPA INFO software and associations between COPD and other co-morbid conditions were analyzed using chi-square test.

Results: 24,000 doctors commented and provided clean data of 2,04,912 patients (M: 54.1%; F: 45.9%) who visited their clinic/hospital. Of these 6118 (3.0%) patients had COPD. Presence of doctor-diagnosed COPD was strongly associated with presence of chronic heart disease (CHD) (OR: 2.66 (2.3, 3.0; p<0.0001), Hypertension (HT) (OR:2.19 (2.0, 2.4; p<0.0001), Congestive Heart Failure (CHF) (OR:4.55 (3.5, 5.3; p<0.0001), Diabetes (OR: 1.71 (1.6, 1.9; p<0.0001)), Stroke (OR:2.17 (1.6, 2.9; p<0.0001), Arthritis (OR:1.34 (1.2, 1.6; p<0.0001) and Anaemia (OR:1.27 (1.1, 1.4; p<0.0001)). These associations remained even after adjustment for confounding factors.

Conclusion: COPD is strongly associated with the presence of CHD, HT, CHF, Diabetes, Arthritis and Anaemia in an Indian population.
using atomic force microscopy. Both, CAT questionnaire and ADO index were also assessed. Ten smokers with normal lung function were used as controls.

Results: On admission, E in COPD patients (956±422 Pa) is increased compared to controls (439±216 Pa) (p<0.05). Compared to admission, the 14 patients who completed the study improved lung function (FEV1 and PaO2), CAT score (from 23±6 to 13±6), C-RP values and number of leukocytes at convalescence; however, there were no changes in the 11 patients who recovered, no differences were observed between admission and recurrence (907±376 vs 881±359 Pa). A significant association between ADO index and E at admission in COPD patients (r=0.25) (Rho 0.60, p<0.05) was observed. These findings suggest that the rheological properties of neutrophils may be driven by a different underlying inflammatory response.

Supported by SEPAR - 2010, CIBERES Almirall and Esteve.

P3227 Phenotyping of patients with COPD from exhaled air by ion mobility spectrometry
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Background: COPD is a heterogeneous disease including several comorbidities. Different phenotypes have been proposed, among them patients with frequent exacerabations. We investigated whether an electronic nose is sensitive in the detection of such characteristics.

Methods: Thirty stable COPD patients and 26 control subjects breathed at rest into a special 6.5L tube via a valve. Analysis for VOCS was done online by ion mobility spectrometry (IMS, Siemens). It turned out that data could be condensed into 23 volatile compounds and 939 reading points (the retention time yielding a matrix of 23x693 signals. For each matrix element values were compared between groups or within COPD patients by Mann-Whitney-U-test at p<0.005. Columns with numbers of significant rows were considered as different. This handling of multiple testing of correlated data was based on bootstrap results indicating <2 differences occurring by chance at p=0.005.

Results: Ten columns differed between COPD patients and controls, 2 between COPD III versus II, and 2 between patients with (n=14) and without at least one exacerbation during the last year, while the distribution of COPD stages (FEV1) was similar in the latter patients. In single columns the number of significant rows much exceeded the threshold of 10. The analysis of comorbidities also suggested differences in IMS signals.

Conclusion: Breath profiles from a highly sensitive electronic nose correlated with COPD disease severity and characteristics. This might help in the non-invasive differentiation between COPD phenotypes.

Supported by the Competence Network Asthma/COPD funded by the Federal Ministry of Education and Research (FKZ 01GI0801 - 0888).

P3238 Sputum VEGF level increases with treatment of COPD acute exacerbation
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Introduction: The role of vascular endothelial growth factor (VEGF) in COPD pathogenesis has been studied widely; however the change in blood and airway VEGF levels during the treatment of an acute exacerbation has not been investigated. In this study we aimed to evaluate the changes in plasma and sputum VEGF levels during COPD exacerbation.

Methods: 14 subjects (64±10 years) with established COPD participated in the study. Spontaneous sputa and EDTA-plasma samples were collected for VEGF measurement at admission to hospital due to an acute exacerbation of COPD (Anthonisen type I-II) and also at discharge from hospital. During hospitalization (8±1.1 days) patients were treated with systemic corticosteroids (n=12) and/or with antibiotics (n=7). VEGF concentration was measured by ELISA. Data are shown as mean±SD and analyzed with parametric tests.

Results: Sputum VEGF levels positively correlated with FEV1 percent predicted (r=0.61, p=0.02) and FEV1/FVC (r=0.55, p=0.04) at baseline, whereas age, dyspnea, presence of bacteria in sputum, presence of emphysema, diffusing capacity and blood eosinophils higher than 2% were the most important linked if there was a statistically significant correlation between the two variables being explored. Dyspnea, presence of bacteria in sputum by polymorphonuclear reaction, leukocytosis, active smoking, pulmonary hypertension on echocardiography, PaCO2, inspiratory capacity to total lung capacity (ICTLC) and fibrinogen were the most important and interconnected nodes of the exacerbome on admission whereas age, dyspnea, presence of bacteria in sputum, presence of emphysema, diffusing capacity and blood eosinophils higher than 2% were the most important associated factors.

Conclusion: The present study supports the necessity of an novel approach to help understanding the heterogeneity of severe COPD exacerbation.

Supported by FSI 051463 and an unrestricted research grant from GSK.

P3320 Association of gastro-esophageal reflux disease symptoms with COPD severity and acute exacerbations of COPD
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Background: Gastroesophageal reflux disease (GERD) is common in COPD patients but there is little prospective data on the impact of GERD on COPD exacerbations.

Objectives: To evaluate the association of GERD and GERD-related therapy with disease severity and exacerbation frequency in COPD patients.

Methods: 1087 COPD patients and 392 controls were included. GERD symptoms were evaluated with GERD-Q questionnaire and treatment with proton pump inhibitors (PPIs) was recorded. All patients were contacted monthly and acute exacerbations of COPD (AECOPD) and hospitalizations for COPD exacerbations were recorded.

Results: The presence of significant GERD symptoms was more common in COPD patients compared to controls (25.4 vs. 9.0%, p<0.001) and was associated with more severe disease. Frequency of AECOPD and hospitalizations in 1 year was associated with GERD score (r=0.703, p<0.001 and r=0.723, p<0.001, respectively). COPD patients with GERD symptoms experienced more AECOPD and hospitalizations compared to patients without GERD symptoms (4.18±0.79 vs. 3.59±0.79, p=0.001). COPD patients receiving PPIs experienced less AECOPD and hospitalizations than COPD patients who did not receive PPIs, both in the presence of GERD symptoms (1.0±0.69 vs. 4.27±1.60 AECOPD, p<0.001 and 0.90±0.56 vs. 2.69±1.81 hospitalizations, FEV1=16 Pa, p<0.003) and in the absence of GERD symptoms (0.88±0.79 vs. 1.25±1.22 AECOPD, p<0.001, and 0.28±0.47 vs. 0.52±0.75 hospitalizations, p<0.01).

Conclusions: GERD symptoms are significantly associated with COPD exacerbations and treatment with PPIs is related to less exacerbations and hospitalizations.

Different factors may play a role in the pathogenesis of COPD exacerbations (ECOPD). The Exacerbations of COPD in Spain (ECOS) is a multi-center longitudinal study aimed to improve our understanding of the pathobiology and heterogeneity of ECOPD. We aimed to explore the weight and interaction of the different domains that are involved in the heterogeneity of the disease by building a network that link and relate all of them (exacerbome). In the ECOS study we included 99 patients in whom we obtained a battery of tests during hospitalization because of ECOPD, when clinically stable and after discharge. A selection of variables from the demographic, symptoms, lung function, biology, microbiology and imaging domains were analyzed and used to construct the exacerbome, where each node correspond to each of these variables, node size is proportional to the percentage of abnormal values of that particular variable and nodes were linked if there was a statistically significant correlation between the two variables being explored. Dyspnea, presence of bacteria in sputum by polymearce chain reaction, leukocytosis, active smoking, pulmonary hypertension on echocardiography, PaCO2, inspiratory capacity to total lung capacity (ICTLC) and fibrinogen were the most important and interconnected nodes of the exacerbome on admission whereas age, dyspnea, presence of bacteria in sputum, presence of emphysema, diffusing capacity and blood eosinophils higher than 2% were the most important associated factors.
Antibiotic use for hospitalized chronic obstructive pulmonary disease exacerbations: A propensity adjusted analysis

Isabelle Rault1, Florence Le Meunier 1, Coraline Hybiak 1, Houcine Bentayeb 1, Peter Wouters 2, Marie Bontenry 3, Eimeldin, London, United Kingdom; 4Respiratory Medicine, University of Dundee, United Kingdom; 5Respiratory Medicine, Doncaster Royal Infirmary, Doncaster, United Kingdom; 6Respiratory Medicine, Royal Infirmary of Edinburgh, United Kingdom; 7Respiratory Medicine, Ninewells Hospital, Dundee, United Kingdom; 8Respiratory Medicine, Perth Royal Infirmary, Perth, United Kingdom; 9Respiratory Medicine, St. John’s Hospital, Livingston, United Kingdom

Background: Antibiotics are frequently used in the treatment of chronic obstructive pulmonary disease (COPD) exacerbations. However, international guidelines suggest their use should be restricted to specific sub-groups based on the American Thoracic Society Criteria. The aim of this study was to assess the impact of antibiotic therapy on outcome in COPD.

Methods: We conducted a multi-centre prospective observational study assessing patients hospitalized with COPD exacerbation. Multivariable logistic regression was used to compare outcomes in patients treated with and without antibiotic therapy, including adjustment using a propensity score and adjustment for recognised predictors of 30-day mortality. The outcome of interest was 30-day mortality and length of hospital stay.

Results: Of 1031 patients included in the study, Median age was 74 years (interquartile range 63.75–81.78) and 48.7% were female. Mean FEV1 was 46% (standard deviation 19%). 30-day mortality was 5.4%. 818 patients (79.3%) received antibiotic therapy on admission (28.3% combined therapy, 76.6% monotherapy). Antibiotic prescribing based on American Thoracic Society criteria was Type 1: 84% patients received antibiotics. Type 2: 78.6% and Type 3: 70.3%. After adjustment for propensity to receive antibiotic therapy and recognised predictors of mortality, there was no association between antibiotic use and 30-day mortality (OR 0.96 (0.37-2.48), p=0.9) or length of hospital stay (p=0.8).

Conclusion: Antibiotic treatment is frequently used in hospitalised acute exacerbations of COPD. This study did not find any evidence of benefit in terms of mortality or length of hospital stay.

363. EBUS-TBNA: a never ending story

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Introduction: Although ROSE during EBUS-TBNA can reduce the puncture number and diagnostic accuracy in patients with suspected lung cancer.

Methods: We conducted a multi-centre prospective observational study assessing patients hospitalized with COPD exacerbation. Multivariable logistic regression was used to compare outcomes in patients treated with and without antibiotic therapy, including adjustment using a propensity score and adjustment for recognised predictors of 30-day mortality. The outcome of interest was 30-day mortality and length of hospital stay.

Results: Of 1031 patients included in the study, Median age was 74 years (interquartile range 63.75–81.78) and 48.7% were female. Mean FEV1 was 46% (standard deviation 19%). 30-day mortality was 5.4%. 818 patients (79.3%) received antibiotic therapy on admission (28.3% combined therapy, 76.6% monotherapy). Antibiotic prescribing based on American Thoracic Society criteria was Type 1: 84% patients received antibiotics. Type 2: 78.6% and Type 3: 70.3%. After adjustment for propensity to receive antibiotic therapy and recognised predictors of mortality, there was no association between antibiotic use and 30-day mortality (OR 0.96 (0.37-2.48), p=0.9) or length of hospital stay (p=0.8).

Conclusion: Antibiotic treatment is frequently used in hospitalised acute exacerbations of COPD. This study did not find any evidence of benefit in terms of mortality or length of hospital stay.

3254 Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing lung cancer: A randomized study

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Background: We realize a study about patients who get an EBUS-TBNA in 2011. On each of them, our nurses were asked to evaluate the efficacy of the EBUS aspiration through the macroscopic aspect of the sample. The nurses’ responses (RON) were: needle-aspiration negative or needle-aspiration positive. Nurses’ on site evaluations were compared with the final diagnosis obtained by the cytologist (ROC). Our nurses have an experience of EBUS-TBNA since 3 years in routine.

Results: 98 patients (72 men and 26 women) were included in this study. We realize 536 needle aspirations. The most often punctured areas were 7 (66/156, 42%) and 4R (34/156, 21.8%). Lung cancer was diagnosed in 52 of the 98 patients (53%) with most often adenocarcinoma (32/52).

Conclusion: On site evaluation by a non pathologist may optimize efficiency of EBUS-TBNA and is cost-effectiveness.

3256 Role of molecular and cellular techniques applied to EBUS-TBNA of mediastinal lymph nodes for lung cancer staging

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Introduction: Accurate NSCLC staging is of major importance since it dictates the choice of treatment and prognosis. EBUS-TBNA is a minimally invasive method to sample mediastinal lymph nodes. The most important identification of cancer biomarkers is important to improve EBUS-TBNA staging.

Aim: Assess the feasibility and role of EBUS-TBNA combined to the identification of tumour-associated antigens and tumour-associated immune responses to diagnose lymph node metastases and pathological characteristics in lymph node aspirates.

Methods: In a prospective study, EBUS-TBNA samples from 57 patients with confirmed or suspected lung cancer were analysed by cytopathology, flow cytometry (FACS) and reverse-transcriptase polymerase chain reaction (RT-PCR).

Results: All samples were adequately processed by the 3 different techniques. Among the 47 samples diagnosed with tumour cell by cytopathology, 70% showed the presence of cytokeratin-19 (CK-19) cells by FACS and 83% of the SCLC were CK-19 negative. CK-19 phenotype and gene expression were significantly correlated (r = 0.901) and cells with this phenotype also expressed CEA, sialyl Lewis X and CD44+ in 22.2%, 25.0% and 18.7% of cases. The expression of the EPCAM gene was significantly higher in the cytopathologically diagnosed cases (p = 0.03). The analysis of immune cells profile in the aspirates of these patients revealed a decrease in total leukocytes (p = 0.023) and a decrease in monocytes (p = 0.039).

Conclusions: The combination of molecular and cellular biology techniques with EBUS-TBNA might be a feasible option to improve NSCLC staging and offer an individualized diagnostic and therapeutic approach to lung cancer patients.

3257 Endobronchial ultrasound guided biopsy followed by real-time PCR is an applicable method to analyse SHOX2 methylation level in mediastinal lymph nodes of lung cancer patients

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Previous studies have shown that SHOX2 DNA methylation can potentially serve as a tumour marker in lung cancer patients. DNA methylation of SHOX2 could have been assessed in serum and bronchial aspirates. This study aimed to find out, if there is an opportunity to analyse SHOX2 DNA methylation level in lymph node tissue obtained by endobronchial ultrasound guided biopsy in context of diagnosis and lymph node staging.

Tissue from mediastinal lymph nodes was taken from ten patients with proven lung
In five cases the tissue was obtained by transbronchial forceps biopsy, in other five by transbronchial needle aspiration (TBNA). Samples were treated with lysis buffer, excluding the unmethylated 5hmC DNA from amplification. A real-time PCR duplex assay was then used to quantify the amount of total DNA, as well as methylated DNA. DNA was successfully extracted and analysed by real-time PCR. Valid measurements of SHOX2 DNA methylation level could be achieved in all samples, as well.

These outcomes allow comparing SHOX2 DNA methylation level in patients suspected to have lung cancer in further studies. DNA methylation level of SHOX2 by real-time PCR is an applicable procedure to analyse SHOX2 DNA methylation level in mediastinal lymph nodes of lung cancer patients.

3258

Endobronchial ultrasound-guided fine needle aspiration in the same procedure

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Introduction: Current papers show usefulness of a combined endobronchial and endoscopic ultrasound-guided fine needle aspiration (EBUS-FNA and EUS-FNA) of mediastinic adenopathies (1,2).

Aim: To analyse the initial results of EBUS-FNA of mediastinic adenopathies in a tertiary hospitals bronchoscopic unit.

Methods: Descriptive, prospective study of all the ecobronchoscopic procedures done May 2011-January 2012. EBUS-FNA was performed when no endobronchial accessibility of SHOX2 or its aspiration considered non representative by rapid onsite evaluation. Mediastinoscopy was performed when no diagnosis was yielded with the endobronchoscope.

Results: 54 patients underwent a bronchoscopic procedure in that period. In 9 cases EBUS-FNA was performed (16.7%). Region 7 in 4 cases and 4L in 5 cases were sampled. In every case we started with an EBUS exploration: 5 of them were non representative with EBUS-FNA and in 4 cases no accessible adenopathies were found with EBUS.

EUS-FNA yielded the following diagnosis: 3 non Hodgkin lymphomas, 2 lymphoid hypereplasia with atrophic lymph nodes (with posterior mediastinoscopic biopsies in which no evidence of malignancy was proven), 1 epithoroid lung cancer, 1 colorectal carcinoima’s metastasis, 1 sarcoidosis and 1 secondary amyloidosis. Every EUS-FNA was representative and no technique complications were described.

Conclusion: Every case in which EBUS-FNA was performed, was diagnostic, no false negatives were observed. This suggests that EUS-FNA done in the same procedure is beneficial in those procedures in which EBUS-FNA does not yield a conclusive diagnosis.

1Herth FJ et al. Chest. 2010;138:790-4

3259

Endobronchial ultrasound-guided sampling can be used for successful molecular sampling in routine clinical practice

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Introduction: The combination of EUS- and EBUS-FNA is a reasonable and safe technique for mediastinal restaging in NSCLC patients, and after our data, in patients with negative results of the continued endoscopic technique, a surgical restaging of the mediastinum might not be mandatory.

3261

Combined endosonographic staging followed by cervical mediastinoscopy in the real world, do we still need it?

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Introduction: The combination of EUS- and EBUS-FNA is an accurate preoperative staging method in NSCLC, challenging the status of cervical mediastinoscopy (CM) as the gold standard. In a recent RCT combined endoscopic staging (CES) had greater sensitivity compared to CM. After negative CES, a CM had to be performed in 11 patients to find one positive result (Annema JAMA 2010). Defranchi [JAMA 2010] found 4 patients (9.5%) with positive lymph nodes that were not found in the cervical staging. Defranchi had greater sensitivity compared to CM. After negative CES, a CM had to be performed in 11 patients to find one positive result [Annema JAMA 2010]. Defranchi [JAMA 2010] found 4 patients (9.5%) with positive lymph nodes that were not found in the cervical staging. After our data, in patients with negative results of the continued endoscopic technique, a surgical restaging of the mediastinum might not be mandatory.

1, Stanislaw Orzechowski1, Jerzy Soja 2, Juliusz Pankowski4 , 3, 4L – 27, 7 – 61, 8 – 4). CUS-NA revealed metastatic lymph node involvement in 7/63 patients. A total of 21 patients were found N2 positive after negative CM, of which 14 were N2+ nodes in the right paratracheal stations 2R and 4R, only accesible for EBUS. A diagnostic sensitivity, specificity, accuracy, PPV and NPV of the restaging CUS-NA was 62% (95% CI – 60–90), 95% (95% CI – 85–97), 80%, 91% (95% CI – 80–100) and 74% (95% CI – 71–91), respectively. No complications of CUS-NA were observed.

Conclusions: CUS-NA is a reasonable and safe technique for mediastinal restaging in NSCLC patients, and after our data, in patients with negative results of the continued endoscopic technique, a surgical restaging of the mediastinum might not be mandatory.
364. Treatment of lung cancer

3262 Bevacizumab (Avastin®) aerosol therapy (AT) inhibits primary and metastatic tumor growth in a murine model with human non-small cell lung cancer (NSCLC).

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Rationale: Avastin is used by systemic delivery only in lung cancer treatment, although the potential AT administration exists. AT of Avastin may increase drug concentration in the tumor and so augment the drug efficacy.

Objectives: To evaluate the effect of Avastin AT using mouse models of human (H1299) NSCLC.

Methods: An animal model of advanced disseminated NSCLC by orthotopically inoculated of cultivated human NSCLC cells into animal-lung was developed in our lab. AT was performed 5 times a week from day 5 to day 21 after inoculation using a jet nebulizer and a cage specially constructed for the inhalations. The dosages used were 0.05 mg/kg and 0.005 mg/kg of Avastin. The effect of nebulization on Avastin was assessed in terms of in vitro inhibition of tumor cell growth (XTT assay). In vitro growth of H1299 cells was mildly inhibited by AT Avastin (10%-20%).

Results: 40% reduction of lung/tumor weight and 50% inhibition of regional metastases was seen with Avastin AT. It was well tolerated by the animals without any gross pathological or histological changes in the heart, kidney, liver or spleen. Histological examination of the lungs showed congestion and hemorrhage in the 0.05 mg/kg treated animal, but only minimal findings were seen in the 0.005 mg/kg treated group. Hematological and blood biochemical examination were normal in the treated mice.

Conclusions: We demonstrated efficacy of Avastin aerosol treatment in animal model of NSCLC with minimal side effects. The study opens a new therapeutic approach by aerosolizing Avastin to treat patients with advanced disseminated lung cancer.

3263 Definitive radiation therapy for elderly patients with stage III NSCLC not candidates for combined chemoradiotherapy

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Purpose: Combined chemoradiation is the treatment of choice for locally advanced (stage IIIA-IIIIB) non-small cell lung cancer. However, elderly patients are frequently unable to tolerate this treatment; the benefit of radiation therapy (RT) alone for the management these patients is not well studied. Using population-based cancer data, we evaluated if use of RT alone is associated with improved survival of unresected stage III elderly NSCLC patients.

Methods: Using the SEER registry linked to Medicare we identified 13,522 patients 65+ years of age with unresected stage IIIA-B NSCLC diagnosed between 1992-2009. We excluded cases receiving chemotherapy as well as patients who could not be candidates for RT because they died within 4 weeks of cancer diagnosis. We determined propensity scores for patients receiving RT alone vs. no therapy based on their pre-treatment characteristics. Survival of patients treated with and without RT was compared using Cox regression adjusting for propensity scores. The odds for toxicity requiring hospitalization among patients treated with RT were also estimated, adjusting for propensity scores.

Results: Overall, 7,703 (57%) patients received RT. RT alone was associated with improved overall survival (HR: 0.76; 95% CI 1.00-0.80) and in analyses adjusting for propensity scores. RT treated patients had an increased adjusted risk of hospitalization for pneumonitis (OR: 136; 95% CI 1.18-928) and esophagitis (OR: 8; 95% CI 1.4-17).

Conclusions: These data suggest that definitive RT alone is associated with improved survival in elderly patients with unresected stage III NSCLC. RT was also associated with risk of severe toxicity.

3264 Histology as a potential clinical predictor of outcome in advanced non-small cell lung cancer (NSCLC) treated with vinorelbine and mitomycin (VM) chemotherapy combination

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Introduction: Histology has emerged as an important clinical predictive factor in patients with advanced NSCLC treated with chemotherapy.

Aims: To analyze combined patient level data from 2 phase II trials on efficacy and safety of VM in advanced or metastatic NSCLC, in order to determine histology and other patient and disease characteristics including gender, smoking history and TTF-1 immunohistochemistry (IHC) might be potential clinical predictors of outcome.

Methods: Response rates, undiagnosed survival times and Cox covariate adjusted hazard ratio estimates (HR) were calculated for each subgroup in each individual trial and in the pooled data set.

Results: A total of 175 patients were included in this retrospective analysis. Adjusted HRs for both overall survival (OS) and progression free survival (PFS) consistently favored non-adenocarcinoma (non-AC) histology subgroups, achieving statistical significance for OS in the pooled data (p=0.175; HR 0.677; 95% CI 0.488-0.938; p=0.019) and within one of those two trials (n=65; HR 0.561; 95% CI 0.318-0.988; p=0.045). TTF-1 negative IHC was associated with non-significant favorable OS compared to TTF1 positive subgroup in the cox-adjusted analysis (n=33; HR 1.233; 95% CI 0.55-2.730; p=0.608) and showed a significantly higher response rate (25% vs. 0%; p=0.040). Gender and smoking history were not strongly related to outcome.

Conclusions: These results suggest that non-AC histology and TTF-1 negative IHC may be considered as potential predictors of favorable clinical outcome in the treatment with VM. This approach warrants further investigation in a phase III study.

3265 A mRNA signature predicts outcome of patients (pts) with advanced non small cell lung cancer (NSCLC) treated with cisplatin (C) and vinorelbine (V): A ELCWP prospective study

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Background: C-based doublets are standard 1st line treatment for advanced NSCLC, without good predictor for response and survival, and important toxicity. Our aim is to identify a predictive mRNA signature for response to 1st line C (60 mg/m2 D1) + V (25 mg/m2, D1+8), by comparing mRNA expression between responders (R) and non responders (NR). Results: From 180 pts screened (04/2009 to 11/2011), 34 were assessable; 14 partial responses were observed. Fifty (fold change (FC) > 2) and 19 (FC > 3) mRNA were significantly differentially expressed between R and NR. After a stepwise variable selection, a two-mRNA signature predicted response with 93% sensitivity, 100% specificity, 100% PPV, 95% NPV. By restricting to the 19 mRNA with a FC > 3, a two mRNA signature predicted response with 100% sensitivity, 100% NPV, 70% specificity, 70% PPV. The two models have the same diagnostic performance (p=0.58). A 2 mRNA signature specifically predicting overall survival was designed using mRNA with a FC > 3. It distinguished pts with poor and good survival (HR for death 22.2, p < 0.0001).

Conclusion: mRNA signatures predict response and are prognostic for survival in pts with NSCLC treated with CV in 1st line. The validation of these results in an independent cohort, taking in consideration conventional prognostic factors, is ongoing.

3266 Combination of erlotinib and bevacizumab in non small cell lung cancer patients

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Bevacizumab and Erlotinib have recently been demonstrated to prolong overall survival in patients with non squamous NSCLC. We present the results of a 4 arm trial we designed to evaluate the efficacy and toxicity of the combination of docetaxel, carboplatin, bevacizumab(b) and erlotinib(e) in the first-line treatment of patients with NSCLC. 229, stage IIIb+IV, non squamous NSCLC patients were treated with 2 cycles of carboplatin (AUC5.5)+ docetaxel (100 mg/m2) (CT). After completion of two treatment cycles, pts were evaluated for response and divided into 4 groups: 61/229 continued with 4 more cycles of CT(control group), 52/229 received CT plus E 150mg daily, 56/229 received CT plus B 7.5mg/kg and 60/229 were treated with the combination of CT, E and B until disease progression. The primary endpoint was overall survival(OS).

In the 4 years follow up of the study, there was no statistical difference in survival and time to progression among four groups. After division of pts according to their response in responders and non responders after 2 cycles of chemotherapy, non-
responders who received additional therapy with bevacizumab or combination therapy had a survival benefit (65/4d (349-970) and 681/351-1921 respectively), which is statistically significant compared with the continuation of treatment with cytotoxic chemotherapy (p<0.001). The combination therapy had a comparable safety profile with that of B and E taken individually. Administration of BE±E in combination with first-line chemotherapy, followed by bevacizumab and erlotinib monotherapy as maintenance, has shown promising results in pts with NSCLC, with reduced toxicity as compared with chemotherapy alone, but did not translate into a longer OS.

3267
 TTФ-1 for prediction of response to chemotherapy in patients with locally advanced or metastatic small cell lung cancer (SCLC)

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Background: The thyroid transcription factor-1 (TTФ-1) plays a crucial role in differentiating primary lung from other cancers, especially in adenocarcinoma (AC). Furthermore, data indicate a possible association between TTФ-1-status and overall survival (OS) in AC patients. So far, no impact on OS was described in SCLC patients. Besides OS, it is unknown if the TTФ-1-status influences chemosensitivity of SCLC and might therefore predict response to chemotherapy.

Aim: To compare the response to chemotherapy in a population of patients with SCLC stage III/IV according to their TTФ-1-expression.

Methods: We analyzed 294 patients (f = 110; m = 184) with SCLC stage III/IV (according to UICC-6, stage III, n = 32; IIIB, n = 87; IV, n = 175) diagnosed in our institution between 01/05 and 12/08. Median age was 65 (±10) years. TTФ-1-expression was preoperatively determined. Response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0). The overall response rate (ORR) and the disease control rate (DCR) were calculated and compared between the group of TTФ-1-positive and TTФ-1-negative SCLC.

Results: The information on TTФ-1 and response to treatment was available in 178 (77%) cases. 150 (84%) had TTФ-1-positive and 28 (16%) TTФ-1-negative SCLC. Analyzing the ORR, we observed a better response to treatment for patients with TTФ-1-expression (DCR 90%) as compared to those with TTФ-1-negative SCLC (DCR 71%; p = 0.013). Regarding the ORR, there was no statistically significant difference between both groups (TTФ-1-pos. 75% vs. TTФ-1-neg. 71%; p = 0.642).

Conclusion: TTФ-1-expression may be associated with better response to chemotherapy in SCLC.

3268
 Primary lung cancer treated using radiofrequency ablation – One year outcome data

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Background: Percutaneous image guided radiofrequency ablation (RFA) is increasingly used as an alternative treatment option for patients with inoperable primary non small cell lung cancer (NSCLC) but there are little published outcome data. We report safety & efficacy of RFA in patients with NSCLC (stages I-IV) at 1 year.

Methods: Thirty-eight patients underwent 50 RFA procedures. Thirty-eight patients underwent 50 RFA procedures. Local progression & survival were evaluated prospectively at 3, 6, 9 & 12 months.

Results: Complications, local progression & survival were evaluated prospectively at 3, 6, 9 & 12 months. Statistical analysis was performed using log rank test & Cox regression analysis to determine hazard ratios with 95% confidence intervals (CI). Kaplan-Meier survival curves were plotted to show any differences in the survival pattern using Stata 10.1 (Statacorp, Texas USA).

Results: There were no cases of procedure related mortality. Complications included pneumothorax (61%) of which 10 patients (43%) had an iatrogenically created pneumothorax as part of the procedure, pleural effusion (5%) & respiratory failure (3%).

At 1 year, new (suspected) nodules observed in 21% (n=8), 88% of patients with tumours <3cm were progression free compared to 76.9% of tumours >3cm (p=0.36).

Mean time to progression for all cases 11.4 months (CI 10.7-12.1).

Overall & cancer specific 1 year survival were 86.8% & 92.1% respectively.

Conclusion: RFA is a safe, effective & well-tolerated treatment option in patients with inoperable primary lung cancer (stages I-IV).

3269
 Prognosis of patients with a lung cancer admitted in intensive care unit

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IMPRS (IMP) was a 24-wk, randomised, double-blind study comparing imatinib vs. PBO in 202 symptomatic pts with severe PAH despite ≥2 PAH-therapies with PVR >300 dyn s cm⁻5. A 3-yr open-label extension is ongoing. In the extension, IMP imatinib pts continued on maintenance dose (200 or 400mg once daily [QD]) while IMP PBO pts received imatinib 200mg QD, increasing to 400mg QD if tolerated. Data lock for the present analysis was 11 Nov 2011. 144/150 pts entered the extension (66 IMP imatinib, 78 IMP PBO). Median overall exposure in the extension was 276 days. At extension entry, mean±SD 6MWD had increased from IMP baseline by 43±55 vs. 5±63m for IMP imatinib vs. IMP PBO pts. In IMP imatinib pts, improvements in 6MWd were maintained after 48 wks of imatinib (24 wks in IMP + 24 wks in extension: 45±64m increase from IMP baseline [n=54]). In IMP PBO pts, 6MWd increased 16±4tm from IMP baseline after 48 wks imatinib in extension (n=20). There were 6 deaths in the extension, all in IMP PBO pts. AEs in the extension included nausea (36.8%), peripheral oedema (27.8%), peripheral oedema (22.2%), vomiting (22.2%), and nasopharyngitis (20.8%). SAEs in ≥3% of patients included RV failure (7.0%), dyspnoea (4.2%), worsening PAH (4.2%), syncope (4.2%), subdural haematoma (SDH, 4.2%) and device-related infection (3.5%). Unexpectedly, SDH occurred in 8 pts (2 in IMP, 6 in ext), all in patients on imatinib and anticoagulation. 5 pts with SDH recovered, 1 died of SDH and 2 died of unrelated causes. Efficacy and safety assessments continue every 6 months to provide additional data regarding benefits and risks of imatinib in advanced PAH. Imatinib is currently not approved for treatment of PAH.

365. Pulmonary circulation: clinical treatment
3272
The anti-proliferative effects of apelin on pulmonary adventitial fibroblasts
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Background: Pulmonary arterial hypertension (PAH) involves remodelling of the pulmonary artery resulting in right heart failure. Apelin is an endogenous peptide with physiological actions in the cardiovascular system. Pre-clinical models indicate that apelin deficiency may mediate or contribute to the pathogenesis of PAH which involves pulmonary artery fibroblasts (PAF).

Objectives: To determine if Apelin had an effect on the proliferation and migration of rat PAF.

Methods: PAF were isolated from Sprague Dawley rats. The PAF were incubated in normoxic and hypoxic conditions (35mMgHg for 24h) and proliferation in response to Apelin was assessed. The presence of the Apelin receptor (API) was detected by Western Blotting. PAF were also cultured to 100% confluency and the cell monolayer was scratched and cell migration was determined after incubation with apelin.

Results: API receptor was detected in PAF cells. Hypoxia alone increased the proliferation of PAF and this effect was abrogated with the addition of 200nM Apelin.

Conclusions: Apelin can reduce the increased proliferation of PAF to hypoxia and reduce the migratory capacity of these cells. Apelin may have anti-remodelling properties that require further investigation.

3273
Cicletanine in pulmonary arterial hypertension (PAH): Results from a phase 2 randomized placebo-controlled trial
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Cicletanine (CIC) is an anthrapyrazine with vasorelaxant and diuretic properties. Potential efficacy was observed with compassionate use of CIC in worsening PAH. A controlled study investigating the safety and efficacy of CIC for PAH was performed.

162 subjects were randomized to 12 weeks of placebo (n=61) or CIC at doses of 150 mg qd (n=39), 150 mg bid (n=40) or 300 mg qd (n=42). Subjects could be on stable doses of an endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, parenteral prostanoxol, or any 2-drug combination. The primary analysis was comparison of change in 6-minute walk distance (6MWMD) following 12 weeks of treatment with daily doses of CIC 300 mg (150 mg bid+300 mg qd; n=80) to placebo. Secondary analyses included dyspnea, WHO functional class, NT-proBNP, and a subset analysis of pulmonary hemodynamics (n=50).

The adverse events reported more frequently with CIC were nausea, hypokalemia, and fatigue, consistent with known properties of diuretics. Although CIC was generally well-tolerated, no improvements in exercise tolerance, symptoms or hemodynamics were observed in patients with PAH after 12 weeks of CIC treatment.
**3275**

**Pulmonary hypertension due to alveolar hypoventilation: Functional impact and improvement of haemodynamics and exercise capacity under non-invasive positive pressure ventilation**

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**Background:** For pulmonary hypertension (PH) due to lung diseases guidelines recommend treatment of the underlying disease. Due to preserved cardiac index (CI) in alveolar hypoventilation the functional impact of elevated pulmonary artery pressure (PAP) is not clear. The impact of non-invasive positive pressure ventilation (NIPPV) on exercise capacity of patients with PH due to alveolar hypoventilation is unclear.

**Objective:** To characterize the functional impact of PH due to alveolar hypoventilation and the haemodynamic and functional consequences of NIPPV.

**Methods:** Analysis of hemodynamics and functional capacity of 18 patients with daytime PH due to alveolar hypoventilation. The analysis included the data from baseline after a complete diagnostic work-up and after 3 months of NIPPV.

**Results:** Compared with a mean PAP of 49±12 mmHg, a CI (3.2±1.66), a 6-minute walking distance (6-MWD) of 303±13 m and severely elevated nt-pro-BNP levels, mPAP correlated negatively with maximal workload (R=−0.7166, p=0.029) and six-minute-walking distance (R=−0.621, p=0.010). Under NIPPV, we found a significant reduction of mPAP (17.75 mmHg, p=0.005), NT-pro-BNP serum levels (−2110 pg/ml, p=0.0014), improvement of the 6-MWD (+33 m and +131 m, p=0.0082) and maximal workload (+18 W, p=0.028). CI did not change significantly. Changes of workload and mPAP correlated negatively (R=−0.7545, p=0.0305).

**Conclusions:** Despite preserved CI elevated mPAP has a functional impact for patients with PH due to alveolar hypoventilation. NIPPV leads to a significant reduction of PH and improvement of exercise capacity.

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**3276**

**Improved right ventricular function after substantial afterload reduction in patients with pulmonary arterial hypertension**

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**Introduction:** In pulmonary arterial hypertension (PAH), increased load leads to right ventricular (RV) dysfunction. We showed that despite a modest reduction in pulmonary vascular resistance (PVR) after treatment, RV function can decrease resulting in poor prognosis1.

**Aims:** To characterize the functional impact of PH due to alveolar hypoventilation and the haemodynamic and functional consequences of NIPPV.

**Methods:** Analysis of hemodynamics and functional capacity of 18 patients with daytime PH due to alveolar hypoventilation. The analysis included the data from baseline after a complete diagnostic work-up and after 3 months of NIPPV.

**Results:** Compared with a mean PAP of 49±12 mmHg, a CI (3.2±1.66), a 6-minute walking distance (6-MWD) of 303±13 m and severely elevated nt-pro-BNP levels, mPAP correlated negatively with maximal workload (R=−0.7166, p=0.029) and six-minute-walking distance (R=−0.621, p=0.010). Under NIPPV, we found a significant reduction of mPAP (17.75 mmHg, p=0.005), NT-pro-BNP serum levels (−2110 pg/ml, p=0.0014), improvement of the 6-MWD (+33 m and +131 m, p=0.0082) and maximal workload (+18 W, p=0.028). CI did not change significantly. Changes of workload and mPAP correlated negatively (R=−0.7545, p=0.0305).

**Conclusions:** Despite preserved CI elevated mPAP has a functional impact for patients with PH due to alveolar hypoventilation. NIPPV leads to a significant reduction of PH and improvement of exercise capacity.

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**3277**

**Inhaled corticosteroids and bone mineral density in children: A prospective 12-year follow-up study after early-life wheezing**

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**Background:** Inhaled corticosteroids (ICS) are the drugs of choice for asthma. Corticosteroids can have many detrimental effects on bone mineralization and growth, despite of inhaled administration.

**Aims and objectives:** To evaluate the association between the long-term use of ICS in childhood and bone mineral density (BMD) in teenagers.

**Methods:** Ninety-one children hospitalized for wheezing at age <24 months were respectively followed until 12.2 (median) years of age. ICS use was collected by interviewing the parents, supplemented by data from patient records. Cumulative doses, the duration of ICS use and systemic steroid doses were calculated. At the last check-up, BMD (BMDareal, g/cm²) was measured by dual energy X-ray absorptiometry (DXA) in 89 children, and apparent volumetric BMDs (bMDvel, g/cm³) were measured for the lumbar spine and femoral neck. Height, weight and pubertal stage were recorded.

**Results:** The regular use of ICS at age <6 years was associated with a lower BMDareal of the lumbar spine (mean 0.76, 95%CI 0.71-0.81 vs. 0.88, 94.80-0.92; p=0.006). A lower BMDareal and bMDvel of the femoral neck were associated with higher cumulative doses of ICS at 0-12.2 (median) years of age. Pearson’s correlation coefficients were r (r2) = 0.320 (0.10) for BMDareal and r (r2) = 0.291 (0.08) for bMDvel. Age, sex and pubertal stage were significantly associated with both BMDareal and bMDvel, but did not confound the results.

**Conclusions:** The use of ICS during childhood may be related to a decrease in BMD at early teenage, though the clinical manifestations of reduced BMD usually occur later in adulthood.

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**3278**

**Inhaled corticosteroids and risk of oropharyngeal colonization by streptococcus pneumoniae in children with asthma**

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**Introduction:** Recent epidemiological studies have raised concerns about possible link between use of inhaled corticosteroids (ICS) and risk of pneumonia in patients with chronic obstructive pulmonary disease. This cross-sectional study aimed to investigate association between ICS and oropharyngeal colonization by Streptococcus pneumoniae (S. pneumoniae) among children (up to 18 years old) with asthma.

**Methods:** Two age-matched groups of patients were consecutively recruited: 1) Exposed group: children who had persistent asthma and were being treated with daily ICS for at least 30 days; 2) Non-exposed group: children who had asthma and were not being treated with ICS. Oropharyngeal specimens were measured before and after 4 weeks of treatment with oropharyngeal colonization by Streptococcus pneumoniae (S. pneumoniae) among children (up to 18 years old) with asthma.

**Results:** A total of 192 patients (96 in each group) were included in the study. In
the exposed group, the mean daily dose of ICS was 400 mcg of beclomethasone or equivalent and the mean duration of treatment was 8.6 months. The prevalence of oropharyngeal colonization by S. pneumoniae was higher among children exposed to regular use of ICS than among those exposed to reduced or frequent use of ICS. Parents of children with the lowest and highest adherence rates were identified. One group of (highly educated) parents deliberately did not use ICS according to doctor’s advice, but adjusted the ICS dose based on their perception of asthma control in their children, leading to regular use of ICS, but at a dose lower than prescribed. The other group of parents (most with lower educational levels) were faced with barriers impeding regular ICS use. These barriers included chaotic family life and parenting problems. A common and consistent finding was the low adherence rate in children 8-12 yrs of age, who were given full responsibility for taking their ICS without parental support or supervision. Conclusion: Assessment of ICS use in children with asthma prevents intentions of non-adherence, family driven barriers remain an important cause of non-adherence. The excessive responsibility put on school-aged children to organize their own ICS medication taking is a common and possibly modifiable barrier.

3281 Pulmonary immunoglobulin E levels and the response to anti-immunoglobulin E antibody therapy in paediatric severe therapy resistant asthma

Iman Al Darraji,1,2 Alios Spokes1,2, Cara Bossley1,3, Timothy Oates1,4 1Princess Amalia Children’s Clinic, Isala Klinieken, Zwolle, Netherlands; 2unit population of children with asthma Barriers to adherence to inhaled corticosteroids in a high adherent population of children with asthma

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TUESDAY, SEPTEMBER 4TH 2012

Background: Most acute wheezing episodes in preschool children are associated with viral respiratory tract infections, most commonly rhinovirus. Rhinovirus, like RSV, decreases extra-cellular ATP leading to airway surface liquid dehydration. This, along with sub-mucosal edema, mucus plaques and inflammation cause failure of mucus clearance (MC). Such preschool children do not respond well to available treatments, including oral steroids. This calls for pro-MC and pro-hydration treatment like hypertonic saline.

Methods: Randomized, controlled, double-blind study. Forty one children (mean age 31.9±11.7 months, range 1-6 years) were divided into two groups: (a) 20 children (median age 5.9 yrs, range 4-13 yrs) who were asked to use saline (0.9%) and (b) 21 children (median age 4.9 yrs, range 1-6 yrs) who were asked to use hypertonic saline (3%). Both groups were given a continuous nebulized saline (0.9%) or hypertonic saline (3%) mist in the early morning. Both groups received the same inhaled treatments. The primary outcome measured was length of stay (LOS) and secondary outcomes were admission rate (AR) and clinical severity score (CS). Results: LOS was significantly shorter in the HS than in the NS group: median (range) 2 (0-6) days, versus 3 (0-5) days (P=0.027). AR was significantly lower in the HS than the NS group: 62.2% versus 92%. CS improved significantly in both groups but did not reach significance between them.

Conclusion: HS inhalations significantly shortens LOS and lowers AR in preschool children presenting with acute wheezing episode to the ED.
cell recruitment, and protected from allergen-induced tissue inflammation and goblet cell metaplasia. Protection against asthma was achieved following delivery of modified mRNA either before or after the onset of allergen challenge, demonstrating its potential as both a preventative and a therapeutic. Mechanistically, Foscpx3 upregulation was critical in downregulating IL-23 and IL-17 production, and recombiant IL-23 or IL-17 expression during challenge abolished protection conferred by Foscpx3 mRNA. Taken together, our results provide evidence that chemically modified Foscpx3 mRNA protects against allergic asthma in vivo, which may pave the way for considering modified mRNA as a safe therapeutic tool for the treatment of asthma, allergy and beyond.

367. Cardiovascular disease and sleep-disordered breathing

3285 Prediction of cardiovascular risk from nocturnal pulse wave signal using the autonomic state indicator technology

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Introduction: Analysis of continuous physiological signals measured by pulse oximetry during sleep may provide a novel method to assess cardiovascular (CV) risk. The sleep period appears to be a particularly useful window for assessment.

Methods: Subjects (n=520, 346 males, age 55.0±13.4 y, BMI 29.9±6.1 kg/m²) were referred to five sleep centers in Germany and Sweden. CV risk factors were assessed and subjects were classified by the ESC/ESH risk matrix into five separate risk classes. The autonomic state indicator (ASI) algorithm extracted patterns of the peripheral pulse wave and SpO2 signal by amplitude and time/ frequency analysis from the overnight digital photoplethysmographic recording and computed a CV risk score (range 0.1–1.5) corresponding high levels of heart rate variability. Nine defined parameters (irregular pulse, RCDc, pulse rate variability, pulse wave variability, pulse propagation time, oxygen desaturations, duration of periodic symmetric desaturations and baseline SpO2) were used to determine the final score.

Results: In the validation group (n=390), the developed algorithm detected high CV risk in ESC/ESH scores 4 and 5 patients with a sensitivity of 74.5% and specificity of 76.4%. The area under the ROC curve was 0.80. The ASI CV risk score was elevated in patients with an already established CV endpoint (MI ±0.34, p<0.001). Successful TAVI had a significant impact on CSA, but not on OSAS; p<0.001. TAVI results (AI ≥ 2) presented with no change in OSAS (T 10.5±7.8% to 12.5±6.5%, p=0.5) and an increase in central respiratory events (26.3±13.2% to 29.2±18.4%, p=0.036). Conclusion: There is a high prevalence of OSAS and CSA in pts in TAVI candidates. Successful TAVI had no significant impact on OSAS, but improved CSA significantly. TAVI resulting in moderate to severe AI is accompanied by a deterioration of CSA. Presence of CSA after TAVI may indicate prognostically relevant haemodynamic alterations in AI and/or heart failure.

3286 Mortality in heart failure patients with nocturnal Cheyne-Stokes respiration receiving adaptive servoventilation (ASV) therapy

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Sleep-disordered breathing (SDB) with Cheyne-Stokes respiration (CSR) is of major prognostic impact in heart failure (HF) patients. Adaptive Servoventilation (ASV) therapy was recently introduced to specifically treat CSR in these patients. First results on mortality (time of death, left-ventricular assist device (LVAD) device implantation and heart transplantation (HTX)) of a prospective registry are presented.

A total of 186 HF patients (NYHA II ≤ LEF ≤ 45%, treated according to present HF guidelines, with nocturnal CSR) were referred to five sleep centers in Germany and Sweden. Mean age at inclusion (168 male, 91%) was 67.6±13.1 y, BMI 28.5±4.1 kg/m², NYHA functional class 2.6±0.6, NT-proBNP levels 2722±3.420 pg/ml, left ventricular ejection fraction 31±8% and peak VO2 during cardiopulmonary exercise testing 14.4±4.7 ml/kg/min. AHI before ASV initiation was 38.8±14.8, apnoea-index 22.2±15.2. After 20.7±6.1 months a total of 35 patients (18.8%) reached an endpoint: 28 (15.1%) died, 6 (3.2%) received HTX and one (0.5%) LVAD implantation. Within the follow-up period, ASV therapy was discontinued by 26 patients (14.0%) and 15 patients (8.1%) met indication for cardiac resynchronization therapy (CRT).

Mortality in HF patients with nocturnal CSR and ASV treatment remains high. If there is any reduction in mortality and/ or hospitalization is currently be investigated by 2 randomized controlled trials, first results are not expected before 2014. With 14% discontinuation, ASV therapy seems to be well tolerated and accepted.

3287 Sleep-disordered breathing in patients undergoing transfemoral aortic valve implantation for severe aortic stenosis

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Purpose: We examined the prevalence of sleep-disordered breathing (SDB) in patients (pts) with severe aortic valve stenosis before and after transfemoral aortic valve implantation (TAVI).

Methods: 79 pts (50% males, average age 83.0±6.3 years) had cardiorrespiratory polygraphy (PG) screening before TAVI. 62 of them (48.4% males, mean age 82.5±6.9 years) underwent a second PG screening 21.0±4.7 days after TAVI.

Results: 49 (62.0%) pts had OSAS, 25 (31.6%) and only 5 (6.3%) presented without significant SDB (apnoea-hypopnoea-index, AHI <5.0). Of 62 pts evaluated before and after valve implantation 36 (58.1%) had OSAS, 21 (33.8%) presented with CSA and no SDB was detected in 5 pts (8.0%). SDB was more severe in CSA compared to OSAS (AHI 34.5±18.3 vs 18.0±12.6, p<0.001). Successful TAVI had a significant impact on CSA, but not on OSAS; pts with optimal TAVI results (aortic valve regurgitation, AI ≤ grade 1) demonstrated a significant reduction of central respiratory events (39.6±19.6% to 23.1±16.0%, p<0.05), while no changes were detected regarding OSAS (18.8±13.0% to 20.2±15.3%,p=0.40). Pts with prismatic CSA-TAVI results (AI ≥ 2) presented with no change in OSAS (10.5±7.8% to 12.5±6.5%, p=0.5) and an increase in central respiratory events (26.3±13.2% to 29.2±18.4%, p<0.036).

Conclusions: There is a high prevalence of OSAS and CSA in pts in TAVI candidates. Successful TAVI had no significant impact on OSAS, but improved CSA significantly. TAVI resulting in moderate to severe AI is accompanied by a deterioration of CSA. Presence of CSA after TAVI may indicate prognostically relevant haemodynamic alterations in AI and/or heart failure.

3288 PAI-uPA system in patients with obstructive sleep apnea syndrome (OSAS) in CPAP treatment

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Background: Prothrombotic state in OSAS play a role for cardiovascular risk. Plasminogen activator inhibitor (PAI) is one of the primary regulators of the fibrinolytic system. We evaluated plasma levels of PAI and PAI/uPA and their correlation with Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI) and percentage of time with SpO2<90% (T<90%) before and after 1 month with CPAP.

Methods: Thirty-nine patients (age 57±1.54; BMI 34.5±1.07) with OSAS (AHI 28.4±3.16; ODI 35.7±3.4; T<90% 23.1±3.3) 20 smokers (S) and 19 no smokers (NS), and 16 age matched healthy control subjects were studied. Before and after 1 month with CPAP, uPA and PAI were measured in serum by ELISA.

Results: At baseline, PAI levels were higher in OSAS compared to controls (95.36±3.99 and 83.96±6.06 ng/ml, respectively). PAI levels were similar in S and NS subjects and were inversely related to AHI, BMI, ODI and T<90% in OSAS. PAI was higher in S compared to NS subjects; moreover, it was slightly higher in the controls compared to the OSAS (S 0.23±0.03, NS 0.22±0.02; S 0.206±0.01, NS 0.182±0.02 ng/ml, respectively). In OSAS uPA levels were inversely related to AHI, BMI, ODI and T<90%; uPA/PAI ratio was higher in controls compared to OSAS. PAI levels after CPAP slightly decreased, while uPA levels slightly increased. We observed an increase in uPA/PAI ratio from 1.90±0.04 and 2.56±0.55 to 2.14±0.32 and 3.14±0.79, in S and NS patients respectively.

Conclusions: Our preliminary data are compatible with an impairment of fibrinolytic activity in OSAS. The increase of uPA/PAI ratio after CPAP suggests a role of the PA system in the reduction of cardiovascular risk through the decrease of the prothrombotic state.
3289
Treatment of central and obstructive sleep apnea in stable heart failure patients with auto-ventilator reduction severe sleep fragmentation – A randomized controlled trial
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Background: It is of debate, whether treatment of central sleep apnea (SA) reduces sleep fragmentation. Therefore, we tested, whether auto-ventilator reduction (ASV, BiPAP-ASV, Philips Respironics) reduces sleep fragmentation in heart failure (HF) patients with severe central or obstructive SA.

Methods: 42 patients with HF (age 66±9y, LVEF <40%) and SDB (apnea-hypopnea index, AHI 48±19/h, 51% central SA) were randomized to either ASV (n=21) or optimal medical treatment alone (control, n=21). Polysomnography (PSG) and 5 days of actigraphy with centralized scoring by blinded raters were obtained at baseline and 12 weeks.

Results: In the ASV-group AHI and central AHI were significantly suppressed compared to the control-group (-41±12/h, ±p<0.001 and -24±14/h, ±p<0.001, respectively). The arousal index (AIr), sleep stage 1 (S1), PSG and the fragmentation index (actigraphy) were significantly reduced (-14.7±2.1/h versus 2.6±13.3/h, ±p=0.032 and 36±47 versus -6±41 min, ±p=0.005 and -11±4.6±10 versus -2.9±4.9 h, ±p=0.002, respectively) and sleep efficiency (SE) and daytime activity duration (actigraphy) significantly increased in the ASV-group compared to controls (5.2±1.0 vs. 1.0±1.0 h, ±p=0.01 and 21±4.5 vs. 24±4.1 min, ±p=0.009, respectively). Effects of ASV on AHI, S1, SE and daytime activity duration were similar in HF patients with obstructive and central SA (p>0.05 for all comparisons).

Conclusions: ASV-treatment significantly improves sleep fragmentation similarly in HF-patients with either central or obstructive SA. These effects were associated with a modest increase of daytime activity duration.

3290
Tea sound intensity relates to daytime high blood pressure in non-apneic snorers
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Background: The relationship between snoring and cardiovascular diseases had been assumed to be due to existing sleep-disordered breathing (SDB). Recently, we have reported that snoring sound intensity as assessed by ambient sound (TS-Leq) was 1.74 in the non-apneic normal-weight patients. It may suggest a pathologic role of non-apneic snoring.

Conclusions: The increased heart rate and the higher prevalence of dysmhrhythmias at altitude are consistent with increased sympathetic tone associated with hypoxemia. AC reduces bradyarrhythmias at altitude, possibly by improving sleep disordered breathing. Grant: Swiss National Science Foundation; Lung League of Zurich; Clinical Trials Center, University Hospital of Zurich, Switzerland.

3292
Impact of CPAP treatment on the changes of maxki+ k channel beta subunit-1 expression in patients affected by sleep apnea-hypopnea syndrome (SAHS)
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Regulatory function on the vasodilatation of the maxki+ k channel beta subunit has been described in mouse model. CPAP treatment was shown to be related with an increase of the beta subunit expression.

Objective: To determine the relations between oxymetric and endothelial situation and subunit beta1 expression in the moment of recruitment and after 3 month of CPAP in SAHS patients.

Methods: The study population consisted of 43 OSA patients living at 600m altitude. We included patients with severe central or obstructive SA. CPAP was titrated to control AHI <5/h, at altitude on placebo, heart rate was higher and dysrhythmias were more prevalent than at 490m. AC reduced bradyarrhythmias, apnea/hypopneas and improved oxygen saturation (table).

Dysrhythmias, oxygen saturation and breathing disturbances

490m Altitude, placebo 490m Altitude, AC
Heart rate, bpm 67 (60; 76) 75 (68; 83)* 73 (67; 81)*
Blood pressure events, 1/d 0.0 (0.1) 3 (0.178) 0.0 (0.179)
Ventricular extrasystoles, 1/d 24 (18, 30) 31 (4; 428) 26 (24; 29)*
Asthma and/or urticarial events, 1/d 0.0 (0.1) 0 (0.1) 0 (0.2)
Nocturnal oxygen saturation, % 93 (92; 94) 87 (86; 89)* 89 (87; 91)*
Apnea-hypopnea index, 1/h 51 (42, 73) 70 (56, 89) 54 (46; 63)*

Conclusions: The increased heart rate and the higher prevalence of dysrhythmias at altitude are consistent with increased sympathetic tone associated with hypoxemia. AC reduces bradyarrhythmias at altitude, possibly by improving sleep disordered breathing.

3293
Ventilatory response to hypercarbia in newborns of smoking and substance abusing mothers
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Infants of smoking and substance abusing mothers have an increased risk of sudden infant death. A possible explanation for the association is that such infants have neurodevelopmental abnormalities which adversely affect the control of ventilation.

366. New developments in paediatric respiratory physiology

3294
Acetazolamide improves cardiac dysrhythmias in patients with obstructive sleep apnea at altitude. A randomized controlled trial
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Background: Untreated lowlanders with obstructive sleep apnea syndrome (OSA) benefit from acetazolamide (AC) during an altitude stay in terms of improved nocturnal oxygenation, breathing disturbances and sleep quality (Nussbaumer-Ochsner, Chest 2012). The current study evaluates whether AC reduces the increased rate of cardiac dysrhythmias at altitude.

Methods: 43 OSA patients living at ≤600m discontinued CPAP 3 days before baseline examination at 490m and during 2 altitude sojourns at 1860-2500m for 3 days each, one on AC 2x250mg/d, the other on placebo, according to a randomized cross-over design. Holter ECG and polysomnography were performed at 490m and at altitude.

Results: At altitude on placebo, heart rate was higher and dysrhythmias were more prevalent than at 490m. AC reduced bradyarrhythmias, apnea/hypopneas and improved oxygen saturation (table).

Dysrhythmias, oxygen saturation and breathing disturbances

490m Altitude, placebo 490m Altitude, AC
Heart rate, bpm 67 (60; 76) 75 (68; 83)* 73 (67; 81)*
Blood pressure events, 1/d 0.0 (0.14) 3 (0.178) 0.0 (0.179)
Ventricular extrasystoles, 1/d 24 (18, 30) 31 (4; 428) 26 (24; 29)*
Asthma and/or urticarial events, 1/d 0.0 (0.1) 0 (0.1) 0 (0.2)
Nocturnal oxygen saturation, % 93 (92; 94) 87 (86; 89)* 89 (87; 91)*
Apnea-hypopnea index, 1/h 51 (42, 73) 70 (56, 89) 54 (46; 63)*

Conclusions: The increased heart rate and the higher prevalence of dysrhythmias at altitude are consistent with increased sympathetic tone associated with hypoxemia. AC reduces bradyarrhythmias at altitude, possibly by improving sleep disordered breathing.

Grants: Swiss National Science Foundation; Lung League of Zurich; Clinical Trials Center, University Hospital of Zurich, Switzerland.
Aims: To test the hypothesis that infants of substance abusing mothers (SA) and of smoking mothers (SM) compared to infants of non substance abusing, non-smoking mothers (controls) would have a poorer ventilatory response to hypercapnia.

Methods: Infants were assessed before maternit/neonatal unit discharge. Respiratory flow (and tidal volume) was measured using a plethysmograph inserted into a face mask placed over the infant’s mouth and nose. The ventilatory responses to three levels of inspired carbon dioxide (baseline = 0%, 2% and 4% CO2) were assessed.

Results: 8 SA, 15 SM and 15 control infants were assessed. The birth weight of the SM group was higher than the SA group (p=0.01). At baseline SA infants had a higher respiratory rate (p=0.03) and minute volume (p=0.049) compared to controls and SM infants (Table). Both the SA and SM infants had a lower respiratory response to 2% CO2 (p=0.02) and 4% (p=0.004) CO2.

Conclusion: These results are consistent with infants of smoking and substance abusing mothers having a damped ventilatory response to hypercapnia.

3294 The acute effect of surgical repair of mitral valve insufficiency on airway and respiratory mechanics and pulmonary hemodynamics in children Iliona Malaspinas, Lionel Chok, Maurice Begaht, Wald Halbre, Ferenc Petek.

Introduction: Increased pulmonary blood flow and pressure were shown to be responsible for the lung function impairment in children with congenital heart diseases. We investigated the acute effect of surgical repair of the mitral valve insufficiency (MVI) leading to postcapillary pulmonary hypertension is reflected in the mechanical properties of the respiratory system, and whether surgical repair of MVI improves respiratory mechanics in children.

Methods: Airway resistance (Raw), respiratory tissue damping (G) and elastance (E) were measured using the multiple breath inert gas washout (MBW) technique in 25 children with MVI under general anaesthesia before and immediately after surgical repair of the MVI. Concomitantly, pulmonary arterial pressure (PAP) was directly measured in the pulmonary artery before aortic cannulation and chest closure.

Results: Surgical repair of MVI led to a significant decrease in the mean PAP for a decrease (from 33.0 ± 5.2 to 22.0 ± 4.8 mmHg, p=0.004). These postoperative pulmonary haemodynamics changes were associated with significant decreases in Raw (5.5 ± 1.1 to 4.4 ± 1.1 cmH2O/l, p=0.008) with no significant effects on G (11.5 ± 5.2 to 10.1 ± 3.1 cmH2O/l, p=0.07) and H (60.2 ± 9.5, 65.2 ± 13.7 cmH2O/l, p=0.2). Postoperative changes in Raw and PAP exhibited no significant correlation.

Conclusion: These results demonstrate an immediate improvement of airway function after surgical repair of MVI in children. Further experiments are needed to clarify the direct effect of the postoperative decrease in postcapillary pulmonary hypertension and vascular engorgement in this beneficial change. The acute effect of surgical repair of mitral valve insufficiency on airway and respiratory tissue mechanics and pulmonary hemodynamics in children.

Regional pulmonary function testing by electrical impedance tomography in healthy children and children with asthma Barbara Vogt, Gunnar Elke, Philipp von Bismarck, Tobais Ankermann, Norbert Weiler, Ian Frenich.

Introduction: Electrical impedance tomography (EIT) is able to assess regional dynamic lung volume changes and to determine spatial distribution of lung function in the chest cross-section. The aim of our study was to examine the regional lung function in healthy children and children with asthma before and after exercise.

Materials and methods: 10 healthy children (11±3 yr, mean±SD) and 10 children with asthma (12±3 yr) were examined by EIT during conventional pulmonary function testing at baseline and after stairs running for 5 min. EIT data were acquired at 33 scans/s (GE-MF CareFusion, Höchberg, Germany). Regional forced vital capacity (FVC), forced expired volume in 0.5 s (FEV0.5) and tidal volume (VT) were determined in 912 EIT image pixels before and 3 min after exercise. Spatial heterogeneity of ventilation was characterized by the coefficient of variation (CV) calculated from all pixel values of FVC, FEV0.5 and VT.

Statistical analysis: A Mann-Whitney test was used to compare the non-parametric data between healthy children and children with asthma. Children with asthma were divided into three groups: non-atopic children, atopic children and children with severe atopy.

Results: Significant exercise-dependent differences in CVFVC were found in both patient groups whereas CVFEV0.5 and CVVT were not affected by exercise. CVFVC was significantly different between the healthy children and children with asthma after but not before exercise. CVFVC and CVVT were not significantly different between the groups both at baseline and after exercise.

Conclusion: EIT detected regional lung function differences between healthy children and children with asthma during forced full expiration. Future analysis should aim at characterization of peripheral airways by novel EIT-derived measures of regional lung function.

3297 Ventilation inhomogeneity in children with cystic fibrosis and primary ciliary dyskinesia Bettina Greil, Frederik Bachwald, Astrid Mader, Per Gustafsson, Kim N. Nielsen.

Introduction: The diagnostic value of the FOT depends on breathing. Inspira- tion usually provides better breathing. The information may be important to improve the diagnostic of asthma based on bronchial reversibility.

Methods: A cross sectional study was performed in 24 children with PCD and 25 with CF, matched by age and FEV1. N2 MBW in triplets (Exhalyzer D, EcoMedics AG) and spirometry were performed within one occasion in clinically stable patients. Lung Clearance Index (LCI), an index of global VI, and specific indices of VI arising in the conductive (Scond) and the acinar (Sacin) airway zones were measured. The aim at characterization of peripheral airways by novel EIT-derived measures of ventilation inhomogeneity to children with CF and PCD.

Results: There was no significant difference in LCI, Scond and Sacin (z-scores) between the two patient groups, although LCI, z-scores tended to be higher in PCD (Table 1).

Conclusion: In contrast to our expectations severity of peripheral airway involve- ment is similar in children with CF and PCD.

Ways to shorten the lung clearance index measurement II – How long to wash?
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Background: Inert gas multiple-breath washout (MBW) derived lung clearance index (LCI) is a sensitive lung function parameter in subjects with mild cystic fibrosis (CF) lung disease, but rarely measured in clinical routine due to lack of available equipment and lengthy protocols. Using an available nitrogen (N2) MBW setup (Exhalzyler D, Eco Medics, Switzerland), we assessed shortened N2MBW protocols for LCI.

Methods: Thirty-three school-aged children with CF and 21 controls performed triplicate N2MBW measurements. LCI was calculated as cumulative expired volume over functional residual capacity determined during N2MBW at 9% (1/11th) and 2.5% (1/40th, the current standard) end-tidal N2 concentration.

Results: LCI differed significantly between healthy and CF children at both concentrations. The 9%-LCI was modestly associated with final 2.5%-LCI (R2 = 0.7) but took less time and was of similar diagnostic value. Comparing 9%- and 2.5%-LCI, mean (SD) test duration was 1.0 (0.9) and 2.2 (1.0) min; mean (95%CI) area under the receiver operating characteristic curve was 0.9 (0.8-0.9) and 0.8 (0.8-0.9), and upper limits of normal LCI (4.5 and 8.4) correctly classified 72% and 74% of children, respectively. Mean (SD) coefficient of variation was 5.7 (3.9)% for 9%-LCI and 5.7 (3.2)% for 2.5%-LCI.

Conclusion: LCI determined at 9% end-tidal N2 concentration during N2MBW is (3.9)% for 9%-LCI and 5.7 (3.2)% for 2.5%-LCI.

appropriate pediatric lung function reference equations for ethnic minorities are lacking. We investigated the extent to which differences in body proportions as indicated by the sitting/standing height ratio (Sit/Stand Ht) explain ethnic differences in FEV1.

Methods: As part of the SLIC study (commenced 2011), standard anthropometry including sitting height and spirometry were assessed in multi-ethnic London school children. FEV1 was expressed in Z scores to adjust for sex, age and height (Stanojevic2009). Statistical analysis was by univariable and multivariable regression.

Results: 379 healthy children (age: 5-10y, 43% boys; 31% White, 44% Black, 11% Asian –0.5 (–0.7; –0.2) –0.3 (–0.6; –0.1), other –0.5 (–0.7; –0.2) –0.3 (–0.6; –0.1).

Conclusion: This study shows that Sit/Stand Ht accounts for some of the differences amongst ethnicities in FEV1, and provides further evidence that sitting height should be an essential part of standard anthropometry. Further work to explore the extent to which differences in body shape, size and composition contribute to ethnic differences in lung function is in progress.
after virtual resection, these data did correlate well with the observed postoperative data ($R^2=0.88<0.01$, $R^2=0.55<p<0.01$; $R^2=0.45,p<0.01$).

**Conclusion:** RFI does provide insights in the influence of LRS on the postoperative airway volumes, resistances and internal flow redistribution and can be used to predict postoperative lung mechanics.

### 3.302

**Intraoperative marking of a small pulmonary nodule with the multi-axis angiography system.**

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**Introduction:** Often cases are difficult to identify the localization of small pulmonary nodule during operation. preoperative CT guided marking have been described. However, there were some problems including iat embolism, pneumothorax or detection ratio. Now, we used Artis zeego (Siemens co ltd, Germany) which drew up a CT-like image during operation to determine the localization of the pulmonary nodules. This is the first report of intraoperative marking using the Artis zeego.

**Material:** Artis zeego is the first multi-axis angiography system based on robotic technology that can be positioned the way a physician wants. It can be controlled with far greater ease and precision than conventional C-arm system.

**Methods:** The patient was fixed lateral position under general anesthesia, and was sterilize and draped on the operation table. After marking to the pleura where was predicted the nearest portion from the nodule with a clip under the VATS view, Artis zeego was entered and provide a CT-like image. After Artis zeego was disconnected from the patient, the excision region was determined by the image.

**Results:** Four patients, five small pulmonary nodules were performed this procedure. All regions were successfully detected by the image and removed completely. Since this system did not provide to detect pulmonary regions, there were some problems including narrowing of the bed for lateral position, the little device, the elbow or equipments were easy to strike on the machine when rotation.

**Conclusions:** This procedure could be an extremely useful and safety method for intraoperative marking a small pulmonary nodule. We also need to resolve some problems of this procedure such as the devices.

### 3.303

**The concept of prevention of postoperative respiratory complications in lung surgery.**


**Objectives:** Disciform atelectases can be a predictor of a severe postoperative respiratory complications. The aim of the study was to elaborate a set of measures aimed at prevention of these complications in patients subjected to operations on the lungs.

**Materials and methods:** We compared two comparable (in terms of surgery, comorbidities, age) groups of patients underwent lung resection. Two modes of ventilation were used during the operation. In group I (n = 313) ventilation regimen was CMV, standard techniques were used to create expiratory training with PEEP 2. In group II (n = 310) high frequency jet ventilation (HFJV) was carried out (VT = 2 ml; k g-1; f = 100 min-1; I: E = 1:2). In the postoperative period in group I traditional ventilation was conducted. In group II non-invasive mechanical ventilation (Noninvasive HFJV) was used in Continuous Positive Airway Pressure mode (VT = 2 ml; k g-1; f = 300 min-1; I: E = 1:1), inspiratory training was applied. Chest radiograph was undertaken next day after surgery.

**Results:** In Group II, compared with the group I reduction in the incidence of disciform atelectases was noted in first two days after surgery by 3.4 times.

**Conclusion:** On the base of the results obtained we formulated the concept of prevention postoperative respiratory complications after lung resections, which is as follows: 1.Intraoperative - conducting HFJV mode VPN, 2. On the first day after surgery, x-ray control to detect the beginning of the disciform atelectases 3. Holding in the immediate postoperative period of non-invasive mechanical ventilation in mode CPAP/PEEP 4. In the delayed postoperative period breathing exercise to improve the expanding of the lungs.

### 3.304

**Exercise test as preoperative predictor before pulmonary resection surgery.**

Bret Daniel,1 Numa Roa,3 Elena Lopez4 Santa Maria, Maria Alice 1, Juan B Galder1.1 Pulmonary Dpt, Cruces Hospital, Barakaldo, Bizkaia, Spain; 2Pulmonary Dpt, Cruces Hospital Cibers, Barakaldo, Bizkaia, Spain

**Exercise test (V02) before pulmonary resection surgery was incorporated into the new guidelines (A.Brunell Eur Respir J 2009; 34: 17-41) in the case that the patient presents a FEV 1 and/or TICO < 80% predicted, assuming that the exercise test reproduce the situation of cardio-respiratory overload that occurs during the surgical intervention.

**Material and methods:** Prospective descriptive study, three months, which included 48 patients evaluated for possible lung resection due to lung neoplasms who presented values less than 80% in the FEV 1 or TICO and performed a maximum exercise test to complete the preoperative assessment.

**Results:** Mean age (65±8 years); 41 M, 7F. According to the retrieved V02 patients were divided in 3 groups and comparing the values of the FEV 1 and TICO in each group Table 1.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>FEV1</th>
<th>TICO</th>
</tr>
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<tbody>
<tr>
<td>0-10 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11-20 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>21-30 years</td>
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</table>

25 patients presented a DLCO and FEV1% < 80%, of them 4 presented a V02 between 10-15, 14 between 15-20 and 7 > 20. Correlations between FEV1 VS V02(0.478,P < 0.001) and V02 VS TICO(0.287, P <0.065).

28/48 patients were operated and in the postoperative follow up (1 month) there was no death and 8 (28.5%) of them had postoperative complications (2 empyema, 2 hemothorax, 1 fistula, 2 pneumonia, 1 respiratory failure). These patients presented the following functional parameters FEV1 (166±74), DLCO 51±8, 17.4 ml/kg/min V02.

**Conclusions:** Patients with mechanical and/or decreased gas exchange (< 80%), present a lower (V02 max.) The use of the algorithm that includes as initial step exercise test predicts a good postoperative surgery.

### 3.305

**Six minute walk test (6MWT) in patients with diagnosis of lung cancer – Clinical value in physiological evaluation candidates for surgical treatment.**

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The lung function testing (LFT) and assessment of exercise capacity in patients with lung cancer are important tools for qualification for the surgery and estimation the risk. However the commonly used 6MWT is not recommended by the current guideline as a reliable method of evaluation (Brunelli 2009).

The aim of the study was to analyze the differences in LFT and 6MWT between patients with and without complications after lung resection. The analysis included 127 operated pts (mean age 63±13 yrs, 80 M, 47 F), with histopathologically confirmed NSCLC. Patients with a history of previous lung resection, chemotherapy or radiotherapy were not included into the study. The comparison of LF and 6MWT was performed and the differences between pts without (86 pts) and with (41 pts) postoperative complications (e.g. arhythmias, PAL, hemorrhage) were noted. FEV1 2.4 vs. 2.1L, p=0.01 (91.3 vs. 73.5%, p=0.001), FEV1/FVC 69.2 vs. 60.3% (p=0.001), ppoFEV1 1.9 vs. 1.6L, p=0.01 (71.9 vs. 51.3%, p<0.001), 6MWT distance 430 vs. 415m (ns), SaO2 start 96.9 vs. 95.5% (p=0.001), SaO2 min 95vs. 92.2% (p<0.001). In univariate analysis ppoFEV1 p>0.05, 6MWT distance and minimal value of SaO2 during the test were significant prognostic variables.

**Conclusions:** Patients with postoperative complications had lower lung function indices (FEV1, ppoFEV1) and lower minimal saturation during 6MWT than those with uneventful postoperative course. Those findings suggest that 6MWT, highly reliable in estimating exercise tolerance in COPD patients, ILD and IAHP, can be valuable also in assessment of lung cancer patients, candidates for surgical treatment.

### 3.306

**Effect of pre-operative short-term rehabilitation on peak V02 in patients with NSCLC.**

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Preoperative fitness is best assessed with cardio-pulmonary exercise testing (CPET) in patients with non-small cell lung cancer (NSCLC). Peak Oxygen consumption (V02 peak) is predictive of short-term complications after thoracic surgery. Feasibility and effect of short-term (2 to 3 weeks) rehabilitation on fitness and short-term outcomes are unknown.

We planned a pragmatic, randomized controlled trial (RCT) comparing short-term rehabilitation (R) with usual care (UC) in patients with operable NSCLC.

**Method:** This ongoing study enrolls patients after baseline CPET from 2 centres in
3607
Structured light plethysmography for the non-contact estimation of chest and abdominal motion changes after thoracic surgery: pilot experience
Iris Levai1, Simon Baker2, Willem de Boer2, Richard Iles3, Aman Coonar2.
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Introduction: Structured Light Plethysmography (SLP) is a non-contact method of studying chest and abdominal motion which can relate to tidal and spirometric volumes. This can also be studied with a 3D-viewer.

Methods: We obtained serial data from 10 patients who underwent thoracic surgery. They were scanned pre and postoperatively with a PneumaScan-P2™ device (PneumaCare, Cambridge, UK). A checkerboard grid of light was projected onto the patient's chest area. Two digital cameras, recorded the grid movement during breathing. Data was presented as a respiratory volume trace over time and as Konno-Mead plots for left v. right hemithorax and chest v. abdomen movement. A post-operative patient is shown in figure 1.

Results: In some patients following thoracic surgery we demonstrate reduced chest wall motion on the operated side. We find improvements in chest wall movement over the recovery period. In one patient no significant difference in pre and post op scans can be found. This patient had virtually no pain post-op and returned to work 5 days after his limited thoracotomy and lung resection.

Conclusions: SLP can objectively measure chest wall movement in thoracic surgery patients. There may be a role for it in monitoring post-operative recovery and we are exploring this further.

370. Lung, heart, muscles and brain: the pathway of oxygen during exercise in health and COPD

370B
Lung structure and function in a rat model of emphysema: A longitudinal study
Marja Saabu1, József Tola1, Balázs Maá1, Harikrishnan Parameswaran2, Erzsébet Bartolák-Suki3, Béla Suki4, Zoltán Hantos5. 1University of Szeged, Department of Medical Physics and Informatics, Szeged, Hungary; 2Boston University, Biomedical Engineering Department, Boston, MA, United States

Our aim was to evaluate the long term structure-function relations in a rat model of emphysema. Rats were treated with porcine pancreatic elastase to produce PPE, n=21 or saline (controls, C, n=19) intratracheally. Before the treatment (day 0) and 3, 10, 21 and 105 days thereafter, respiratory impedance was measured with forced oscillation technique and tissue elastance (H) was calculated. At 3, 21 and 105 day the lungs were fixed, sections were obtained and stained with hematoxylin and eosin, modified Movat’s, Masson’s and Alcian blue method to visualize elastin, collagen and proteoglycans. Randomly selected regions were photographed. The images were automatically segmented and the equivalent diameter of alveolar airspaces (D), mean elastin (Me), mean collagen content (Mc) and mean proteoglycan ratio (Mp) were measured. H decreased through the time-course in the treated animals (p<0.001). D was different between the control and the treated groups at 21 (p=0.027) and 105 days (p=0.004). Me increased in the treated groups (21 d, 105 d; p<0.001), Mc decreased in the treated groups (3 d, 21 d; p<0.001) and Mp was different between the 2 groups (21 d p<0.001, 105 d p<0.016). Multiple linear regression revealed significant correlations between H, D and Me/Mp (r2=0.47, p<0.001; r2=0.712, p<0.001; r2=0.547, p=0.042). We conclude that the progression of emphysema in the PPE model occurs by gradual septal wall failures leading to enlarged airspaces, which in turn decreases the tissue elastance of the lung. This irreversible process results in strong functional and microstructural relations with the components of the extracellular matrix.

3709
Cerebral cortex blood flow, oxygen delivery and oxygenation during normoxic and hypoxic exercise in healthy humans
Zafiris Louvaris1,2, Ioannis Vogiatzis1,2, Helmut Habazettl1, Vasileios Andrianopoulos1,2, Harrieth Wagner3, George Zakynthinos1, Charis Roussos4, Peter Wagner5. 1Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, "M. Simou, and G.P. Livanos Laboratories", National and Kapodistrian University, Athens, Greece; 2Department of Physical Education and Sport Sciences, National and Kapodistrian University, Athens, Greece; 3Institute of Physiology, Charité Campus Benjamin Franklin, Berlin, Germany; 4Institute of Anesthesiology, German Heart Institute, Berlin, Germany; 5Department of Medicine, University of California San Diego, La Jolla, CA, United States

Background: During maximal hypoxic exercise a reduction in cerebral oxygen delivery may constitute a signal to terminate exercise.

Aim: To investigate whether the rate of increase in cerebral cortical oxygen delivery is limited in hypoxia compared to normoxic exercise.

Methods: We assessed frontal cerebral cortex blood flow using near infrared spectroscopy and the light-absorbing tracer indocyanine green dye, as well as frontal cortex oxygen saturation (StO2%) in 11 cyclists during incremental exercise to the limit of tolerance (WRmax) in normoxia and acute hypoxia (FiO2=0.12).

Results: In normoxia, cerebral cortex blood flow and oxygen delivery increased (p<0.05) from baseline to sub-maximal exercise reaching peak values at near-maximal exercise (80% WRmax: 287±9, 81±23% and 75±22% increase relative to baseline, respectively), both leveling off thereafter up to WRmax (328±10%). Cerebral cortex StO2% did not change from baseline (66±3%) throughout graded exercise. During hypoxic exercise, cerebral cortex blood flow increased from baseline to sub-maximal exercise peaking at 80% WRmax (213±6%, 60±15% relative increase) before declining towards baseline at WRmax (289±5%). Despite this, cerebral cortex oxygen delivery remained unchanged from baseline throughout graded exercise, being at WRmax lower than at comparable loads (287±9%) in normoxia (by 58±13%). Cerebral cortex StO2% fell from baseline (58±6%) on moderate exercise in parallel with arterial oxygen saturation, but then remained unchanged to exhaustion (47±4%).

Conclusion: Cerebral cortex oxygen delivery is limited in hypoxia compared to normoxia, thus potentially compromising maximal exercise capacity in hypoxia.
3310 Cerebral cortex oxygen delivery and exercise limitation in patients with COPD
Joannas Vorgiatzi1,2, Zafeiris Louvaris3,4, Helmut Habscheid1,4, Vassileios Andrianopoulos1, Harrieth Wagner2, George Zakynthinos1, Charis Roussos1, Peter Wagner3, 1Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, "M. Simou, and G.P. Livanos Laboratories", National and Kapodistrian University, Athens, Greece; 2Department of Physical Education and Sport Sciences, National and Kapodistrian University, Athens, Greece; 3Institute of Physiology, Charité Campus Benjamin Franklin, Berlin, Germany; 4Institute of Anesthesiology, German Heart Institute, Berlin, Germany; 4Department of Medicine, University of California San Diego, La Jolla, CA, United States

Background: During hypoxic exercise in healthy humans, limited frontal cerebral cortex oxygen delivery may signal the brain to cease exercise.

Aim: Whether in patients with COPD exercising-induced arterial O2 desaturation, frontal cerebral cortex oxygen delivery is reduced, remains unknown.

Methods: By near infrared spectroscopy, we measured both frontal cerebral cortex blood flow (CBF) using indocyanine green dye, and cerebrovascular O2 saturation (%SO2) in 12 COPD patients during constant-load exercise at 75% of peak capacity. Subjects exercised breathing air, 100% O2 or normoxic heliox, the latter two in balanced orders.

Results: Time to exhaustion breathing air was less than for oxygen or heliox (394±3 vs. 670±3 and 637±46 sec, respectively). In each condition, CBF increased from rest to exhaustion. At exhaustion, CBF was higher breathing air and heliox than oxygen (50.4±2.3 and 31.4±3.5 vs. 26.6±3.2 ml min-1 ·100g-1, respectively), compensating lower arterial O2 content (CaO2) in air and heliox, and leading to similar frontal cerebral cortex oxygen delivery (air: 5.3±0.4 O2; 5.5±0.6 and heliox: 5.6±1.0 O2 min-1 ·100g-1 respectively). In contrast, end-exercise %SO2 was greater breathing oxygen compared to air or heliox (67±4 vs. 57±3 and 53±3%, respectively), reflecting CaO2 rather than frontal cerebral cortex oxygen delivery.

Conclusion: Prolonged time to exhaustion is explained by oxygen and heliox despite similar cerebral cortex oxygen delivery as in air, lower %StO2 with heliox than oxygen, yet similar endurance time, and similar %SO2 on air and heliox despite greater endurance with heliox, do not support the hypothesis that cortical oxygen delivery is important in limiting exercise capacity in COPD.

3311 Tissue oxygenation profiles during prolonged exercise in hypoxia
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Introduction: Tissue oxygenation is altered during hypoxia (H) at rest and during exercise(1). It remains however debated whether these perturbations are similar between tissues as well as between cerebral areas implicated in motor output. The purpose of our study was to assess the effect of hypoxic exposure on quadriceps, prefrontal (PFC) and motor cortices oxygenation during prolonged submaximal cycling in H.

Methods: A 4-h wash-in period, either in normoxia or H, 12 subjects performed a 80-min cycling exercise at 45% of their maximal aerobic power (N4F0=21%, H4F0=11%). A third condition (H4F0=9%) consisted in a 80-min resting period in which the arterial saturation (SpO2) reached during H4F0 was matched by adjusting FiO2, Oxy(HbO2)- deoxy(Hb) and total[THb]-haemoglobin changes were measured on each site by near-infrared spectroscopy.

Results: H4F0 and N4F0 resulted in similar SpO2 reduction (~20%). Quadriceps exercise-induced [HbO2] reductions were associated with increased and unchanged [THb] in N4F0 and H4F0 respectively, while [THb] dropped significantly in H4F0. PFC showed a large [THb] increase at exercise with a four-fold [HbO2] increase in N4F0 compared to H4F0. Motor cortex showed similar [HbO2] changes than PFC in H4F0 but not at exercise. Indeed, motor cortex [THb] was stable in H4F0 and N4F0 while [HbO2] decreased and [HHb] increased in N4F0, these latter changes being significantly accentuated in H4F0.

Discussion: This study quantifies for the first time the respective effects of prolonged cycling exercise and SpO2 drop on muscle and cerebral oxygenation responses in H and demonstrates important specificities between tissues and cortical sites.


3312 Exercise testing confirms the role of impaired central circulatory function and elevated right ventricle stroke work index in patients undergoing lung transplantation
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Introduction: Right ventricular (RV) workload assessed by RV Stroke Work Index (RWSWI) is a negative predictor of outcome in acute respiratory failure. Cardiopulmonary exercise testing (CPET) may have a role in detecting central circulatory impairment (CCI) in patients before lung transplantation (LTx) at risk for impaired RV function.

Aims and objectives: To demonstrate correlation of ventilatory inefficiency (VI) on CPET for detection of CCI in patients before LTx with RWSWI.

Methods: 172 patients undergoing evaluation for LTx who had CCI and right heart catheterization were included. RWSWI (stroke volume index*mean pulmonary arterial pressure = mean right atrial pressure*0.0136) was calculated from invasive hemodynamic data. Pearson’s correlation, significance 0.05, was assessed between RWSWI and CPET parameters.

Results: RWSWI correlates highly with VI and inversely with hemodynamics on CPET, but not with peak capacity or workload.

Correlation of RWSWI and CPET parameters

<table>
<thead>
<tr>
<th>RVSWI</th>
<th>Pearson Correlation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VE</td>
<td>-0.241</td>
<td>0.006*</td>
</tr>
<tr>
<td>Peak VW</td>
<td>-0.273</td>
<td>0.001*</td>
</tr>
<tr>
<td>Peak DBP</td>
<td>-0.178</td>
<td>0.033*</td>
</tr>
<tr>
<td>Peak PetCO2</td>
<td>-0.263</td>
<td>0.005*</td>
</tr>
<tr>
<td>Residual PetCO2</td>
<td>-0.216</td>
<td>0.009*</td>
</tr>
<tr>
<td>Peak VE/VCO2</td>
<td>0.204</td>
<td>0.013*</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>-0.124</td>
<td>0.136</td>
</tr>
<tr>
<td>Peak W</td>
<td>0.069</td>
<td>0.415</td>
</tr>
</tbody>
</table>

p<0.05; VE: Minute Ventilation; SBP: systolic blood pressure; DBP: diastolic blood pressure; PetCO2: Pressure of end tidal CO2; VCO2: Rate of carbon dioxide produced; VO2: volume of oxygen consumed.

Conclusions: High right ventricular workload correlates with ventilatory inefficiency and impaired hemodynamics on CPET. Thus, exercise parameters may predict right ventricular work and LTx outcomes.

3313 Additive effects of non-invasive ventilation to hyperoxia on pre-frontal cerebral oxygenation during exercise in patients with COPD
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Rationale: Changes (Δ) in cerebral oxygenation (COx) during exercise are modulated by the dynamic coupling between O2 delivery (cerebral blood flow and arterial O2 content) and O2 utilization. Non-invasive positive pressure ventilation (NIV) adds benefit to HiOx in increasing pre-frontal cerebral oxyhemia. Non-invasive ventilation (NIV) improved muscle and cerebral COx at sub-maximal levels of exercise compared to HiOx (p<0.05). Iso-work rate Qr was larger with HiOx-alone on COx during ramp-incremental exercise in patients with moderate-to-severe COPD.

Methods: Thirty non-hypocapnic males (FEV1=48±15.1% predicted) were randomly assigned to receive each intervention on different days. ΔCOx was determined by near infrared spectroscopy (fold-changes in HbO2), oxyhemoglobin saturation by pulse oximetry (SpO2), and cardiac output (Qt) by impedance cardiography.

Results: As expected, SpO2 remained near 100% throughout the tests (p<0.05). Area under ΔCOx on HiOx was significantly correlated with ΔQt (r=0.82). Peak exercise cardiac output did not differ between interventions (74±20 W vs. 78±19 W; p<0.05). NIV-HiOx was associated with larger increases in ΔCOx at sub-maximal levels of exercise compared to HiOx (p<0.05). Iso-work rate Qr was larger with NIV-HiOx than HiOx (2.6±1.0 vs. 1.6±0.6 fold-changes, p<0.05) and related to improved stroke volume (p<0.05).

Conclusions: NIV adds benefit to HiOx in increasing pre-frontal cerebral oxygenation in patients with COPD, an effect associated with enhanced central haemodynamic responses to exercise.

3314 Central hemodynamics, pleural pressure and normoxic helioxduring exercise in patients with chronic obstructive pulmonary disease
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Background: Altered pulmonary mechanics, due to airway obstruction, are thought to hamper cardiac function during exercise in patients with COPD. If so, improving airflow would lead to an enhanced cardiac function.

Methods: Pleural pressure, dynamic hyperinflation and central hemodynamics, by right heart catheterisation, were simultaneously measured in patients with moderate to very severe COPD at rest and during exercise; both in ambient air and while breathing a normoxic helium-oxygen mixture (heliox).

Results: Seventeen patients were included (FEV1; 53±17%, FEV1/FVC: 42±10%).

TUESDAY, SEPTEMBER 4TH 2012
Breathing heliox lowered expired pleural pressure at rest (3.8±2.6 to 1.8±2.3 mmHg) and during exercise (8.2±3.6 to 6.1±3.3 mmHg), both p<0.05. During exercise we did not find any improvements in stroke volume or cardiac output. At rest we found improvements in cardiac output (6.1±4.1 to 6.6±4.1 L/min/m²), stroke volume (80±22 to 87±19 ml/m²) and mixed venous oxygen saturation (66±6 to 69±6%, all p<0.05). Dynamic hyperinflation did not improve with heliox.

Conclusion: Heliox breathing did not affect cardiac function during exercise. This implies that altered pulmonary mechanics do not substantially affect cardiac function during exercise in COPD.

P3315 Evaluation of mechanisms determining endothelial function in patients with COPD
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Background: COPD is associated with increased cardiovascular mortality. Factors contributing to vascular damage in patients with COPD are mostly unknown. However, it has been suggested that airflow limitation, systemic inflammation, oxidative stress, sympathetic activation, hypoxia and impaired physical activity may lead to endothelial dysfunction and undergo this association.

Objective: To determine the impact of airflow obstruction, systemic inflammation, oxidative stress, sympathetic activation, hypoxia and physical activity on endothelial function in COPD.

Methods: In patients with stable COPD (GOLD stage I–IV) assessments of endothelial function by flow-mediated dilatation (FMD), conventional cardiovascular risk factors (PCoA-score), airflow obstruction (FEV1), systemic inflammation (CRP), oxidative stress (malondialdehyde), sympathetic activation (baroreflex sensitivity), hypoxia (blood gases) and physical activity (steps per day) were performed. Associations between endothelial function and these potential underlying mechanisms were assessed in univariate and multivariate analysis.

Results: 106 patients (35% GOLD stage III, 25% III, 40% IV) were included. In univariate analysis FMD correlated with FEV1 (ρ=0.53, p<0.001), baroreflex sensitivity (ρ=0.25, p=0.01), and steps per day (p=0.07, p=0.01) but not with CRP, malondialdehyde, hypoxia or PCoA-score. In multivariate analysis all proposed mechanisms only FMD and steps per day were independently associated with FMD.

Conclusions: Endothelial function in COPD seems to be primarily determined by the severity of airflow obstruction and the level of physical activity.

P3316 Poor treatment outcomes of XDR-TB patients in resource-limited settings
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Background: According to the last report of the World Health Organization 69, countries have diagnosed at least one case of extensively drug-resistant tuberculosis (XDR-TB). Treatment success rates for XDR-TB have been highly variable. To determine the impact of airflow obstruction, systemic inflammation, oxidative stress, sympathetic activation, hypoxia and physical activity on endothelial function in COPD.

Objective: To compare XDR-TB-related treatment outcomes (i.e. culture conversion and mortality) in MHI vs. LI countries

Methods: A comparative retrospective evaluation of a European (Italy and Estonia) vs. South African datasets, which included only culture-confirmed XDR-TB cases, was performed. Covariates, potentially associated to negative or positive treatment outcomes, were partially explored.

Results: A total of 235 XDR-TB patients were enrolled [61 from Europe (70.5%, males) and 174 (51.2% males) from South Africa]. Their mean (standard deviation) age was 47.0 (12.2) and 35.2 (11.2) years, respectively (P<0.001). HIV co-infection was significantly more frequent in the South-African cohort (82/174, 47.1%, vs. 25/58, 3.5%; P<0.001). A higher proportion of deaths was recorded among South African XDR-TB cases (61/174, 35.1%, vs. 14/61, 23.0%; P=0.08). By contrast, the proportion of culture converters during anti-TB treatment was significantly higher in the European group (28/57, 49.1%, vs. 33/174, 19.0%; P<0.001). HIV co-infection was significantly associated with death, but not culture conversion, in the combined cohort (aOR: 2.37; P=0.008).

Conclusion: Unfavorable outcomes, although common in both settings, are more frequent in a resource-poor setting. These data can inform prevention and treatment strategies for XDR-TB in different settings.

P3318 The incidence of multi drug resistant tuberculosis among patients receiving standardized treatment regime for suspected MDR-TB
Sahlin Augusto Le1, Joven Gongon1, Lawrence Raymond1,2, Vivian Lofranco1,2, Vincent Balanag1. 1Pulmonary Medicine, Lung Center of the Philippines, Quezon City, Philippines; 2Public Health Domiciliary Unit, Lung Center of the Philippines, Quezon City, Philippines

The LCP-PMDT started the implementation of Standardized treatment regime for all smear positive Drug Resistant tuberculosis suspects. The appropriateness of these regimes need to be evaluated. This is a Descriptive prospective cohort study, the objective is to determine the Incidence of MDR-TB among patients receiving Standardized Treatment regime for suspected MDR-TB. 256 patients received standardized treatment regime,180 patients have available culture and DST results, 76 patients still have pending culture and DST results. Of the 180 patients with available culture and DST results, 113 were confirmed MDR-TB. 55 of 72 (76.3%) patients belonging to the others Non-DOTS multiple treatment group were confirmed MDR-TB compared to 7 (30.3%) patients with Non-DOTS with single treatment. 17 of 18(94%) patients who belonged to category I failure group were confirmed MDR-TB. 5 of 11 (45.5%) patients under Category I RAD, 8 (33.3%) of 24 patients under category I relapse were confirmed MDR-TB. 11 of 20 (55%) patients under category II relapse and 10 (90.1%) of 11 patients under category II failure were confirmed MDR-TB.

Conclusion: MDR-TB occurs more frequently among the standardized regimen II group (category I failure, category II failure, and other Non-DOTS with multiple treatment).

Recommendations: Initiation of standardized regimen for MDR-TB for patients with Category I failure, Category II failure, category II relapse and those with Non-DOTS with multiple treatment while awaiting the results of the DST. Category II treatment regimen, should be used in category I RAD and category I Relapse pending culture and DST results.

P3318 Non-pharmacological factors for the emergence of drug resistance in patients of pulmonary tuberculosis: An Indian overview
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Objective: To evaluate the impact of non-pharmacological factors on the emergence of drug resistant tuberculosis in eastern Uttar Pradesh.

Material and methods: 150 diagnosed cases of drug resistance pulmonary tuberculosis via culture and sensitivity were evaluated of their socio-economic background with special reference to their literacy, annual income, housing, reason of discontinuation of treatment, migration status etc. Data was collected and analysed statistically.

Observation: Prevalence of drug resistance was more in large families(76%), with lower housing area per person(62%), with at least one migration history(75.3%), having at least one member previously sputum positive(65.3%) and lower annual income(66%). Also was more in illiterate(58%). The reason of discontinuation were adverse effect(18%), resolution of basic symptoms/early asymptomatics(40%), advised by unqualified doctors(12%), social stigmat(8%), and non affordable private treatment(15.3%).

Table 1. Reason of discontinuation of drugs

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of discontinuation</th>
<th>Percentage of total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No discontinuation</td>
<td>10, 66%</td>
<td>10, 66%</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>27, 18%</td>
<td>27, 18%</td>
</tr>
<tr>
<td>Resolution of basic symptom</td>
<td>60, 40%</td>
<td>60, 40%</td>
</tr>
<tr>
<td>Advised by unqualified doctors</td>
<td>18, 12%</td>
<td>18, 12%</td>
</tr>
<tr>
<td>Fear of related social stigma</td>
<td>12, 8%</td>
<td>12, 8%</td>
</tr>
<tr>
<td>Can’t afforded expenditure of treatment</td>
<td>25, 15.3%</td>
<td>25, 15.3%</td>
</tr>
</tbody>
</table>

Conclusion: Role of socioeconomic factors can’t be denied in emergence of drug resistance. Patient centered approach especially proper counselling may help in this regard.
P3319
The efficacy of a rifabutin-containing regimen for rifabutin-susceptible multi-drug-resistant tuberculosis
Kyung-Wook Joo, Wonju Jin, Iwhoon Ly, Young Ju Jung, Sang-Do Lee, Woo Sung Kim, Dong Soon Kim, Tae Sun Shim. Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Objective: We investigated the efficacy of rifabutin (RBU)-containing regimen for the treatment of RBU-resistant multidrug-resistant tuberculosis (MDR-TB).

Methods: From 256 patients diagnosed with MDR-TB at Asan Medical Center in South Korea between January 2006 and December 2010, 39 patients (15.2%) were susceptible to RBU. Of these 39 patients, nine patients who were appropriately treated with a RBU-containing regimen were included. Twenty-seven MDR-TB patients who were resistant to RBU, were selected as a control group, and the outcomes of both groups were retrospectively compared.

Results: In the nine patients with RBU-susceptible MDR-TB, their mean age was 43.7 years and the proportion of extensively drug-resistant TB (XDR-TB) was 44.4% (4/9). Baseline characteristics and the drug resistance pattern (except RBU) did not differ between the two groups. Treatment success (cure in six (66.7%) and treatment completion in three (33.3%)) on the other hand, the treatment success rate was 48.1% (13/27) and treatment failed in 14 (51.9%) of the 27 patients in the control group (p = 0.012).

Conclusions: RBU seems to be useful in the treatment of MDR-TB in patients who are susceptible to RBU.

P3320
Treatment outcomes of MDR-TB cases registered in Bucharest sector 4 during 2006-2010
Mirela Tigau, Ileana Dediu, Emilius Bejan, TB and other Chronic Diseases, "Marius Nasta" Institute of Pneumology, Bucharest, Romania

Introduction: Although the TB incidence rate declined significantly in Romania in the last decade, from 142.2/100,000 in 2002 to 90.2/100,000 in 2010, the MDR-TB remains at a rate of attendance (2.9% in new and 10.9% in retreated cases).

Objective: To analyze the treatment outcomes of MDR-TB cases registered in the TB Dispensary of Bucharest Sector 4, in order to optimize the TB control in its territory.

Material and methods: We conducted an observational retrospective study of 78 MDR-TB cases registered in Sector 4 between December 2004-December 2008.

Data have been collected from the TB register of the dispensary, TB information system, treatment records and epidemiological surveys.

Results: Out of 78 MDR-TB patients, 35 have been included in the DOTS Plus project financed by the Global Fund (GLC group) and 43 have been treated from NTP resources (NTP group). Chronic patients represented 11.5% in GLC group and 30.9% in NTP group. Overall success rate was 3 times higher in the GLC group (82.8%) than in the NTP group (25.3%).

Conclusions: For tuberculosis control it is important to include patients in DOTS Plus project because this group shows higher success rates at the end of the treatment (82.8% vs 25.3%).

P3321
Treatment outcome of multi drug resistant tuberculosis patients in modified DOTS-PLUS: A new strategy
Rajendra Prasad 1, Abhijeet Singh 2, Rahul Srivastava 2, Ramawadh Singh Kushwaha 3, Rajiv Garg 3, Sanjeev Kumar Verma 3, Girdhar Belur, Medical University, Tomsk, Tomsk area, Russian Federation; 2Department of Tuberculosis and Pulmonology, "Marius Nasta" Institute of Pneumology, Bucharest, Romania, 3Tuberculosis of Lungs, Tomsk Regional Clinical Tuberculosis Hospital, Tomsk, Tomsk area, Russian Federation

Background: MDR-TB remains a worldwide problem which is difficult to treat and has greater risk of relapse. Multi Drug Resistant tuberculosis (MDR-TB) is an increasing worldwide problem which is difficult to treat and has greater risk of relapse.

Objective: To analyze long term treatment outcome with second line drugs in patients with MDR-TB.

Methods: A prospective cohort study analyzing 98 consecutive patients with MDR-TB attending the Dept of Pulmonary Medicine, CSMMU, between June 2000 to Feb 2010 with follow-up till February 2012. All the patients were given modified DOTS Plus Protocol of Revised National Tuberculosis Control Programme (RNTCP). Treatment included monthly follow up, adherence check up, radiological and bacteriological assessment (spumum smear advised monthly till conversion then quarterly; culture for MBT at 0,6,12,18,24 months); intense health education and monitoring of adverse effects. Patients outcome considered as cure when atleast 2 of the last 3 cultures were negative and as failure when the same were positive.

Results: All the patients had resistance to at least Isoniazid and Rifampicin with mean no. of 3.02 drugs and were sereogative for HIV. Default rate and expiry rate at the completion of 24 months of treatment were observed to be 7(7.1%) and 10(10.2%) respectively. Mean smear and culture conversion time were 3.4±3.2 months (1-11) and 4.6±2.5 months (4-12) respectively. Spumum smear and culture conversion rate were 75(8102.5%) and 71(817.5%) respectively with only 10(10.2%) patients remained culture positive. Significant side effects were experienced in only 17.4% patients.

Conclusions: Modified DOTS-PLUS strategy can be model for treatment of MDR-TB in private sector.

P3322
Failure in treatments of patients according DOTS-PLUS program
Medico-social predictors
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The problem of treatment patients who suffering from multi drug resistance tuberculosis of lungs (MDR-TB) is one of the symptoms of phthisiology now. Efficiency of treatment of this group patients according the program DOTS-PLUS fluctuates in a range 61%-77%, and failure in treatment is registered in 3%-14% of cases in different countries. The purpose of our research is revealing predictors of failure in treatment of the patients suffering MDR TB.

200 MDR TB patients who were treated under program DOTS-PLUS in the Tomsk region (from 2000 to 2008) have been included in case-control study. Patients with failure in treatment (n=100) were in the main group, and patients (n=100) who were cured were in the comparison group.

The age of patients varied from 16 till 75 years. The deficiency of body weight (BMI < 15.99 and less) has brought to the formation failures in treatment (OR 11.0). Revealing cavernous tuberculosis at the initial stage increased risk of failure more than in 5 times (OR 5.69). The complications increasing risk of failure in treatment were respiratory insufficiency (OR 3.25), anemia (OR 13.78) and hemoptysis (OR 3.80). For therapy failure following accompanying diseases had prognostic value: pathology of urinary system (OR 6.62), chronic not obstructive bronchitis (OR 2.43), pathology of gastrointestinal tract (OR 2.32) and pathology of the heart (OR 3.52).

Thus development of MDR TB and efficiency of its treatment depends from both social, and medical factors which are necessary to consider at the initial stage of treatment and to apply measures for their minimization.

P3323
Success of the patient-oriented approach to MDR-TB treatment in Tomsk Oblast, Russia, 2000-2009
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MDR-TB reservoir decreased from 29.3% (2003) to 10.4% (2009). MDR-TB treatment effectiveness: 63.1% - cured, 12.6% - failed, 8.3% - died, 13.78 - treatment failed.

In 2000-2009, 1141 MDR TB patients were treated in Tomsk Oblast (civilian sector). MDR-TB treatment effectiveness: 63.1% - cured, 12.6% - failed, 8.3% - died, 13.78 - treatment failed.

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In 2000-2009, 1141 MDR TB patients were treated in Tomsk Oblast (civilian sector). MDR-TB treatment effectiveness: 63.1% - cured, 12.6% - failed, 8.3% - died, 13.78 - treatment failed.
Methods: A descriptive analyses of 93 consecutive patients with MDR-TB attending the Department of Pulmonary Medicine, CSMMU, between June 1998 to February 2008 with follow-up till December 2010. All patients were admitted for average duration of 70 days and received a regimen chosen from Kanamycin, PAS, Ethionamide, Cycloserine, Fluoroquinolone, Isoniazid, Ethambutol and Pyrazinamide. Patients outcome was considered as cured when all sputum examination were negative and as failure when the same were positive. Results: All the patients had resistance to at least Isoniazid and Rifampicin with mean no. of 3.38 drugs. Average duration of pretreatment chemotherapy was 34.5 (10-62) months. Of 93 patients enrolled, 75 completed the treatment as planned, 5 patients died during treatment, and 13 patients abandoned it or lost to follow up. Considering the best scenario cure rate was 93.33% (70/75) and in worst scenario cure rate was 75.27% (70/92). Out of 75 cured, 68 came for follow-up for mean duration of 53.3 (10-98) months. Relapse rate was 9.33% (7/75). Significant side effects were experienced in 13 (13.98%) patients. Conclusions: In MDR-TB patients, regimen consisting of Ethionamide, PAS, Fluoroquinolone and Cycloserine with injection Kanamycin in initial 4.6 months appears to be safe and effective. MDR-TB can be cured successfully with appropriate combination chemotherapy for an adequate duration requiring a strategic approach. P3325 Peculiarities and results of treatment in XDR pulmonary tuberculosis (PTB) Sergey Skornyakov, Jeyg Motus, Elena Kildyusheva. Research Department, Urals Research Institute for Phthisiopulmonology, Ekaterinburg, Russian Federation Conclusions: First-line drugs were administered, adverse effects of drugs were identified, side effects were experienced in 13 (13.98%) patients. Objective: To evaluate the effectiveness and safety of the individual-tailored regimens of MDR-TB treatment based, in common case, on K/Cap, Ofl/Lev, Pt, STZ/Smx, KMx/SMx. Those patients were divided for at least 2 years. Later-generation fluoroquinolones - Lfx or Mfx. When resistance to Kmo we used Cm. Of oral bacteriostatic 2nd –line Pto, Cx, PAS. Of drug group 5 - AmClx/Clr. Ctr. Artificial pneumoperitoneum was applied in 26 patients, surgery was performed in 16. Results: Cure was achieved in 37 (63.7%) patients including those subjected to collapse therapy and/or surgery. Late results were followed in 50 cases. Culture remains negative in 32 (64%) of patients including 22 of 26 after collapse therapy and 14 of 16 after surgery. That was confirmed by multiple spum culture examination in terms of more than a year. Conclusion: The development of XDR PTB resulted from close household contact, sputum culture examination in terms of more than a year. P3326 Evaluation of characteristics and treatment results of patients treated as multidrug resistant tuberculosis (MDR-TB) Necati Yilmaz1, H. Arap2, Tulin Kuyucu3, Ates Baran1, Mualla Partal1, O. Kaya Koksalan, I. Aksay1, A. Kose1. 1Chest Disease, H.M. Sutcu, 2Chest Disease, H.M. Sutcu, 3Medical TB Epidemiology Laboratory, Institute for Medical Experimental Research (DETA), Istanbul University, Istanbul, Turkey. The development of XDR PTB resulted from close household contact, sputum culture examination in terms of more than a year. Conclusion: The development of XDR PTB resulted from close household contact, sputum culture examination in terms of more than a year. P3327 Use of linezolid in complex MDR-TB cases Yi-Wen Huang1, Hui-Chen Tsai1, Chin-Nien Chang2, Wen-Ta Yang2.1Pulmonary and Critical Care Unit, 2Surgery Department, Changhua Hospital, Taichung County, Taiwan; 1Tuberculosis Department, Taichung Hospital, Taichung, Taiwan. Introduction: The control of tuberculosis is facing challenges with the development of drug resistance as more drugs are used. Complex MDR-TB has recently emerged as a global public health issue. In Taiwan, there are around 600 new MDR-TB cases with 1.0% new TB cases, 6.2% treatment cases and 10.0% XDR-TB. Treating MDR-TB has become much more difficult, a new treatment regimen is mandatory. Aim: To evaluate the effectiveness and safety of the individual-tailored regimens (ITR) for new and re-treatment TB patients, based on total both express and liquid and solid media DST and accessibility to TB drugs of the all lines (the present Moscow TB Control Center setting). Background: MDR-TB treatment based, in common case, on K/Cap, O/Lev, Pt, Cs, PAS and, depend on the drug-resistance pattern (DRP), E and/or Z. But the adequate chemotherapy regimen (min 3-4 drugs) is often impossible due to the DRP and/or drugs intolerance. Aim: To make treatment outcome analysis and to determine the factors associated with unfavourable treatment results in cases with MDR-TB. Conclusions: This study shows high mortality rate in MDR-TB cases during two years after treatment initiation. XDR-TB is the strongest predictor of poor treatment outcomes. Previous TB treatment, weight loss and positive smears for acid-fast bacilli at the start of treatment are the other important factors associated with unfavourable treatment results. P33328 Treatment outcome and factors associated with unfavourable treatment results in cases with multidrug-resistant tuberculosis in Bulgaria for the period 2009-2010 Vladimir Milanov1, Mariya Zambirova1, Tonka Vareva1, Elizabeta Bachiyiska2, Antoniya Koletova1. 1National Tuberculosis Reference Laboratory (NTRL-B), National Center of Infectious and Parasitic Diseases (NCIPS), Sofia, Bulgaria; 2Manager, Specialized Hospital for Active Treatment of Lung Diseases, Gabrovo, Bulgaria. A retrospective study of all patients with MDR-TB in Bulgaria who started treatment for the period September 2009-March 2010 was performed. Aim: To make treatment outcome analysis and to determine the factors associated with unfavourable treatment results in cases with MDR-TB. Materials and methods: Medical records, recording and reporting forms for the MDR-TB cases included in treatment and TB registries of the NTRL-B were examined. Results: A total of 50 MDR-TB patients with mean age 45.8 years started treatment during the period. The male to female ratio was 2.3:1. Nineteen patients (38%) were new, and the other 31 cases were previously treated: 12 relapses (24%), after failure – 8 (16%), after default – 10 (20%). The median duration of recorded disease before treatment was 3.1 years (range, 0-13). None of all the patients tested for HIV had a positive result. Eight cases were found with XDR-TB during the treatment: 4 in 2010, and 4 – in 2011. Treatment was given for 18-24 months, including at least 12 months after culture conversion. Twenty four months after beginning of treatment, 24 patients (48%) were cured, 19 patients (38%) died, and one patient (2%) interrupted treatment. The cases with XDR-TB had higher mortality rate than the other MDR-TB cases (75% vs. 30.9%). Conclusion: This study shows high mortality rate in MDR-TB cases during two years after treatment initiation. XDR-TB is the strongest predictor of poor treatment outcomes. Previous TB treatment, weight loss and positive smears for acid-fast bacilli at the start of treatment are the other important factors associated with unfavourable treatment results. P3329 The individual-tailored treatment regimens for multidrug-resistant tuberculosis Tatiana Ivazhanskaya, Sergey Borisov, Natalia Litvinova, Yulia Garmash. Clinical Department, Moscow Research and Clinical Center for TB Control, Moscow, Russian Federation Background: MDR-TB treatment based, in common case, on K/Cap, Off/Lev, Pt, Cs, PAS and, depend on the drug-resistance pattern (DRP), E and/or Z. But the adequate chemotherapy regimen (min 3-4 drugs) is often impossible due to the DRP and/or drugs intolerance. Aim: To evaluate the effectiveness and safety of the individual-tailored regimens (ITR) for new and re-treatment TB patients, based on total both express and liquid and solid media DST and accessibility to TB drugs of the all lines (the present Moscow TB Control Center setting).
Methods: The prospective unblinded non-randomized one-centered study includes 66 pulmonary TB patients, 18-71 y.o., 40 male and 26 female. MDR-TB in 38 pts (14 new and 24 re-treatment), XDR-TB in 28 (4 and 24). The ITR included in all cases first/second-line TB drugs (accordingly DRP and drug tolerance) and linezolid (Lz), in 42 pts moxifloxacin (Mox) was used and azithromycin (Az)/clarithromycin (Cl), meropenem (Mrn)/imipenem + cilastatin must be added.

Results: The sputum smear conversion for MDR-TB pts - 97,4% (37/38, 36 - at the end of the 8th week) and for XDR-TB - 82,1% (23/28, 20 - at the end of the 16th week). The severe side-effects, attributed to Lz, were obtained in 5 pts (7,6%): peroneal neuropathy (3 pts, Lz excluded in 1), obstinate vomiting (1 pt, Lz excluded) and anemia (2 pts, Lz continued). The severe tachycardia, attributed to Az, were obtained in 1 pts (Az excluded).

Conclusion: The regimens, based on second-line TB-drugs (include Mox) and drugs from the WHO’s “fifth group” are well-tolerated and high effective in MDR- and XDR-TB, but require the timely drug susceptibility testing and the full set of the expensive drugs.

P3330

Study of isoniazid-resistant tuberculosis including outcomes in a high prevalence area in London

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Background: Isoniazid resistance is the most common form of mono drug resistance in tuberculosis (TB). There has been an outbreak of isoniazid-resistant TB in North London. An outbreak committee has made recommendations.

Aim: To study isoniazid resistant TB patients attending Newham community chest clinic.

Methods: The notes of 31 isoniazid-resistant TB patients treated between 2004 to 2009 were studied. The reference laboratory gave confirmation of resistance.

Results: The age range was 17 to 73 (median 32). Male: female - 2.1:1. 72(3%) patients had the North London outbreak strain. Of the 31 patients (2065%) had pulmonary involvement, 11(35%) had extensive disease and 8(26%) were sputum smear positive. The extra-pulmonary presentations were lymphadenopathy, abscesses and miliary TB in 13(5%) patients. 10(3%) cases had risk factors for resistance - HIV, previous TB, alcohol, drug abuse and being in prison. 14(45%) patients had risk factors for non-adherence were given directly observed therapy. 17(55%) had treatment supervised weekly by community pharmacists. Patients received a 12month regime containing rifampicin, pyrazinamide and ethambutol, or a 9-month regime that also included moxifloxacin. 7(23%) patients had drug adverse effects. 30(97%) patients completed treatment successfully.

Conclusion: The majority of our patients were not associated with the outbreak. Treatment completion rates were satisfactory, and exceeded the target (90%) set by the TB outbreak control committee. There was no difference in treatment completion rates between the two regimes.

Reference:

P3331

Drug resistance trends and patterns of mycobacterium tuberculosis isolates from pulmonary tuberculosis patients at a tertiary care hospital in Turkey

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Objective: To determine the proportions and patterns of resistance to commonly used tuberculosis (TB) drugs (isoniazid (INH), rifampicin (R), ethambutol (E) and streptomycin (S)) among pulmonary TB patients and assess potential risk factors for drug resistance.

Methodology: Strains were collected from 1584 sputum smear negative or positive pulmonary TB patients with culture positive in tertiary care hospital of Turkey. Specimens were cultured in liquid and solid media, and drug susceptibility tests were performed for first-line drugs including isoniazid, rifampicin, streptomycin, ethambutol and pyrazinamide.

Results: Drug susceptibility testing (DST) has been obtained from all samples 442 (27.9%) of 1584 isolates were resistant to at least one of five antibiotics tested. 380 (18.9%) isolates were resistant to isoniazid; 168 (10.6%) to streptomycin; 137 (8.6%) to ethambutol; 220 (13.9%) to rifampicin. 146 isolates (9.2%) were multidrug resistant. Results also showed 49% of patients were below the age of 40 years.

Conclusion: Regardless of previous treatment history, the high resistance observed in isoniazid, which is a first-line drug. Treating culture-positive TB patients based on DOTS together with strengthened control programs should therefore be considered in the management of TB patients.

P3332

How big is the problem with MDR-TB cases in Macedonia? A retrospective analysis of cases registered in the National MDR-TB Register in Macedonia from 2001 till 2011

Biljana Iljevska Poposka1, 1Thoracic Medicine, Royal Free Hospital, Skopje, Macedonia, The Former Yugoslav Republic of

Background: Multi-drug resistance tuberculosis (MDR-TB) is one of the most challenging problems in the National Strategy for control tuberculosis in Macedonia. The aim of this study was to present all patients with MDR-TB who were registered in the National MDR-TB Register in Macedonia from 2001 till 2011.

Material: 32 patients who were treated with individualized therapeutic regimes were enrolled in the study. Patients follow-up ended when an outcome was recorded or, in December 2011 for those still on treatment.

Results: 29 patients were with bacteriological confirmation, and 3 cases were suspected for MDR-TB. MDR-TB cases participate with 0,5-4,6% in the total resistant strain obtained from positive culture during the last six year. 30 patients (93,75%) had acquired resistance and only 2 patients (6,25%) had primary MDR resistance. Time to culture conversion was two months or less in the most of patients. The results of treatment outcome are: 9 patients were cured (28,12%), 13 patients (40,62%) died, 5 patients interrupted the treatment (15,62%) and 5 patients (15,62%) are still on treatment. No one patient had XDR-TB initially, but only one cases emerged XDR-TB during the treatment.

Conclusion: To improve management and treatment results of MDR-TB patients in Macedonia, we need more efforts in providing necessary medications, clinical conditions and treatment under direct control.

P3333

Comparison of moxifloxacin and ofloxacin in treatment of multidrug resistant pulmonary tuberculosis

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Multidrug resistant tuberculosis (MDR-TB) is defined as pulmonary tuberculosis caused by isoniazid and rifampicin resistant. Fluoroquinolones must be involved in standard treatment regimen of MDR-TB. Effect of old and the new generation fluoroquinolones are compared on sputum conversion to treat MDR-TB. 63 MDR-TB patients included. Patients were divided into two groups according to usage of ofloxacin and moxifloxacin. 26 patients used moxifloxacin and 37 patients used ofloxacin. Mean age was 32.7±12.3 in moxifloxacin group and was 38.1±1.4 in ofloxacin group. Gender distribution(F/M) in moxifloxacin and ofloxacin group was 2/24, 14/23, respectively. All patients were HIV negative. Sputum conversion, culture conversion and treatment period were compared between two groups.

Table 1. Comparison of sputum conversion, culture conversion and treatment time with use of Moxifloxacin and Ofloxacin

<table>
<thead>
<tr>
<th></th>
<th>Moxifloxacin (mean ± SD)</th>
<th>Ofloxacin (mean ± SD)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Sputum conversion</td>
<td>1.81±1.58</td>
<td>1.78±1.08</td>
<td>0.276</td>
</tr>
<tr>
<td>Culture conversion</td>
<td>1.96±1.31</td>
<td>1.81±0.81</td>
<td>0.857</td>
</tr>
<tr>
<td>Treatment time</td>
<td>21.12±7.08</td>
<td>21.68±5.43</td>
<td>0.545</td>
</tr>
</tbody>
</table>

Maun-Whitney U test 95% confidence interval.

There was no significant difference in sputum conversion and culture conversion and treatment time between two group (p>0.05).

Conclusion: In spite of the declared information that moxifloxacin is more efficient than ofloxacin in treatment of MDR-TB; in this study there was no significant difference in sputum conversion, culture conversion and treatment time. Although patient number is not a lot, this result can make us think that economic reasons are important when selecting the quinolone group for the treatment.

372. Paediatric bronchology

P3334

HRCT features do not predict the clinical course in children with protracted bacterial bronchitis

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Background/Aim: Chronic wet cough suggests endobronchial infection. We
aimed to investigate the relation between the initial radiological findings and clinical course as well as the evolution of radiological findings in patients whose clinical findings persisted despite treatment.

Methods: We retrospectively reviewed 90 patients aged 0.6 to 16.4 years, with chronic endobronchial infection. In 25 (27.8%) patients follow-up HRCT scan was performed (1st group), 6-38 months apart (median 13 mo) based on clinical grounds, mainly on the durability of symptoms despite long courses of antibiotic treatment and physiotherapy; the remaining 65 (72.2%) had a remitting course and a second scan was not considered necessary (2nd group). Severity of involvement was assessed with Bhalla score and presence of bronchiectasis, per se.

Results: Radiological findings on the first HRCT did not differ between the 2 groups (Bhalla scores: 2.7±0.3 and 2.6±0.3, p=0.80; presence of bronchiectasis: 10 and 27; p=0.9 in the 1 and 2nd group, respectively). In 1st group 10 children had bronchiectasis in the 1st HRCT scan compared with 14 in the 2nd scan (p=0.10). Bhalla scores did not differ between the 1st and the 2nd CT scan (mean values:±sd: 2.7±0.2 and 2.9±0.4, respectively, p=0.60). There was no difference in bronchoscopic bronchoalveolar lavage findings.

Conclusion: Radiological findings do not suffice to predict the clinical course of protracted bacterial bronchitis. Although the literature suggests that radiological findings in such cases are reversible, this is not the rule. Apart from the intensity of treatment, there are probably other - yet unidentified- factors that determine the final outcome of the disease.

P3335 Bronchoscopic findings in children with primary ciliary dyskinesia: Most but not all bacterial bronchitis

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Chronic bacterial infections of the lower respiratory tract (LRTI) are a relevant problem in patients with primary ciliary dyskinesia (PCD) and therefore a continuous antibiotic treatment regime is often used. However, it remains unclear if all of these children indeed have relevant chronic LRTI and thus profit from antibiotics. Data on bronchoalveolar lavage fluid (BALF) with cytological and microbiological analysis in PCD patients are still lacking.

In a retrospective study BALF findings of 19 children with PCD were analyzed and the clinical course of patients treated with antibiotics has been investigated. Median age of the patients at the time of bronchoscopy was 10 year (range 4-17 years). Sputum inversion was seen in 10 patients. The main symptoms leading to bronchoscopy were chronic cough, recurrent bronchitis or pneumonia. Lung function was performed in 17 patients before bronchoscopy. FEV1 ranged between 62-114% (median 80%). In the BALF of 12 patients significant bacterial counts (>10^5 CFU/l) have been detected. The most frequent isolated species was Haemophilus influenzae (n=10) and Streptococcus pneumoniae (n=3) were the most frequent isolated species. In all of the cases a BALF-cytology was performed a granulocytic inflammation was detected. In further analysis these findings correlated with a worse lung function before bronchoscopy (FEV1 <80%) and a significant improvement of lung function under antibiotic therapy.

Bronchoscopy is a safe diagnostic method in children with PCD to distinguish between patients with LRTI from these without infections. This has an extensive clinical relevance because we could show that patients with a proven infection profit from an antibiotic therapy.

Conclusions: FB is valuable in the assessment of patients with extrathoracic tracheomalacia since HCTs cannot be recommended as a safe approach (radiation of the thyroid). However, CT scans provide a more accurate estimation of extrathoracic tracheomalacia as it is not influenced by the effects of general anestheis.

P3337 Bronchoscopic findings and interventions in patients with long-term tracheostomy

Andreas Pfleger, Ernst Eber. Department of Paediatrics and Adolescence Medicine, Medical University of Graz, Austria

Aims: To describe airway abnormalities identified by flexible bronchoscopy (FB) in patients with long-term tracheostomy (LTT) and interventions as a consequence of FB findings.

Methods: Records of patients with LTT followed from Jan 08 to Dec 11 were reviewed. FBs were performed as routine surveillance FBs, additional scheduled FBs, or because of disease or tracheostomy related complications. Resulting interventions (ventilator -, cannula -, or medication changes, and surgical interventions) and extra caregiver trainings were recorded.

Results: In 52 patients (20 f, 32 m) 210 FBs were performed. 30 patients had LTT for long-term ventilation, 22 as a bypass for upper airway obstruction. Median age was 4.5 yrs (0.1-32.7). In 97 instances FBs were performed transanula, in 93 via the cannula, and in 20 via both routes. In 13 instances (6%) complications led to FBs; in 23 (11%) additional scheduled FBs, and in 174 (83%) surveillance FBs were performed. The mean frequency of FBs was 1.1/patient and year (0.25-2.7). The most common findings were airway malacia in 38%, clinically relevant granulation tissue in the suprastomal region in 8%, at the end of the cannula in 7%, and in other regions in 13%. Cannula changes were performed in 21%, ventilator changes in 4%, and surgical interventions in 3%. 12% of the caregivers received extra training on correct suction techniques.

Conclusions: In this series of patients with LTT we found a high incidence of airway abnormalities. As FB findings resulted in interventions in a quarter of our patients we recommend that FB should be performed at least once a year. Patients with significant airway pathology, however, may benefit from more frequent endoscopic evaluations.

P3338 Nasal nitric oxide measurement using continuous aspiration by hand-held device discriminates patients with primary ciliary dyskinesia from healthy subjects

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Background: Low nasal nitric oxide (nNO) has been reported in subjects with primary ciliary dyskinesia (PCD) and healthy subjects. No study compared nNO measured using continuous nasal aspiration in PCD and healthy subjects by a hand-held device.

Aim: To find out whether nNO measured by a hand-held analyser using the continuous aspiration method discriminates PCD from healthy subjects.

Methods: Twenty-three PCD patients (median age, 15.8 yrs; range, 4.6-32.8) and 23 healthy controls (age, 15.7 yrs; range, 4.3-32.1) measured nNO with a hand-held electrochemical device (NIOX MINO®, Aerocrine AB) during oral breathing through a mouthpiece.

Results: Median (range) nNO values were 12 (5-62) and 506 (215-777) ppb in PCD and controls, respectively (p<0.001). Sensitivity and specificity at different cut-off points for nNO are reported in the Table.

Conclusions: Measurement of nNO by the hand-held device using the continuous aspiration method has an excellent sensitivity and specificity in distinguishing PCD from healthy subjects. Its wider use might result in an increased number of detected individuals suspected to have PCD.

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**Cut-off points (ppb)** | **Sensitivity (%)** | **Specificity (%)**
---|---|---
36 | 78 | 100
44 | 83 | 100
51 | 87 | 100
58 | 91 | 100
138 | 100 | 100

Conclusion: Measurement of nNO by the hand-held device using the continuous aspiration method has an excellent sensitivity and specificity in distinguishing PCD from healthy subjects. Its wider use might result in an increased number of detected individuals suspected to have PCD.
The effect of air pollution can play a role in the development and/or the exacerbations of chronic lower airway diseases (CLADs) in children.

The aim of this study is to investigate the association between the major component of inhalable particulate matter (PM10), black carbon, contained in lower airway macrophages (AMs) of children with CLADs and variables that may affect individual exposure.

We studied 24 children undergoing FOB for CLADs. For each child the area of the black material (BM) in AMs, sampled by bronchoalveolar lavage, was determined by analysis of digitized light microscopic images of random AMs; median carbon content of AMs was obtained calculating the area (μm²) of BM.

Children had a median age of 6 years (range 2.9-16.6); they were affected by current lower airway infection in 12 cases (PCD in 2), by asthma in 7, by chronic cough in 3 and by laryngospasm in 2 cases. There was a correlation between the median area of BM and air PM10 levels during the week before FOB (ρ<0.001).

No significant correlation was found between FEVI measured in 14 children. No significant difference in black area size in AMs was detected comparing children based on sex, underlying disease or household. Preschool-children had a larger median black area in AMs than school-children, even if the difference was not significant (0.071 μm² vs 0.35 μm², p=0.35).

In conclusion the median area of BM in AMs is correlated to air pollution exposure in children affected by CLADs, but it seems not to correlate to underlying diseases, age, sex and FEVI. A larger study group is necessary to better define the correlation of PM10 and CLADs in children.

Identification of KCNRG, a bronchial autoantigen, in a children with IPEX syndrome

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IPEX syndrome is a rare disorder of immune regulation caused by mutations in the FOXP3 gene, which is required for the suppressive function of naturally arising CD4+ CD25+ regulatory T cells. It is associated with the presence of common autoantibodies associated with autoimmune disorders.

We report an infant, who manifested at first week after birth a type 1 diabetes mellitus and eczema. IPEX syndrome was confirmed by proved V408M mutation in the FOXP3 gene. At one month old he developed wheezing, cough, respiratory distress without infection. Despite treatment with salbutamol and budesonide nebulized, he was still symptomatic. High-resolution tomography scan showed hyperinflation, trapping, and ground-glass opacities. Analysis of bronchoalveolar lavage showed 1 350 000 cells/ml, with 65% alveolar macrophages without infection. Autoantibodies to KCNRG were present in serum at one month and still persist at nine months. Treatment with mycophenolate mofetil was started because of combination of severe diarrhea, persistent respiratory symptoms with an optic neuromulbeulized corticotherapy. One month after the beginning of immunosuppressive therapy the corticotherapy was reduced.

KCNRG, a potassium channel regulating protein expressed in bronchial epithelial cells. The presence of this antibody was first described in the polyendocrine syndrome type 1. The presence of this antibody in another autoimmune syndrome confirms the fact that KCNRG is a major bronchial autoantigen.

The recognition of pulmonary autoimmune phenomenon is important because the airways bronchiolitis in this case respond well to immunosuppression.
P3344 Pulmonary alveolar proteinosis due to a novel mutation in CSF2RA


Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by pulmonary accumulation of surfactant protein. Congenital forms can result from mutations in granulocyte macrophage-colony stimulating factor (GM-CSF) receptor genes, leading to impaired differentiation of alveolar macrophages. We present the case of a 3-yr-old girl born to consanguineous parents presenting with progressive dyspnoea, cough and failure to thrive. Her arterial oxygen saturation was 80% while breathing ambient air and dropped to 50% during agitation. Chest radiographs showed bilateral opacities, and high-resolution computed tomography (CT) revealed interlobular densification with typical “crazy paving” pattern. Due to a milky, opaque appearance of bronchiolalveolar lavage fluid (BALF) and a strongly PAS-positive staining in histology, the diagnosis of PAP was suspected. After whole lung lavage (WLL), significant clinical improvement occurred. Oxygen saturation increased to >90% and follow-up chest radiographs showed partial clearing. Currently, the patient is undergoing WLL every 4-6 weeks. After 10 months of treatment, she has gained 9 kg of weight, visits kindergarten, and has a good quality of life. The patient’s serum- and BALF- GM-CSF concentrations were significantly elevated. Functional analyses of neutrophils and monocytes showed significantly reduced GM-CSF responsiveness. Sequencing revealed a novel mutation in exon 2 of the GM-CSF receptor alpha chain gene (CSF2RA). Regarding long-term treatment, she has gained 9 kg of weight, visits kindergarten, and has a good quality of life.

Background: Pulmonary alveolar proteinosis is a rare disease characterized by pulmonary accumulation of surfactant protein. Congenital forms can result from mutations in granulocyte macrophage-colony stimulating factor (GM-CSF) receptor genes, leading to impaired differentiation of alveolar macrophages. We present the case of a 3-yr-old girl born to consanguineous parents presenting with progressive dyspnoea, cough and failure to thrive. Her arterial oxygen saturation was 80% while breathing ambient air and dropped to 50% during agitation. Chest radiographs showed bilateral opacities, and high-resolution computed tomography (CT) revealed interlobular densification with typical “crazy paving” pattern. Due to a milky, opaque appearance of bronchiolalveolar lavage fluid (BALF) and a strongly PAS-positive staining in histology, the diagnosis of PAP was suspected. After whole lung lavage (WLL), significant clinical improvement occurred. Oxygen saturation increased to >90% and follow-up chest radiographs showed partial clearing. Currently, the patient is undergoing WLL every 4-6 weeks. After 10 months of treatment, she has gained 9 kg of weight, visits kindergarten, and has a good quality of life. The patient’s serum- and BALF- GM-CSF concentrations were significantly elevated. Functional analyses of neutrophils and monocytes showed significantly reduced GM-CSF responsiveness. Sequencing revealed a novel mutation in exon 2 of the GM-CSF receptor alpha chain gene (CSF2RA). Regarding long-term treatment, she has gained 9 kg of weight, visits kindergarten, and has a good quality of life.

P3345 An unusual development in a girl with recurrent croup – Case report

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Background: Recurrent croup is common in childhood. Rare congenital and acquired pathologies may mimic viral croup.

Case: A girl with previously suspected laryngomalacia was admitted with a first episode of croup at 8 months of age, only partially responding to inhaled adrenalin. Laryngoscopically, the dorsal tracheal mucosa bulged into the subglottic area causing a 50% narrowing of the airway, and a CT showed a soft tissue mass, but not suggestive of a hemangioma that was not suggestive of a hemangioma. In view of the inconspicuous appearance, the rapid recovery from the croup, the young age, and the location it was decided not to biopsy the lesion. After an uneventful observational period with decreasing symptoms the girl presented again at 4 years of age with a typical OSAS. With respect to the personal history, a bronchoscopy was made that confirmed significant adenotonsillar hypertrophy, but also revealed marked growth of the subglottic mass. A transtracheal biopsy was performed, and a plexiform neurofibroma was found. Due to the infiltrative growth of the neurofibroma, extensive surgery including partial tracheal resection became necessary. Eventually, the diagnosis of neurofibromatosis (NF) type 1 was made.

Conclusion: Neurofibromata in NF1 may occur in the laryngeal area, presenting early in infancy mimicking common croup.

P3346 Type IV laryngotracheoesophageal cleft: A case of success

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Introduction: Laryngotracheoesophageal clefts (LITEC) are extremely rare congenital anomalies. Mortality and morbidity is high due to difficulty in assure newborn stability, surgical approach and associated comorbidities.

Clinical case: A 12 days male newborn, without relevant prenatal history, was admitted in NICU with feeding problems and suspected tracheoesophageal fistula. Pulmonary parenchma was preserved. After initiation of ventilatory support he developed severe acute respiratory distress. Diagnosis of a type IV LITEC, extended to carina, was made by emergent rigid laryngoscopy with immediate selective intubation of right bronchus. Multidisciplinary surgical correction was performed 48 hours after, with international expertise collaboration. Tracheoesophageal separation was made by median sternotomy, requiring cardiopulmonary bypass. Few days after surgery the newborn underwent gastrotomy, fundoplication and tracheostomy because of severe tracheomalacia causing difficulties in ensure noninvasive ventilation. At 3 months a small bleeding granuloma near carina was coagulated with YAG laser. Consecutive endoscopic evaluations showed a partial LITEC dehiscence. Successful transversal surgical correction and definitive tracheostomy decannulation was made at 10 months. By 20 months he had a normal growth and development, with little hoarseness, sporadic cough and almost full oral feeding.

Conclusion: Type IV LITEC is the rarest and severest form of laryngeal clefts. This was an atypical presentation without any severe respiratory distress in the first hours of life and any prenatal or pulmonary findings. These aspects and the prompt expertise intervention assured an excellent outcome without major comorbidities.

P3347 Whole lung lavage with PAP in a 12 year old female using ET tube under GA

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Alveolar proteinosis is a rare disease in children as the rare cause of severe respiratory failure. In 2002 report at least 410 cases were reported world-wide. The estimated annual incidence is 0.36 and the prevalence 3.76 cases/million population. In neonates the mortality is 100% Lung transplantation improves survival. In adults, PAP is mainly seen in males at the age of 40-55. In female children alveolar proteinosis is rare. PAP is characterized by intra-alveolar accumulation of proteinaceous material. It is not associated with inflammation and lung architecture is preserved. Case study: A 12 year old girl was admitted with breathlessness, cough, with two weeks duration. She was referred from a private hospital in Salem with X-ray and CT features of PAP. alpha. She was taken up for medical traumatology. CT scan repeated showed features of alveolar proteinosis. After stabilizing her with intubation and antibiotics she was taken up for whole lung lavage on the right side. Since the double lumen catheter of 26 size could not permit insertion of bronchoscope, through 6.5 ET tube under general anesthesia Right lung was lavaged with about 1700 ml of normal saline. The catheter tolerated the procedure well. She was kept in the ventilator for one day and exubated. The saturation went up to 90%. The left lung was washed after one week. The saturation and clinical signs and symptoms improved. She is again admitted on 22/12/2011 for the next lavage session. The treatment for alveolar proteinosis is whole lung lavage in adults. We report the case in a young girl (rarely reported)treated with whole lung lavage using ET tube (rarely tried).

P3348 Endoscopic laser-assisted management of pediatric airway lesions: A single institution experience

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Background: Laser endoscopic surgery is increasingly being used in the treatment of pediatric airway disorders. It is a safe and effective technique when used by experienced surgeons.

Aims: We evaluated the outcomes of laser therapy in a selected group of patients with congenital and acquired airway lesions.

Methods: The medical charts of patients who were treated for airway disorders with diode laser between January 2008 and December 2011 at a tertiary care children’s hospital were reviewed. All the procedures were performed endoscopically using rigid or flexible instruments. Data included relevant history and physical examination, diagnostic work-up, number of laser procedures, complications, and outcomes.

Results: 37 patients who had laser surgery were identified.13 girls and 24 boys with a mean age of 20 months (range, 3 days-12 years). 47 laser surgeries were performed, representing 1.2 procedures per patient. Indications for laser therapy were: Laryngomalacia 11 cases (29%), granulation tissue 8 (21%), vocal cord paralysis 7 (19%), laryngeal stenosis 5 (13%), vascular-lymphatic malformation 3 (8%), subglottic cyst 1 (2.7%), congenital tracheal stenosis 1, and papillomatoasis 1 case. In 7 patients (19%), other concomitant endoscopic procedures were performed. Two complications were identified: Postlaser bleeding and aspiration in one patient, and subcutaneous emphysema and pneumothorax in another patient. In 89% of patients, partial or complete clinical improvement occurred after laser therapy.

Conclusions: Endoscopic laser surgery is a safe and effective technique when treating airway disorders in children. It is a good alternative to open surgery in selected patients either used alone or in combination with other endoscopic procedures.

P3349 Endobronchial blockers: A tool in the interventional flexible bronchoscopy in children

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Introduction: Techniques for selective lung ventilation usually involves the use of large devices or tools not designed for the airway. Placement in children is difficult and a variety of complications have been reported.

Objectives: To evaluate the efficacy and safety in selective ventilation and selective lobar blockade of a recently developed tool, the Arndt endobronchial blocker.

Methods: A prospective study was performed analyzing all children who underwent a bronchial blockade between 2008 and 2011. We use the 5 Fr Arndt blocker
and a pediatric fiberoptic bronchoscope (2.8mm). The following variables were recorded: age, indication, location, duration and number of insertion attempts, other techniques performed, complications, and effectiveness assessed by the surgeon or pediatric intensivist.

**Results:** Blocker placement was successful in 17 of 18 patients. Median (range) age was 37 (14-78) months. 9 cases = 2 years old. The main indications were thoracic surgery, pulmonary bleeding and persistent bronchopulmonary fistula. Number of attempts needed was 1 to 4 (median 1). Average time for positioning the blocker was 7.5 minutes. In 3 procedures, we injected saline (Tissucol) through the 2Fr central lumen of the blocker. The most frequent complication encountered was dislodgement toward main bronchi or trachea in 5 cases, related to turning the patient into a lateral position. They were managed deflating the cuff and placing the blocker again. Average satisfaction after the procedure (assessed from 1 to 5) was 4.7.

**Conclusion:** Arndt endobronchial blockers are useful. Our initial experience has shown that placement with a fiberoptic bronchoscope is easy, acceptably rapid and effective.

**P3350**
The use of transbronchial biopsies in pediatric lung diseases in a tertiary care hospital in Bogota, Colombia
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A total of 12 Transbronchial Biopsies (TBB) were performed in pediatric patients during the last year at the Hospital Universitario San Ignacio, using an adult small bronchoscope (5.5 mm outer diameter Olympus).

**Results:** In 9 patients adequate lung tissue for histological diagnosis was obtained. In two patients with HIV infection, respiratory symptoms and chest x-ray abnormalities, pathogens were identified and successfully treated positive ZN (13 y.o. female) and P. Jiroveci (12 y.o. female). Several patients presented with dyspnea and mosaic patterns in the chest x-ray: in three cases the information was useful, and all of them improved after treatment. 12 y.o. male in whom lung metastasis were found (successful chemotherapy initiated), 14 y.o. male in whom capillaritis was found (improvement after treatment). In an 8 y.o. male insufficient sample was reported. In patients with malignancies, useful information was provided: in patients with lymphomas and lung infiltrates CMV was identified and treated (10 y.o. male) and P. Jiroveci was found in two patients with leukemia. The only complications were a small pneumothorax that did not require intervention and hypotension in a septic HIV patient that was sent to Intensive Care for management.

**Conclusion:** The Transbronchial biopsy is an effective and safe procedure to obtain lung tissue for histologic diagnosis in a variety of conditions such as tumors, infections or pulmonary infiltrates and that can be considered as first–line diagnostic procedure in pediatric patients.

**References:**

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**373. Medical access to the pleura**

**P3351**
A pilot study for benign central airway stenosis: Local injection of triamcinolone acetonide through an endobronchial blocker
Yu Chen, Shiyue Li. Respiratory Medicine, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, China

**Objectives:** To evaluate the efficacy and security of local injection of Triamcinolone acetonide (TA) for benign central airway stenosis (BAS).

**Methods:** Forty intractable BAS patients were selected and averagely divided into treatment group and control group. Local injection of TA was used to cover entire stenosis lesions. Interventional procedures were combined to manage complicated airway stenosis. After a 6 months follow-up, compared two groups with airway diameter, stricture rate, dyspnea score, and clinical stabilizations before and after the treatment.

**Results:** No statistically significant differences in the two groups. A 6 months follow-up, 16 patients remain stable after treatment, besides 4 patients appear restenosis in treatment group, compare with Control group 20 cases restenosis. Restenosis interphase time and clinical stabilization time was markedly increased. No local injections related complications was recorded.

**Conclusion:** Local injections of TA therapy combined with traditional interventional techniques for BAS has good curative effect. It shows advantages in long-term efficacy, few side-effects, and good safety.

**Table 1. TA group treatment results**

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>Airway diameter (mm)</th>
<th>Stricture rate (%)</th>
<th>Dyspnea score</th>
<th>Clinical stationary time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before TA treatment</td>
<td>3.10±1.80</td>
<td>77.06±13.63</td>
<td>3.45±0.51</td>
<td>10.95±5.49</td>
</tr>
<tr>
<td>After TA treatment</td>
<td>9.30±2.34</td>
<td>26.82±12.69</td>
<td>0.35±0.49</td>
<td>98.75±55.58</td>
</tr>
</tbody>
</table>

**Statistics**
13.102 10.455 20.743 5.724

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**P3352**
Role of single port medical pleuroscopy using optical biopsy forces in diagnosing malignant pleural effusion
Debabountain Bhattacharyya, M.S. Barthwal1, C.D.S Katoch1, Anand Arora2.
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**Introduction:** Medical pleuroscopy is useful in early confirmation of malignant pleural effusion. Optical biopsy forces help in getting adequate number and amount of specimen from a single port giving a small incision.

**Aims and objectives:** To assess the efficacy and safety of single port medical pleuroscopy using optical biopsy forces in diagnosing malignant pleural effusion.

**Methods:** This is a retrospective study of all patients who had been histopathologically proved to have malignant pleural effusion by single port diagnostic medical pleuroscopy using optical biopsy forces between January 2009 and January 2012 in a tertiary care hospital in India.

**Results:** 39 patients (25 males and 14 females) underwent medical pleuroscopy during the period of study with a possible diagnosis of malignant pleural effusion. Mean age of patients was 4 years (ranging 70-82). 37 patients (94.9%) were confirmed to have malignancy by medical pleuroscopic biopsy. Adenocarcinoma was the commonest malignancy – 15 (40.5%), followed by squamous cell carcinoma – 11 (29.7%), small cell carcinoma – 5 (13.5%), poorly differentiated carcinoma – 3 (8.1%), malignant mesothelioma – 2 (5.4%), and non-Hodgkin’s lymphoma (2.7%). Reports were inconclusive in two patients. VATS biopsy subsequently confirmed them to be adenocarcinoma and mesothelioma respectively. Complications encountered during the perioperative period included: superficial wound infection in one (2.5%), and air leaks more than 7 days in two (5.1%) cases.

**Conclusions:** Single port medical pleuroscopy using optical biopsy forces has a high diagnostic rate in malignant pleural effusion. The procedure is also safe.

**Table 2. TA group compare with control group after 6 months follow up**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Airway diameter (mm)</th>
<th>Stricture rate (%)</th>
<th>Dyspnea score</th>
<th>Clinical stationary time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.50±1.64</td>
<td>64.80±13.35</td>
<td>2.70±0.92</td>
<td>11.35±4.39</td>
</tr>
<tr>
<td>TA</td>
<td>8.70±2.52</td>
<td>29.17±4.55</td>
<td>0.55±0.76</td>
<td>98.75±55.58</td>
</tr>
</tbody>
</table>

**Statistics**
6.658 8.161 7.844 7.070

p<0.01.

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**P3353**
Medical thoracoscopy performed using FOB & single rigid port under conscious sedation
Vijay Kumar Channammehthy, Aparna Mazumreddy, Anamika, Abhijeet Ingle, Amitha Reddyreddy. Department of Pulmonary, Critical Care & Sleep Medicine, Yashoda Super Speciality Hospitals, Hyderabad, AP, India

**Background & Objectives:** Pleural effusion can remain undiagnosed following thoracentesis in a significant number of cases. We evaluated our own technique for performing thoracoscopic under conscious sedation using a 7mm rigid port and a flexible fiber optic bronchoscope for the diagnosis of patients with unilateral pleural effusion. We evaluated cost of care by comparing the same procedure with rigid thoracoscopy.

**Methods:** Twenty four patients with unilateral pleural effusion who underwent thoracoscopy under conscious sedation using a 7mm rigid port and a flexible fiber optic bronchoscope during April 2011 to Feb 2012 were retrospectively studied. Two patients who underwent rigid thoracoscopy for evaluation of undiagnosed effusion were taken to consideration for cost analysis.

**Results:** Thoracoscopy done under conscious sedation using FOB and a 7mm port is a safe procedure to perform in the diagnosis of pleural effusion in all cases. The visualization of the pleura and lung using this instrumentation was adequate for to acquire an impression. A forces biopsy of the pleura could therefore be easily and effectively performed. Cost analysis does reflect 30% decrease in cost to patient.

**Conclusion:** This technique is considered to have clinical utility as a diagnostic tool for evaluation of pleural effusion. This method is safe and effective. As procedure was performed with FOB, it is user friendly for a pulmonologist and inexpensive to the patient.

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**601s**
Usefulness of semiflexible thoracoscopy under local anesthesia for patients with unknown pleural effusion

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Background: Pleural effusion may arise from a wide range of diseases. However, it is difficult to make a diagnosis by thoracocentesis or needle biopsy. Recently, semiflexible thoracoscopy has been performed under local anesthesia for diagnosis or treatment of pleural diseases.

Objectives: To determine the benefit and safety of the thoracoscopy for the diagnosis of unknown pleural effusion or the treatment of pleural diseases.

Methods: Between April 2001 and June 2011, we performed the thoracoscopy in 39 patients (31 men and 8 women) who could not be diagnosed by cytotologic and bacteriologic examinations of pleural fluid by thoracocentesis. We used a semiflexible thoracoscope (LFT 240, Olympus Medical Systems Co., Tokyo, Japan) for the observations of pleural cavity, and obtained pleural biopsies from abnormal areas of parietal pleura.

Results: We underwent semiflexible thoracoscopy in 29 patients for diagnosis of pleural diseases and 22 cases were provided the pathological diagnosis (6 pleuritis carcinomatosa, 2 malignant mesothelioma, 1 synovial sarcoma, 7 effuyma, 3 tuberculosis pleural effusion, 2 rheumatoid arthritis and 1 sarcoidosis). In addition, semiflexible thoracoscopy was performed for the treatment in 10 cases with acute or chronic empyema for the purpose of detachment of fibrin, destruction and removal of the septum.

Conclusions: Semiflexible thoracoscopy under local anesthesia can be safely performed by pulmonary physicians. It is considered an easy and useful examination for the diagnosis of pleural diseases.

Use and comparison of a fiber optic bronchoscope as an alternative to a purpose built thoracoscope

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Background: Mechanical failure of (fiber optic thoroscope) FOT at our unit, which was an established investigation in pleural disease led to a search for an alternative.

Objective: To demonstrate the use of a fiber optic bronchoscope (FOB) for local anesthesia thoracoscopy and to compare it with a purpose build thoracoscope.

Methodology: The new procedure was similar to standard local anesthetic thoracoscopy with the difference being an 8mm internal diameter endotracheal tube used as the trochar through which FOB was inserted. 22 patients with undiagnosed unilateral plural effusion underwent the procedure from July to November 2011. Their results were compared to those obtained using purpose built FOT in 22 consecutive patients from January 2011.

Results: Modified FOB thoracoscopy was successful in 77% of patients while purpose built FOT was successful in 86%. All failures were attributed to lungs not collapsing due to adhesions. Time taken to empty fluid from the pleural cavity and total procedure times were longer with FOB. The biopsy size using FOB was significantly smaller. Histological diagnostic yield was matched in both groups. Histological evidence of TB was obtained 22%(5) in FOB group and 27%(6) in the FOT group. A universal complication in both groups was post procedure pain which was relieved with use of simple analgesics. Other procedure related complications were not encountered in both groups.

Conclusion: A modified procedure with FOB can be used safely with a reasonable success rate to investigate pleural disease by experienced operators although there are limitations.

Talc pleurodesis in malignant pleural effusions: A 5-year experience

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Introduction: Talc pleurodesis is an excellent therapeutic option in patients with malignant pleural effusions (MPE), however the best method to perform it remains a matter of debate.

Objectives: To compare two different methods of talc instillation in terms of clinical efficacy and safety in patients with MPE.

Methods: Retrospective study of patients with MPE submitted to talc pleurodesis between 2006 and 2010. Two different techniques were compared: thoracoscopic talc poudrage (TP) and talc slurry through the chest tube (TS).

Results: A total of 93 patients were evaluated (47 TP group, 46 TS group). Clinical demographics and primary malignancies were similar in both groups. The overall complication rate was 54.8%, without significant difference between the two groups. Most frequent complications were thoracic pain (32,3%), fever (24,7%), subcutaneous emphysema (7,5%) and prolonged drainage (5,4%). No serious complication or death was registered. The average length of hospital stay was 8 days in the TP group vs 19,7 days in the TS group (p=0,001). The average chest drain and suction duration was 5,6 days in the TP group vs 19,7 days in the TS group (p=0,001). Among patients alive at 30 days, efficacy in local control of MPE was 82,5% in the TP group (33/40) vs 72,1% in the TS group (31/43) (p=0,259). There was no difference in mortality between the two groups (p=0,336).

Conclusion: Talc pleurodesis was a safe and effective palliative treatment for patients with MPEs. Patients who underwent thoracoscopic talc poudrage had a significant shorter length of hospital stay and chest drainage duration. There was no difference regarding complications, efficacy and mortality.

Performing biopsies during semirigid thoracoscopy is often a difficult and time-consuming task due to the low mechanical power when using dedicated flexible forceps. Biopsies by cryoprobe could overcome these limitations. The purpose of this study was to compare the feasibility, size and quality of the specimens obtained by cryobiopsy with specimens obtained by flexible forceps.

Fifteen patients with pleural effusion of unknown origin that underwent semirigid thoracoscopy were included. Biopsies were obtained using a flexible autoclavable cryoprobe 20416-032 (ERBE, Germany) 2,4 mm in diameter or flexible FB-55CD-1 Olympus forceps.

Reference:
P3359
The change of complication rate in chemical pleurodesis after replacement of
talc preparation from small to large particle size – A longitudinal cohort study
Hoi Nam Tse1, Ka Yan Wai1, King Ying Wong2, Kwok Sang Yee2, Lai
Yun Ng2
1Medical Department, Kwong Wah Hospital, Hong Kong, Hong Kong; 2Department of TB and Chest Unit, Wong Tai Sin Hospital, Hong Kong, Hong Kong
Background: Talc particle size is an important determining factor for complication
in talc pleurodesis.
Aims: To investigate any change in complication rate for talc pleurodesis after
replacement of talc preparation from small to large particle size.
Methods: It is a longitudinal cohort study conducted in Kwong Wah Hospital,
Hong Kong. Talc preparation was changed from small (mean diameter <10μm) to
large particle size (Steritalc®; mean size: 31.3μm) since 1st Jan,10. Patients who
received new talc preparation (1st Jan 10 to 31st Dec,11) were compared to those
received old talc preparation (1st Jan07 to 31st Dec09). The safety profile and
efficacy of pleurodesis were compared between the 2 groups.
Results: 141 patients were recruited. Since the change of talc preparation from
small to large particle size, ARDS was totally eliminated. Post-pleurodesis fever
was significantly reduced from 30.7 to 9.4%, resulting in a significant drop in
antibiotic use.
Table 1. Complications rate in chemical pleurodesis since the change of talc preparation from
small to large particle size.

<table>
<thead>
<tr>
<th></th>
<th>Small particle size</th>
<th>Large particle size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>(3/88) 3.4%</td>
<td>(0/53) 0%</td>
</tr>
<tr>
<td>Post-procedure Fever</td>
<td>(27/88) 30.7%</td>
<td>(5/53) 9.4%</td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td>(12/88) 13.6%</td>
<td>(25/53) 3.8%</td>
</tr>
<tr>
<td>Mean decrease in SpO2</td>
<td>-2.4%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Moreover, the efficacy of chemical pleurodesis was not jeopardized.

Conclusions: There was a significant reduction in complication rates in chemical
pleurodesis after replacement of the talc preparation from small to large particle size.

P3360
Chest drain safety checklist
Burhan Khan, Hamid Amrty Raud. Department of Respiratory Medicine, Darent Valley Hospital, Dartford, Kent, United Kingdom
Background: Intercostal chest drains are amongst the most invasive procedure a
medic will undertake; not infrequently by a junior trainee. Adverse events un-
fortunately are well reported with chest drains, the UK’s National Patient Safety
Agency (NPSA) reported1, little is known about the learning curve attributed to the procedure.
Aim: To devise a chest drain proforma to improve patient safety and prevent
adverse and never events.
Methodology: We used an iterative model building upon the WHO surgical safety
checklist. Results: We devised and piloted a “Chest drain safety check list” utilising a
2-person stepwise approach.

Conclusion: This checklist represents a process that should lead to a systematic
and safe approach to inserting chest drains.

P3361
The need for including pleural procedure sessions in respiratory physicians’
job planning in the United Kingdom
Rahul Makherje1, Shiv Shukla2, Vikas Punnumiya1, Milan Bhattacharya2, Richard Steyn3
1Department of Respiratory Medicine & Physiology, Heart of
England NHS Foundation Trust, Birmingham, West Midlands, United Kingdom; 2Department of Thoracic Surgery, Heart of England NHS Foundation Trust, Birmingham, West Midlands, United Kingdom; 3Department of Respiratory Medicine, Milton Keynes NHS Foundation Trust, Milton Keynes, United Kingdom
Background: In 2008, the UK National Patient Safety Agency (NPSA) issued an
alert for risks associated with insertion of intercostal chest drains (ICD) and high-
lighted issues related to insertion by non-specialists and by inadequately trained or
supervised junior doctors.
Methods: In an acute hospital (catchment population about 280000), an education
campaign targeted at emergency medicine on-call doctors was started in August
2008 questioning the need for out-of-hours insertion of ICD. Three physician-led
elective sessions/week were introduced in November 2008; trainees were directly
supervised by experienced physicians (consultants); all unavoidable out-of-hours
ICD procedures were reviewed by respiratory consultants.
Results: Fifty-two patients underwent ICD insertion in 5 months: 18 (34.62%)
for pneumothorax; 34 (65.38%) for effusions. Of the 34 with pleural effusions, 31
(91.17%) had radiological imaging pre-procedure. The 3 (8.82%) who had ICDs
without prior radiological imaging were due to suspected empyema thoracis in
the emergency department. Only 2 ICDs (3.84%) - both for pneumothoraces -
were complicated by infection of the pleural space. No other major complications
occurred in the remaining 50 patients. Initial ICD was displaced in 8 patients
needing further ICD insertions (15.38%), confirming a significant improvement
with respect to the local average.
Conclusion: The successful pilot of consultant-led ICD-insertion sessions led to
reduced length of stay, improved outcomes and improved trainee feedback - hence
our policy recommendation to include pleural procedure sessions in physician job
plans which is currently not undertaken uniformly in the UK.

P3362
Medical thoracoscopy: Learning curve of a new service
Arun Khanna, Sanjay Adlakha, George Mabeza, Irfan Wahedna, Robert Berg,
Chris White. Respiratory Medicine, Derby Hospital NHS Trust, Derby, Derbyshire, United Kingdom
Introduction: Many hospitals have, or plan to establish, a Medical Thoracoscopy
(MT) service. Whilst high diagnostic yields and low adverse event rates are widely
reported1, little is known about the learning curve attributed to the procedure.
Aims: To examine the diagnostic rate per annum (‘hit rate’) and learning curve of a
Medical Thoracoscopy service in a large District General Hospital.
Methods: We retrospectively analysed data from our first 100 consecutive MT’s
since November 2008. Procedures were carried out by three Consultants with
experience of Medical Thoracoscopy, one Consultant learning the technique and
trainees under close supervision. ‘Hit-rate’ per year was calculated and trend
analysed to determine the learning curve.
Results: ‘Hit-rate’ was 65% in year 1, 79% in year 2 and 89% in year 3,
demonstrating a steep learning curve for this skill. Histologically confirmed diag-
nosis included mesothelioma (n=34), metastatic lung cancer (n=20; predominantly
non-small cell lung cancer), other metastatic malignancy (n=16;predominantly
Ca Breast), pleural Tuberculosis (n=4), chronic inflammation (n=13) and fibrous
pleural plaque (n=1).Five MT’s were performed for palliative purposes, one had
to be abandoned and six failed to achieve a diagnostic yield. No major procedure
related adverse events were noted during the study period.
Conclusions: This data provides insight into the diagnostic learning curve of a new MT service. Improved patient selection and enhanced operator skills should produce a diagnosis rate of over 90% in year 4. The study also re-confirms the safety and high diagnostic yield of this procedure, even outside the settings of mesothelioma.

Reference:

P3363
Significance and long-term outcome of nonspecific pleuritis after medical thoracoscopy

Xanthi Tsatsaki, Maria Chorti, Niki Marouinis, Maria Kokoletaki, Constantine Mantzaroussis, Vasilis Filadaktis, 1 Second Department of Chest Medicine, Sismanoglou General Hospital, Athens, Greece; 2Department of Pathology, Sismanoglou General Hospital, Athens, Greece; 3Department of Cytology, Sismanoglou General Hospital, Athens, Greece; 4Department of Anesthesiology, Sismanoglou General Hospital, Athens, Greece

Introduction: A specific diagnosis of an exudative pleural effusion (EPE) often poses a clinical challenge for the pulmonary physician. Although medical thoracoscopy (MTH) remains the gold standard technique in the work up of patients with EPE, a definite histological diagnosis will not be established in a significant number of the cases and will therefore be characterized as non-specific pleuritis (NSP).

Objective: To study the outcome of patients with NSP in a group of patients with long term follow up.

Method: A retrospective analysis was performed on 110 patients who underwent thoracoscopy for EPE, over a 7 year period, at our Institution. In 47 (42.7%) cases, that were histologically diagnosed as NSP, long-term follow up was available (a minimum of 24 months). MTH was performed by a respiratory physician, experienced in the procedure, under local anesthesia and IVIM sedation.

Results: A definite histological diagnosis was established in 63 patients. In the remaining 47 (42.7%), 35 men and 12 women with mean age of 64.5 years, the diagnosis of NSP was rendered. Four of the latter (8.5%) were subsequently diagnosed with malignancy after an interval of 3-5 months (2 mesotheliomas, 2 adenocarcinoma). A probable cause was established on clinical grounds in 13 (27.6%) cases. Finally, in 30 (63.8%) patients, the underlying etiology for NSP was not discovered and was therefore, described as “idiopathic pleuritis”.

Conclusions: In our series 3.6% proved to be false negative, after a mean follow up of 4 months. Furthermore, in 27.3% of our undiagnosed EPE cases, a definite diagnosis could not be determined and was characterized as “idiopathic pleuritis”.

P3364
Eosinophilic pleural effusions – Is everything clear?

Jan Plemiski, Pranilek Dvorak, Zuzana Taligova, Renata Sabova, Stanislava Sabova. 2nd Pneumology, Specialized Hospital of St.Zoerardus, Nitra, Slovakia (Slovak Republic)

Introduction: Eosinophilic pleural effusion (EPE) for long time was considered a result of benign concomitant diseases with a good prognosis. Blood or air in the pleural fluid (PF) could cause EPE in most cases. In some EPE the etiology is unknown. Epidemiology is varied from 5-12%. We analysed our patients (pts) with PF and we focused on the group with EPE.

Aim: To share our own experience with diagnosis, differential diagnosis and prognosis of EPE.

Methods: We analysed 390 pts with a definitely confirmed diagnosis of pleural effusion. The diagnosis was confirmed biochemically, cytological analyses of PF, histologically by blind pleural biopsy or by medical thoracoscopy. Cell count was made routinely. Light’s rule was used for the diagnosis of transudates and exudates. EPE was defined when 10% or more eosinophilic leucocytes appeared on a differentials cell count.

Results: 3 M and 19 F, median age 71 years (51-85 yrs) had EPE (3.33%). From them 3 had lung carcinoma, 1 breast carcinoma, 2 pneumonia, 2 heart failure, 1 pnuemothorax, 1 traumatic PL, 1 pancreatitis as diseases causing EPE and only 1/3 had idiopathic EPE (7.6%), or 0.25% from 390 pts. Median of eosinophils in PE was 25% (from 10% to 88%). Ten of the PE were exudates and 3 transudates.

Conclusions: In our cohort of pts with EPE 30.8% had carcinoma and only 1 was idiopathic. Median age is high. Prognosis is better in 2/3 pts and it was interesting that 3 pts had transudates. Also of interest was the lower incidence of EPE in our cohort in comparison to literature sources. EPEs present the inhomogeneous group of pleural diseases with unclear prognosis.

P3365
Occurrence of malignancy after an initial diagnosis of post-thoracoscopy fibroinflammatory pleuritis

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Introduction: Fibroinflammatory (FI) is a common thoracoscopy diagnosis and implies a benign aetiology, however, the number of cases that subsequently result in malignancy is not fully known.

Objectives: To evaluate what proportion of patients with FP following thoracoscopy develop malignancy.

Methods: Retrospective analysis was conducted of all thoracoscopies performed for unexplained exudative pleural effusions between 2005-2009. In cases with an initial histological diagnosis of FP, review of radiology and history for at least 24 months post thoracoscopy was undertaken.

Results: Of 177 thoracoscopies, 90 (49%) were malignant and 87(51%) were non-malignant. FP was the diagnosis in 68 (38%) of cases, with 55(81%) male and a mean age of 72.5 (±10.4) yrs.

In 10 (15%) FP cases the subsequent diagnosis confirmed malignancy, with 5 (7.5%) of mesothelioma. Four had further immediate positive investigation (false negatives), six developed overt malignancy at a later stage. Of the 68 patients 35 (51%) had died, 27(39%) with no evidence of malignancy, with a mean survival of 502 days.

Mean survival of those with malignancy was 534 days p 0.75. Patients who died with a benign process were significantly older, 74 yrs vs. 70.5yrs p=0.043 (±11.4).

Conclusions: The majority of FP cases follow a benign course but need 2 years follow-up, as a proportion develop malignancy after a significant interval. Benign exudative pleural effusion is a poor prognostic marker in the elderly despite the absence of subsequent malignancy.

P3366
Role of Abram’s pleural biopsy in determining the cause of empyema thoracis

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Introduction: Empyema thoracis remains a major problem in developing countries. Clinical outcomes in tuberculous empyema are generally believed to be worse than in non-tuberculous. So with the help of Abram pleural biopsy early detection of the cause of empyema and its treatment could be possible.

Objectives: To evaluate the role of Abram’s pleural biopsy in determining the cause of empyema thoracis.

Methods: A prospective study of patient’s data was undertaken at the Pulmonology department at the largest public tertiary care centre in Karachi, Pakistan. Pleural biopsies for histopathology were obtained using Abram’s pleural biopsy needle from 46 patients admitted with empyema thoracis between August 2010 and August 2011; along with pus for Gram staining, routine culture, AFB smear and AFB culture, and the results of these variables were compared for diagnostic efficiency.

Results: A comparison of the diagnostic tools used showed positive Gram staining in 28 out of 46 (60.9%) cases. Bacterial cultures were positive in 24 (52.1%) of the cases, with the 10 (21.7%) positive for Streptococcus pneumonia, 8 (17.4%) positive for Pseudomonas aeruginosa, 6 (13%) positive for Staphylococcus aureus; and 15 (32.6%) with AFB growth. AFB smear positivity in culture was 4 (8.6%).

Whereas histopathology revealed 28 (60.9%) cases as having acute on chronic pyogenic inflammation, 12 (26.1%) with chronic non-specific inflammation, and 6 (13%) with acute on chronic granulomatous inflammation.

Conclusions: In comparison to other diagnostic techniques, there is no benefit of performing Abram’s pleural biopsy in determining the cause of empyema thoracis. Pus culture has a better yield in specifying the cause in most cases.

P3367
Risk of intrapleural hemorrhage following thoracocentesis

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Background: Diagnostic or therapeutic thoracocentesis is usually a simple and safe procedure. The extent to which coagulation abnormalities induced by antithrombotic therapy (ATT) increase the risk of intrapleural hemorrhage following thoracocentesis is unknown.

Objective: To examine the risk of intrapleural hemorrhage following diagnostic or therapeutic thoracocentesis in patients with or without ATT.

Methods: We conducted a retrospective cohort study of all the diagnostic or therapeutic thoracocentheses performed in our institution over a three-year period (2007-2009). We considered only the procedures performed without ultrasonic guidance. Antiplatelets and anticoagulant therapy at the time of the procedure were recorded. Coagulation parameters (international normalized ratio, partial thromboplastin time, platelet count) and hemoglobin level were also noted. We defined intrapleural hemorrhage as either a recurrent pleural effusion with a fall in hemoglobin >20 grams/liter, or a hemothorax necessitating pleural drainage.

Results: A total of 695 patients underwent 953 thoracocentheses; data were available from 940 of them. 738 procedures (78.5%) were performed on patients on either antiplatelets or anticoagulant therapy. Overall, 7 intrapleural hemorrhages were noted (overall incidence rate: 0.7%), all in patients with antithrombotic therapy (ATT). 7/38 vs. no ATT: 0.02; Fisher’s exact test: p = 0.22).

Conclusion: The incidence of intrapleural hemorrhage following thoracocenthe- sis was low. Although the event rates in patients with or without ATT were not statistically different, all intrapleural hemorrhages occurred in patients with antithrombotic therapy.
The aim of our study was to analyze lung function throughout infancy and adolescence in cohorts of CF patients diagnosed after neonatal screening. We retrospectively evaluated the spirometry of patients born in the years 1992–1994 who had been visited at least three times yearly and compared the decline in FEV1 and FEF 25-75 (both % predicted) in pre-adolescence (pre ado; age range 8–12 years) and during adolescence (age range 13–17 years). The mean decrease in FEV1% was -0.35 (SD ± 1.19) in the pre ado period and -1.41 (SD ±1.17) during adolescence with no significant difference in decline between the two periods, (p=0.45, paired t test). However, the mean variation in FEF 25-75 was 7.9% (SD ± 3.2) in pre ado and -6.7 (SD ±2.6) during adolescence (p=0.009).

Our data show that lung function decreases during adolescence in CF patients as reflected by a loss in FEV 25-75 which is consistent with an anatomical dam-age initially located in smaller peripheral airways. Although FEV1 is universally adopted as a surrogate outcome it seems to be poorly sensitive in evaluating lung disease progression in CF during adolescence.

P3371
Comparative study of three quality of life instruments in adolescent and adults with cystic fibrosis
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Multiple patient reported outcomes have been used in order to measure quality of life in Cystic Fibrosis in Spain, but it is important to find a consensus on which is the most reliable and valid quality of life instrument.

Objective: To compare three quality of life questionnaires widely used among CF patients in order to prove which of them is more valid and reliable when measuring quality of life and disease severity.

Methods: Two disease-specific questionnaires: Cystic Fibrosis Questionnaire-Revised (CFQ-R), and St. George Respiratory Questionnaire (SGQR), and a generic instrument: the Short-form-36 health survey (SF-36), were simultaneously adopted as a surrogate outcome it seems to be poorly sensitive in evaluating lung disease progression in CF during adolescence.

Strong correlations (≥0.70) were found between several of the scales in the three questionnaires: physical functioning, role limitation, energy and vitality, and mental health. The CFQ-R allows a better differentiation of the varying levels of disease severity, plus it has disease-specific scales.

Discussion: An instruments’ validity and applicability should be considered when choosing a questionnaire to measure HRQoL in CF patients. The CFQ-R proved to be the most suitable, although some of its subscales could be reviewed.

P3372
Comparison of the Cystic Fibrosis Questionnaire with the St George’s Respiratory Questionnaire in adult patients with cystic fibrosis
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Background: The Cystic Fibrosis Questionnaire (CFQ-R) is widely used in out- come studies. Nevertheless, correlation with pulmonary function test (PFT) is weak, namely in mild to moderate impairment.

Aim: To prospectively evaluate the accuracy of the CFQ-R with PFT (FEV1, obstructive ventilation defined as ratio FEV1 to vital capacity (FEV1/FVC), and hyperinflation defined as ratio residual volume to total lung capacity (RV/TLC)) and to compare it with the St George’s Respiratory Questionnaire (SGQR).

Methods: Clinical data including PFT were collected. CFQ-R and SGQR were obtained. Spearman correlation was performed.

Results: 32 patients (13 females) with a mean age of 29±11y, body mass index (BMI) of 22.3±3.4kg/m², FEV1 of 67±29%, FEV1/FVC of 0.67±0.14 and RV/TLC of 0.46±0.15 are evaluated. Results of CFQ-R were: physical well-being 74±25, vitality 79±19, eating 93±20, treatment burden 75±19, health perception 72±24, social role 72±18, body image 73±24, role 73±24 weight 77±32, respiration 68±19 and digestion 79±23. Total score of SGQR was 23±17, with following subdomains: symptom 44±25, activity 25±23, impact 15±14. PFT was strongly correlated (p<0.0001) with SGQR activity (FEV1, rh=0.67) and total score (r=0.68), moderately correlated (p<0.005) with CFQ-R physical (0.63) and SGQR symptom score (r=0.59) and weakly correlated (p<0.01) with CFQ-R treatment burden (0.54), health perception (0.57) and role (0.55).

Conclusions: In adult CF patients CFQ-R is only moderately correlated with pulmonary function. In contrast, the SGQR, initial developed for patients with chronic obstructive pulmonary diseases showed a better correlation with PFT.
P3374

The use of high frequency chest wall oscillation during an acute infective pulmonary exacerbation of cystic fibrosis

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Background: Cystic fibrosis (CF) patients hospitalised for an acute infective pulmonary exacerbation require increased airway clearance. Specialist physiotherapists may be a limited resource. We investigated the use of high frequency chest wall oscillation (HFCWO), in addition to usual airway clearance techniques (ACTs).

Objective: The aim was to assess the utility of HFCWO (The Vest, Airway Clearance System, Hill-Rom) as a self administered therapy compared to European ACTs in facilitating recovery from an acute infective pulmonary exacerbation in people with CF when used in addition to supervised physiotherapy.

Method: A non-blinded randomised, controlled design was used. Patients who met inclusion criteria were randomised to control or HFCWO groups. All patients received four daily sessions, two supervised by a specialist CF physiotherapist and two carried out independently. The control group carried out their usual ACTs, the study group used HFCWO with pauses to buflf and cough. The primary outcome measurement was change in FEV1.

Results: n=36 (64% male). Data was analysed using the Wilcoxon Rank Sum test.

<table>
<thead>
<tr>
<th>Control</th>
<th>HFCWO</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) (years)</td>
<td>29.8 (±11.7)</td>
<td>25.8 (±7.3)</td>
</tr>
<tr>
<td>Baseline FEV1 Mean (SD) (mL)</td>
<td>1490 (±900)</td>
<td>1570 (±540)</td>
</tr>
<tr>
<td>Change in FEV1 Median (IQR) (mL)</td>
<td>120 (50, 260)</td>
<td>240 (80, 360)</td>
</tr>
<tr>
<td>Change in FVC</td>
<td>70 (–10, 370)</td>
<td>370 (90, 620)</td>
</tr>
<tr>
<td>Change in FEF25</td>
<td>170 (–10, 540)</td>
<td>500 (–50, 820)</td>
</tr>
<tr>
<td>Change in FEF75</td>
<td>25 (–10, 150)</td>
<td>10 (–30, 50)</td>
</tr>
</tbody>
</table>

Conclusion: Change in FEV1 was not significantly different between groups, however a significant improvement in FVC was demonstrated. HFCWO should be further explored as an adjunct to treatment of infective pulmonary exacerbations of CF.

P3375

Long inhalation time is associated with short treatment time when using the I-neb AAD system in target inhalation mode

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The I-neb Adaptive Aerosol Delivery (AAD) System is designed to emit aerosol only during the inspiratory phase of breathing and can be operated in tidal breathing mode (TBM), in which the user breathes in a normal manner during treatment, or target inhalation mode (TIM), in which the user is guided to longer inhalations via feedback from the I-neb AAD system. The I-neb AAD system is equipped with a patient logging system (PLS) to facilitate the analysis of patient breathing by recording data on treatment time and mean inhalation time per breath per treatment.

Forty nine patients with cystic fibrosis were enrolled in a 13 week handling study; PLS data was analyzed for 43 of these patients. Each patient’s mean treatment (nebulization) time and inhalation time per breath were calculated for treatments taken in TBM or TIM in order to determine the relationship of these variables.

The median of patient mean treatment times for TBM and TIM were 291 and 146 s, respectively. The median of patient mean inhalation times were 2.6 and 6.9 s, respectively. Patients with longer inhalation times generally had shorter treatment times and patients using TIM had shorter treatment times than those using TBM. It might therefore be of benefit for patients using TBM to switch to using TIM.

P3376

Inferior efficacy and safety of tobramycin 300mg/4ml nebulizer solution in patients with cystic fibrosis and chronic Pseudomonas aeruginosa infection

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Introduction: Inhaled tobramycin is considered standard of care for the management of chronic Pseudomonas aeruginosa (Pa) infection in patients (pts) with cystic fibrosis (CF).

Objectives: To compare the long-term efficacy and safety of tobramycin 300mg/4ml nebulizer solution (TNS4: Bramitob ®, Chiesi Farmaceutici S.p.A.) administered over 56 weeks (seven 28-day on/off cycles) was assessed in CF pts chronically infected with Pa.

Methods: A total of 324 CF pts aged ≥ 6 years with baseline 1-second forced expiratory volume (%FVC) ≥ 40% were randomized in an initial 8-week, open-label trial (Core) to receive TNS4 or tobramycin 300mg/5mL (TNS5, Tobi®, Novartis) using PARI Turbo Boy N compressor and PARI LC Plus nebulizer. 209 pts (of which 100 received TNS4 in the Core) continued for an additional 14-week, single-arm extension phase with TNS4 only (Ext). FEV1% predicted and Pa bacterial load in sputum were measured during 14 study visits. Safety was assessed through monitoring of adverse events and audiometry.

Results: Non-inferiority in terms of FEV1% predicted between TNS4 and TNS5 was demonstrated in the Core (mean changes from baseline 7.1% and 7.6%, respectively). After 56-week treatment with TNS4, the mean change from baseline in FEV1% predicted was 5.7% [95% CI: 2.8;8.6]. Reduction in log10CFU/g Pa bacterial load was -1.13 [95% CI: -1.58;-0.68]. No remarkable safety findings were detected.

Conclusions: TNS4 demonstrated a sustained and significant improvement in lung function over a 56-week period and a reduction in Pa density in sputum. TNS4 was safe and well tolerated. Supported by Chiesi Farmaceutici S.p.A.

P3377

Pharmacokinetics of tobramycin nebulizer solution (300mg/4ml) administered by Pari e-Flow rapid vs Pari LC plus nebulizer in patients with cystic fibrosis and Pseudomonas aeruginosa infection

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Introduction: New generation nebulizers are increasingly used to reduce the time required for inhalation, potentially improving patient compliance.

Objectives: To compare the pharmacokinetic (PK) profile of tobramycin nebulizer solution (TNS) 300mg/4ml (Bramitob®) administered with the Pari e-Flow rapid versus the Pari LC plus nebulizer.

Methods: Randomized, crossover trial, enrolling 27 cystic fibrosis (CF) patients with chronic Pseudomonas aeruginosa infection. Patients received two twice-daily, 28-day treatment periods with TNS 300mg/4ml, delivered by either nebulizer, sep-
arated by a 4-week wash-out. Blood and sputum samples were collected on days 1 and 28 over the first 12 and 8 hours, respectively. Primary endpoints were plasma tobramycin maximum concentration (Cmax) and area under the curve (AUC(0-28)) on day 28.

Results: 27 patients were randomized and 25 completed the study. Patients were 18-47 (mean 25.5) years old. On Day 28, the geometric mean ratios (e-Flow rapid vs LC plus) 5.7 (90% CI 0.80-2.33), respectively. Nebulization time was significantly shorter for the e-Flow rapid as compared to the LC plus: 5.7±2.0 versus 12.1±2.2 min (mean ± SD on day 28).

Conclusion: Plasma and sputum PK data support comparable pulmonary delivery of TNS 300 mg/ml, in CF patients using different nebulizers with a shorter nebulization time for the Pari e-Flow device.

Supported by: Chiesi Farmaceutici.

P3378

Temporal changes in the prevalence of respiratory pathogens in children and adolescents with cystic fibrosis (CF)

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Introduction: Changes in the prevalence of respiratory pathogens in CF may reflect improved therapeutic strategies and clinical practice within a CF centre.

Aims: We hypothesized that active microbiological surveillance and a low threshold for low dose nebulised antibiotics might reduce the prevalence of respiratory pathogens in patients with CF.

Methods: Retrospective review of data of patients under full care at a paediatric CF centre in Cardiff between 1998(n=88) and 2011(n=70). We calculated the number of isolates for common pathogens from 1998 onward (expressed as a percentage for each year); mean number of respiratory cultures taken for each patient per year; and the rate of chronic P aeruginosa (Lee 2003) from 2002 onward. Changes in prevalence over time were assessed by linear regression.

Results: Non-significant increase in mean (SD) number of respiratory cultures from 5.3(3.22) to 7.4(2.89) per patient/year. The prevalence of P aeruginosa in fe-no long term nebulised antibiotic therapy decreased significantly from 43.8% in 1998 to 14% in 2011(n= 40, p=0.001), while chronic P aeruginosa infection decreased from 19% in 2002 to 2.9% in 2011(n= 9.9, n=0.001). We also observed significant decreases in the prevalence of A fumigatus (n= 9.9, n=0.001), A influenzae (n=0.58, p=0.03) and B cepacia (n=0.78, n=0.001), and a non-significant reduction in the prevalence of S Aureus with non-significant increases in the prevalence of S maltophilia or MRSA.

Conclusion: Active microbiological surveillance and a low threshold for long term nebulised antibiotics was associated with significant reductions in both the prevalence of P aeruginosa infection and the rate of chronic P aeruginosa infection.

P3379

Long-term linezolid in cystic fibrosis patients chronically colonized with Staphylococcus aureus (SA)

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Treatment of chronic colonization with methicillin-resistant Staphylococcus aureus (MRSA) and non-MR in cystic fibrosis (CF) patients shows a wide variability among CF units. While some caregivers prescribe continuous treatment with inhaled/oral antibiotics, others only treat infectious exacerbations.

Methods: 52 CF patients were included. Mean age was 25.1 years. All patients were chronically colonized by SA (56.9%) and showed a poor clinical progress and respiratory function after receiving several conventional antibiotic cycles to treat infectious exacerbation.

Every patient was prescribed continuous treatment with oral Linezolid: 600mg/12h for 15-21 days every 45 days, for a minimum of 1 year. Serial spirometry, sputum analysis and blood analysis were determined to rule out toxicity derived from a chronic treatment with Linezolid. Health related quality of life was measured every three months with the Cystic Fibrosis Questionnaire-Revised (CFQ-R) to detect any change.

Results: An infection in the pulmonary function drop in FEV1 and FVC was observed, with a recovery and slowing down of this drop after treatment. After a treatment period of at least one-year, no resistances against Linezolid nor serious adverse events were observed. Patient reported outcomes showed improvement in functionality and in clinical symptoms, with a significant decrease of cough and expectoration during the treatment.

Conclusion: Treatment with Linezolid cycles is effective and safe in those patients colonized by SA who present both a clinical and functional torpid progress with conventional treatments. Linezolid allows the stabilization of the symptoms and lung function.

Limitations: Prevalence could have been underestimated as spontaneous breathing was not observed in some children due to anesthetic factors. As technique used was visual estimation there is a potential for observer bias.

Conclusions: A high prevalence of tracheobronchomacia was found in young children with CF. There is a need for further studies to understand the significance of tracheomalacia in CF.

Acknowledgements: Perth division of ARESTCF programme.

P3382

Oral health and some risk factors in children with cystic fibrosis

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Cystic fibrosis (CF) is one of the most common genetic diseases worldwide. Previous studies in patients with CF have reported variable dental caries prevalence and physicochemical properties of saliva. The aim of this study was to investigate prevalence of dental caries and the relation with treatment, salivary flow rate, buffering capacity in children with CF compared with healthy peers.

A cross-sectional observational survey was undertaken in children attending out-patient clinic. Study population included 30 children with CF (mean age 10.2±4.8 years).

The prevalence of ABPA in CF is variable (6-15%). Currently, the role of rAsp f 1 in ABPA diagnosis and treatment monitoring is unknown.

Patients: Serial determinations of serum specific IgE against recombinant AF antigens were analysed yearly during 5 years in 157 adult CF patients. 19 patients fulfilled serologic criteria for ABPA, but only 9 suffered from respiratory symptoms, lung infiltrates or lung function deterioration.

Results: 9 of 157 CF patients (3 women), prevalence 6%, mean age 22 (16-33) years; BMI mean 21 (20-22). In 8/9 Delta F508 mutation was found. At time of diagnosis, 4 patients showed AF colonization, 8 had Pseudomonas aeruginosa (PA). In all patients, total IgE was higher than 500 U/ml, and AF specific IgE was positive. Titrations for rAsp f 1 varied, with highest titrations for rAsp f 1 and rAsp f 2. Two cases with the most torpid progress showed high titers for rAsp f 3. Lung function’s distribution (FEV1) was similar in all cases.

All patients were treated with systemic corticosteroids (3 weeks and gradually reducing the dose after 3-6 months), and itramozone/voriconazole. There were two relapses after two years, which started with respiratory symptoms.

Conclusion: In CF patients, compatible symptoms as wheezing dyspnea and functional-radiological deterioration suggest ABPA diagnosis. During treatment, only total and specific AF IgE titers, as well as lung function, served for monitoring. In our daily practice, specific AF component IgE titration does not provide prognostic nor prognostic advantages, and neither does conventional sputum culture.
years), compared with a control group of 30 healthy children (mean age 9.9±1.4 years). Mean saliva pH was 7.25±0.45 for CF children and 7.45±0.34 for control (p=0.57). Mean salivary flow rate of the CF children was 1.30±0.7ml/min and 1.54±0.9ml/min for the control group (p=0.09). And the mean buffering capacity was 8.47±2.7 for CF children and 8.20±1.58 for control (p=0.64). Among the group of children with CF, 23% of children being carrying free. DMFT (Decayed Missing Filled Teeth) was 0.64±0.45 in children and 7.3±2.7 in control children (p=0.001). Of all CF children, 60% CF brush their teeth once a day. Most of CF children (26±6%) start to brush teeth after 2 years of age. Although CF is a serious systemic chronic disease of childhood, buffering capacity of saliva seems to be higher than control group. Related to this characteristic of saliva, DMFT score of CF children were found to be lower than healthy group.

Background: In Belgium in 2011, 35% of the 15-29 years age group were regular smokers. No information was available about epidemiology of smoking by CF patients in our country. Objectives: a) primary aim: to identify active (AS) and passive (PS) smokers in the Belgian CF patients b) secondary aim: to investigate physical, psychological and behavioural dependence of AS CF patients.

Methods: AS and PS were identified by means of a urinary cotinine dosage. Patients with positive results were asked to meet with a tohacologist, in order to evaluate their expired CO2, their physical, psychological and behavioral dependence to nicotine, and their HAD score.

Results: (Interim analysis) 29 out 706 patients (4.5%, 78.8% of target) had positive urinary cotinine (> 100 mcg/ml), 17 positive patients met the tabacologist (12 AS, 5 PS). Among AS (mean age 28±1.0, 84±58), mean urinary cotinine level was 0.86±0.23 mcg/ml, maximum CO exp 0.8 ±0.33 pmol/min, and CO2 7.1 ±2.7 (p=0.025). Fagreström score was 4.5±1.3 (1-9). 84% had a previous quit attempt. 41% AS smoked cannabis. Anxiety was associated with urinary cotinine level (R=0.825, p=0.009). All AS wished to receive specific help for smoking cessation at their CF reference center.

Conclusions: Active smoking is less prevalent among CF patients in Belgium than in healthy adolescents and young adults. CF AS had developed a moderate physical dependence to nicotine; their urinary cotinine was associated with their anxiety level. Smoking cessation help should be available at CF reference centers.

Comparison of nanoduct versus macroduct sweat test for the diagnosis of cystic fibrosis in the newborn screening programme in Switzerland

James Barben1, Cornia S. Ruegg2, Sabina Gallant1, Claudia E. Kuehlm2.

Background: Newborn screening (NBS) for cystic fibrosis (CF) is based on immuno-reactive trypsinogen (IRT) and 7 CFTR mutations, was introduced in Switzerland during pregnancy 2011. In the pilot phase, we compared the performance of two sweat test methods for diagnosing CF in the NBS.

Methods: All children with a positive screening result were referred to a CF center for confirmatory (diagnostic) testing with: a) the Nanoduct sweat test (conductivity); and b) the Macroduct test (chloride). If sweat test results were positive, borderline or inconclusive, an extensive DNA analysis was performed.

Results: Within one year, 84 children were screened positive. In 30 children the diagnosis of CF could be confirmed, 53 had normal investigations, and 1 child was not yet fully investigated. All details of the investigations were available for 76 children. The children were seen in a CF center at a median age of 24 days. The Macroduct was attempted in 64 children, the Nanoduct in 71 children. A reliable test result was available in 66% (42/64) for the Macroduct and 79% (57/61) for the Nanoduct. In 37 children both sweat tests could be performed; in 19 only the Nanoduct and in 5 only the Macroduct was feasible. In 8 children none of the two sweat tests could be performed, and confirmation or exclusion of CF was based on extensive DNA analysis alone.

Conclusions: In this pilot study, the Nanoduct sweat test showed a better feasibility for use in newborns compared to the Macroduct test, mainly because it needs a lower sweat volume. Analysis of a larger dataset will allow to compare sensitivity and specificity of the two tests for the final CF diagnosis.

Conclusion: Race and ethnicity are significant factors for FeNO values in healthy individuals. Hay fever seems to play an important role in the mean difference between race/ethnicity categories. An objective measurement of atopy is probably needed to clarify this relationship.

Volatile organic compounds exposure and respiratory function in preschoolers from mothers participated in a randomized clinical trial during pregnancy

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Background: Race and ethnicity are factors known to affect the prevalence of respiratory symptoms. Different racial/ethnic groups may have different levels of exposure to volatile organic compounds, which may affect respiratory function.

Methods: We measured FeNO in 162 children (mean age 6-79 years) from 76 multi-racial families. Race and ethnicity was coded as Mexican American (20%), Other Hispanic (11%), Non-Hispanic White (43%), Non-Hispanic Black (20%) and Other Race- Inc. Multi-Racial (5%). Adjustments were made using multiple-linear regression models.

Results: Non-Hispanic Whites have the lowest FeNO values (mean 15.8 ppb, 95%CI 14.5, 16.1) and Other Race - Including Multi-Racial the highest (20.0 ppb (18.6; 21.4)). Race and ethnicity significantly affect FeNO values even after adjusting for age, gender, BMI and reported hay fever in non-asthmatic subjects (B=0.30, p=0.01), but not in individuals with self-reported asthma (B=0.09, p=0.83). However, the mean difference between race/ethnicity categories was reduced after excluding subjects with hay fever.

Conclusion: Race and ethnicity are significant factors for FeNO values in healthy individuals. Hay fever seems to play an important role in the mean difference between race/ethnicity categories. An objective measurement of atopy is probably needed to clarify this relationship.

Environmental exposure and other risk factors for airway diseases

TUESDAY, SEPTEMBER 4TH 2012

P3384

Self-reported race and ethnicity affect FeNO values in healthy individuals

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Methods: We analyzed the valid FeNO measurements (NIOX MINO) recorded in the National Health and Nutrition Examination Survey 2007-10 (n=13,275; age 6-79 years). Race/ethnicity is coded as Mexican American (20%), Other Hispanic (11%), Non-Hispanic White (43%), Non-Hispanic Black (20%) and Other Race - Inc. Multi-Racial (5%). Adjustments were made using multiple-linear regression models.

Results: Non-Hispanic Whites have the lowest FeNO values (mean 15.8 ppb, 95%CI 14.5, 16.1) and Other Race - Including Multi-Racial the highest (20.0 ppb (18.6; 21.4)). Race and ethnicity significantly affect FeNO values even after adjusting for age, gender, BMI and reported hay fever in non-asthmatic subjects (B=0.30, p=0.01), but not in individuals with self-reported asthma (B=0.09, p=0.83). However, the mean difference between race/ethnicity categories was reduced after excluding subjects with hay fever.

Conclusion: Race and ethnicity are significant factors for FeNO values in healthy individuals. Hay fever seems to play an important role in the mean difference between race/ethnicity categories. An objective measurement of atopy is probably needed to clarify this relationship.
Conclusions: Exposure to volatile organic compounds air concentrations in the general environment decrease the respiratory function in Mexican Preschoolers.

P3387
Effects of short-term exposure to air pollution on the levels of exhaled nitric oxide among adults – Results from the ADONIX study in Gothenburg, Sweden
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The fraction of exhaled nitric acid (FENO) is a marker of airway inflammation, used clinically to diagnose and monitor asthma. FENO can be measured at different exhalation flows to monitor different parts of the airways. Air pollution is known to cause adverse health effects, and inflammation has been suggested as a main pathway. In this study we examined whether short-term exposure to ozone (O3), nitric oxides (NOx) or particulate matter less than 10 μm (PM10) are related to increased levels of FENO.

From 2001 through 2008, 5841 randomly selected adults aged 25-75 years in Gothenburg, Sweden, were clinically investigated. FENO measurement at three different flow-rates, and in this study we included FENO measured at the highest (200mls) and lowest (50mls) flows. Air pollution data were collected from an urban and background station, and we studied the effects of the 3, 24 and 120 hour averages preceding the clinical examination. Log-linear regression was applied to estimate the associations of air pollution on FENO.

One inter-quartile range (IQR) increase of NOx, NO2, and SO2 in the average FENO270, and NO2, SO2, and O3 in the average FENO50 was associated with a 5.1% (95% CI 1.7-8.5) increase in FENO270 and 3.6% (95% CI -0.4-3.4) increase in FENO50. For NO2, a small effect was seen for the 24- and 120-hour averages in FENO270, while no clear effect was seen for PM10. The effect of ozone on FENO50 and FENO270 was significantly lower among asthmatic subjects; however the effect on asthmatics could not be separated from null.

In summary, short-term exposure to O3 gives rise to a small increase in FENO270 and FENO50, measures of inflammation in the distal and proximal airways.

P3388
Estimated short-term effects of air pollutants on daily respiratory emergency department visits in three Swedish cities
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Large number of epidemiological studies has found associations between daily changes in ambient particulate air pollution and different kinds of health outcomes. Our aim was to estimate the short-term effects of different air pollutants on daily emergency department visits for respiratory diagnoses in three largest cities in Sweden to find the effects in different environments. Data on daily number of visits from 2001 through 2008 in Stockholm, Gothenburg and Malmö were collected from the national Patient Register and data on daily air pollution concentrations (PM10 and Ozone) on days when available, and data from the local environmental agencies. In addition to visits for all respiratory causes focus was on visits for asthma (ICD10: 345-346) and on associations between air pollution and daily visits in different age classes. Data was analysed using additive Poisson regression models to examine the association between daily visits and the average levels of air pollutants on the day of visit and the day before the visit (lag 0). For each city a statistical model was constructed for each health outcome and also for each age class. For example, a Stockholm model adjusted for the time trend, temperature, relative humidity, birch pollen levels, day of week and public holidays gives an increase of 2% (95% CI 0.5 to 3.6) in daily visits for asthma for all ages per 10 μg/m³ increase in PM10. The estimated effect for children is 2.5% (95% CI 0.7 to 4.4%) and for elderly 4.9% (95% CI 1.1 to 8.8%), respectively. In this study we have found associations between relatively low daily levels of air pollutants and emergency department visits for respiratory diagnoses.

P3389
Impact of close-proximity and background air pollution on lung function of elementary schoolchildren in Guadeloupe (French West Indies)
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Background: Air pollution is often associated with respiratory diseases. High levels of asthma prevalence and severity of respiratory symptoms were found in West Indies, but little is known about the impact of air pollution in these regions. This study aimed at describing air pollution impact on lung function of schoolchildren in Guadeloupe.

Methods: Data from 27 randomly chosen elementary Guadeloupian schools including 1,463 children (8-13 years old) were obtained using a standardized protocol adapted from the second phase of the International Study of Asthma and Allergy Childhood (ISAAC). Two dependent variables were the expiratory flow before run (PEF) and variation of peak expiratory flow after run (ΔPEF) were investigated using several linear mixed models to measure effects of i) medium-term close-proximity pollution (indoor and outdoor) of O3 and NO2 and ii) short and medium term background pollution of O3, NO2, SO2 and PM10. The heterogeneity between schools was assessed by random intercept.

Results: Of 1,463 children, 223 (16%) were found with asthma. The values of PF and PEF were in average 272 L/min (range: 130-460) and -1% (range: -56%-97%) respectively. A 1 μg/m³ increase in outdoor medium-term close-proximity O3 pollution level was significantly associated with a PF decrease (β=-0.32, 95% CI -0.61-0.03). Effect of medium-term background O3 pollution on PF was higher in asthmatic children than non-asthmatic children. No association was identified with the other air pollutants.

Conclusion: Our results suggest that O3 has an acute effect on child lung function in Guadeloupe even with values levels inferior to WHO guidelines.

P3390
Air pollution in Reykjavik and dispensation of drugs for angina pectoris
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Introduction: Ambient air pollution is associated with increase in morbidity from heart diseases. Air pollution concentrations in the Reykjavik area are known to exceed official European health limits several times every year.

Objectives: To evaluate the association between ambient air concentrations of O3, NOx, PM10 and H2S in Iceland’s capital area Reykjavik and the dispensation of drugs for angina pectoris.

Methods: Data on the daily dispensing of drugs for angina pectoris were obtained from The Icelandic Medicine Registry. Data on hourly concentrations of NOx, NO2, PM10, and H2S were obtained from The City of Reykjavik, and The Environment Agency of Iceland. A case-crossover design was used and the study period was January 1st 2005 to December 31st 2009.

Results: Exposure to air pollution was associated with the dispensing of drugs for cardiovascular disease (C01DA). For every μg/m³ increase of NOx concentrations the dispensing of glycerol trinitrates (sub-group C01DA02) increased by 11.6% (at lag 0) and 7.1% (at lag 1). Similarly, an increase by 10 μg/m³ of O3 concentration was associated with 9.0% (at lag 0) and 7.2% (at lag 1) increase in glycerol trinitrate dispensations.

Conclusion: The findings indicate that increased air pollution levels are associated with increased dispensation of glycerol trinitrate. We caution that this is the first study to examine the association between ambient air pollution and dispensation of drugs for angina pectoris, hence further evidence is needed for definite conclusions of this association. Drug dispensing may potentially be a sensitive indicator of health when estimating the effects of air pollution.

P3391
Occupational air pollutants – More hazardous for respiratory health than smoking? Results from the obstructive lung disease in northern Sweden studies
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Background: Both smoking and occupational air pollutants (OAP) are risk factors for impaired respiratory health. Comparisons of their effects and how they interact are scarce.

Aim: To compare the effects of ever smoking and ever OAP on non-malignant respiratory disorders and to assess their interactions.

Material and methods: In a population-based incidence study of asthmatic and bronchitic disorders in northern Sweden, 5896 subjects answered a postal questionnaire in 1996 and in 2006 (79% of the responders in 1996). Cumulative incidences were calculated. Risk factors were analysed in multiple logistic regressions adjusted for possible confounders and the results are presented as odds ratios (OR). Ever/never smoking (S) and ever/never OAP were used as a combined variable with four categories or as dichotomous variables, respectively.

Result: Cumulative incidences for 10 years were for S0/OAP: 3.2-7.4, S1/OAP: 3.3–9.5, S0/OAP: 3.8–11.0, and for S1/OAP: 7.1–15.0. Using a combined variable with S0/OAP as the reference odds ratios were for S1/OAP: 0.99–1.8 with some significant results, S0/OAP: 1.0-2.2, with more significant results, and S1/OAP: 1.4–3.4 with all results significant. Interactions between smoking and OAP were mostly multiplicative for both asthmatic and bronchitic populations. Population attributable risks based on dichotomous variables were for smoking about 15%, for OAP about 20%, and for smoking and/or OAP about 25%.

Conclusion: OAP were at least as strong a risk factor as smoking for impaired respiratory health. Both smoking and OAP ought to be considered as possible confounders.

6095

TUESDAY, SEPTEMBER 4TH 2012
Urban living is a risk factor for allergic sensitization among adults in northern Sweden

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Aim: To assess prevalence and risk factors for allergic sensitization based on skin prick test (SPT) and specific IgE in adults.

Methods: In 2009 a random sample of 737 adults in ages 20-69 years was invited for examinations including SPT and blood sampling for specific IgE. SPT with ten common airborne allergens were performed in 463 subjects aged 20-60 years. A wheal ≥3 mm was considered as a positive reaction. Blood samples for specific IgE were collected in 692 subjects, and specific IgE was analyzed for the same allergens as tested in the SPT. An elevated level of specific IgE was defined as ≥0.35 IU/ml.

Results: In general, the prevalence of allergic sensitization based on SPT and specific IgE, respectively, yielded similar results. The prevalence of any positive SPT was 39% versus 35% for any elevated IgE. p=0.23. The prevalence of sensitization to cat and dog was significantly lower based on IgE compared to SPT, while sensitization to other allergens showed almost identical figures irrespectively of method used. The risk factor analyses based on SPT and IgE, respectively, yielded similar results. The prevalence decreased significantly by increasing age. A family history of rhinitis (OR 3.1; 95% CI 2.0-4.8 for any positive SPT, OR 2.7; 95% CI 1.8-4.0) and urban living (OR 1.7; 95% CI 1.1-2.7 for any positive SPT and OR 1.5; 95% CI 1.0-2.3) were significant risk factors for allergic sensitization. 

Conclusions: A similar sensitization pattern was observed when assessing the prevalence of allergic sensitization by SPT and specific IgE, respectively. Young age, a family history of allergic rhinitis and urban living were significant risk factors for allergic sensitization among adults.

Normal antioxidative enzyme activities in several genes are associated with less bronchial hyperresponsiveness (BHR) among young Danes

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Background and aim: BHR might be associated to the oxidative defense. We hypothesize that genotypes coding for normal antioxidative enzyme activity (AEAs) influence the occurrence of BHR.

Methods: In a cross sectional study 7,271 subjects aged 20-44 year (73% response rate) were recruited using an asthma screening questionnaire. All subjects with asthma (n = 460) and a 20% random sample (n = 728) were clinically investigated, including a bronchial provocation test, skin prick test (SPT) with 13 Aeroallergens, and a blood sample. A bronchial provocation test was available for 956 subjects, and BHR was defined as at least 20% drop in baseline FEV1. Variants in the following genes were genotyped: Glutathione peroxidase, GPX1 (Pro198Leu, rs1050450), manganese superoxide dismutase, SOD2 (Ala16Val, rs4880) and 3 glutathione S-transferases; GSTP1 (Ile105Val, rs1695), GSTT1 (gene copy nr) and GSTM1 (gene copy nr).

Results: The frequency of BHR was 12.8% in the random sample and 42.6% in the asthma sample. Log. reg. models showed a neg. association between being BHR and having at least 4 genotypes coding for normal AEA compared to no normal genotype, OR 0.24 (0.06-0.94) adj. for smoking, FEV1, sex, atopy, height2 and SPT-size of HDM. The result were similar after further adjustments for BMI, age, a family history of rhinitis and urban living were significant risk factors for allergic sensitization. 

Conclusions: A similar sensitization pattern was observed when assessing the prevalence of allergic sensitization by SPT and specific IgE, respectively. Young age, a family history of allergic rhinitis and urban living were significant risk factors for allergic sensitization among adults.

Oxidative stress in obese and nonobese patients with and without asthma

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Rationale: Oxidative stress plays a role in the pathogenesis of many chronic inflammatory lung diseases.

Alternatively, increasing BMI may lead to an increase in airborne oxidative stress and obesity increases the risk for developing new onset asthma in adults and children. Exhaled breath condensate (EBC) collection is a noninvasive method to investigate pulmonary oxidative stress biomarkers.

Methods: We measured exhaled nitrites and nitrites, 8-isoprostane, pH and oxidized (GSSG) glutathione, to assess alveolar oxidative stress in obese patients (52 asthmatics and 135 non-asthmatics) and 118 nonobese (52 asthmatics and 135 non-asthmatics). EBC was collected over 10 min using a refrigerated denser according to European Respiratory Society/ American Thoracic Society recommendations.

Results: We found an increase in the concentrations of GSSG and 8-isoprostanes in both groups of obese patients (both asthmatic and non-asthmatics) compared with nonobese patient (asthmatic and non asthmatic) (p < 0.001) and a slight decrease in the pH of EBC in obese patients with asthma compared with the rest (p < 0.05). In relation to nitrites and nitrites were statistically lower in obese patients with asthma and without asthma than the total non-obese patients.

Conclusions: Our results suggest that obesity leads to an increase proinflammatory mechanisms that could be associated with increased systemic inflammation and oxidative stress and may affect the status or condition of asthma.

Bone mineral density is associated with the risk of non-small cell lung cancer, the HUNT study

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Background: The overall survival in lung cancer is poor. The highest survival has been observed for cancers diagnosed in early stages, so early identification of patients at risk is important. Estrogen receptors have been found in non-small cell lung cancer. This may indicate that estrogen promote carcinogenesis. Estrogen level is associated with bone mineral density (BMD). Hence, BMD might be used as surrogate measure of long term estrogen exposure.

Aim: To investigate whether low BMD is associated with lower risk for lung cancer.

Method: We analyzed data from a cohort study, the Nord-Trøndelag Health Study (HUNT-study) linked to the Norwegian Cancer Registry. 18156 subjects under-
went bone densitometry of the forearm. The results were reported as z-scores and categorized into tertiles. All analyses were stratified by sex. Body mass index (BMI), lung function and smoking were tested as confounders in logistic regression models. BMI and lung function changed the odds ratios less than 10% and were not included in the final model.

**Results:** 72% of the 18156 participants were females. In the low z-score group we found more ever smokers (P < 0.01), but no difference in age and sex distribution between the three z-score groups. In all 194 cases with non-small cell lung cancer were identified. Among these 56% were females, 87% were ever smokers and the mean age was 72±11 years.

In men, low compared to high z-score was associated with a higher risk of lung cancer, OR 3.3 (95% CI: 1.85-5.99) and adjusted for smoking OR 2.93 (95% CI: 1.62-5.32) were found. In women no association with BMI was seen.

**Conclusion:** Low bone mineral density is associated with a higher risk of lung cancer, in men, but not in women.

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**P3397**  
**Individual decline of FEV1 show diversity in COPD**  
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Our objective is to develop methods to gain better understanding of individual development of lung functions in COPD sub-phenotypes. The patients (N=600) have been recruited from two Finnish University Hospitals. Their medical records have been carefully evaluated including spirometry results. A mixed-effects model was used to obtain predictors for the individual development of FEV1. To manage the within-patient variation of consecutive measures, simulation methods were used to determine which patients were presenting significant differences using logistic regression analysis. Our preliminary results suggest that COPD patients show diversity in their risk of future FEV1 decline. Development of robust screening protocols at early stages of COPD might be of value in revealing the rapid decliners.

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**P3398**  
**Age of menarche and risk of asthma: Systematic review and meta-analysis**  
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**Aim:** To conduct a systematic review and meta-analysis of the relationship between the age at menarche and risk of asthma.

**Methods:** A prespecified literature search strategy was used to identify all articles directly addressing the relationship between asthma and age at menarche. We were interested in studies with asthma defined as self-reported asthma, diagnosed asthma or asthma symptoms and in studies defining early menarche as menarche before the age of 12 years of age or younger. Further, we were interested in controlled trials, prospective and retrospective cohort studies, case-control studies and cross-sectional studies with or without modelling.

**Results:** Our searches identified 34 articles of which 8 matched the inclusion criteria (two cross-sectional studies, three case-control studies, two retrospective studies, and one prospective study) with a total of 18124 patients. All articles were consistent in their results, showing a clear positive relationship between asthma and age at menarche. Estimates from the selected studies showed that the risk of asthma was increased between 1.13 and 2.34 times in girls with early menarche.

**Conclusions:** Early age at menarche is associated with increased risk of asthma. Hormonal, immunological, genetic, and environmental factors may act in a developmental context to explain this relationship.

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**P3399**  
**HRT, lung function, respiratory symptoms and menopausal status**  
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Menopausal women using HRT had higher FEV1 (adj diff 70 ml 95%CI=64 to 136) but no increase in respiratory symptoms (OR=1.00 (0.68 to 1.48) compared to menopausal women not using HRT. Menopausal women using HRT had indicated more asthma symptoms (OR=1.65 (0.86 to 3.18)) and indicated lower FVC (adj diff -103 ml 95%CI=4 to 136) but no increase in respiratory symptoms (OR=1.00 (0.68 to 1.48)).

**Conclusion:** The association between HRT and respiratory health was modified by menopausal status. In this population of women in the perimenopause, HRT appeared to be beneficial for respiratory health among menopausal women, but possibly led to adverse respiratory outcomes among those still menstruating. The conflicting evidence in the field might be due to lack of account for menopausal status when investigating effects of HRT.

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**P3400**  
**Age at onset and persistence of eczema and the subsequent risk of asthma and allergic rhinitis**  
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**Background:** Few studies have simultaneously addressed the importance of age at onset and persistence of eczema for the subsequent development of asthma and allergic rhinitis in children.

**Objective:** To examine age at onset of eczema and persistence as predictors for childhood asthma and allergic rhinitis at ages 6, 7 and 12 years.

**Methods:** A prospective birth cohort was recruited comprising 620 infants with a family history of allergic diseases. Telephone interviews were conducted 18 times in the first two years of life, annually from age 3 to 7, and at 12 years to document any episodes of eczema. Current asthma and allergic rhinitis were assessed at ages 6, 7 and 12.

**Results:** Very early-onset (<6 months) persistent eczema was related to current asthma (adjusted OR=6.9, 95%CI 2.4-14.7) and allergic rhinitis (aOR=6.5, 95%CI 1.9-10.9) at age 12 years. Adjustment for anti-allergen sensitisation in infancy dramatically reduced these associations. There was no evidence that early-onset remitting eczema (only present < 2 years) or late-onset eczema (onset > 2 years) were associated with current asthma and allergic rhinitis. These results were consistent with the 6-7 year findings.

**Conclusion:** Eczema which commences very early in life and persists into toddler years is strongly associated with childhood asthma and allergic rhinitis, and is possibly mediated by anti-allergen sensitization. However remitting and late intervention, the risk of diseases associated with early-onset eczema might be reduced.
376. Cellular signalling mechanisms in the airways

P3401 Effect of body mass index on lung function in children
Fabio Cribellaro1, Andrea Bruno1, Giuseppina Cuttica1, Stefania La Grutta1, Marco Meli1, Salvatore Bucchiari1, Giuniana Ferrante1, Silvia Ruggieri1, Giovanna Viegli1.

Background: Asthma and obesity are important health issues in industrialized countries and obesity is a risk factor for asthma. Our study aimed at investigating the effect of body mass index (BMI) on lung function in a large sample of healthy children enrolled in two cross-sectional surveys performed on random samples of children, aged 10-17 years, living in the city of Palermo, Southern Italy. At school, all the subjects completed self-administered questionnaires regarding past and current respiratory symptoms and personal information, and performed spirometry. On a total of 3,200 children, 807 reporting wheeze ever, nocturnal cough, or exercise-induced cough were excluded from the analysis. 2,393 subjects (49% M) were evaluated.

Methods: Height-adjusted lung function measures were plotted against BMI Z-score for each gender and age class, and slope values were computed by linear regression analysis. Height-adjusted FVC and FEV1 were positively correlated to BMI Z-score in both males and females. Slope values (L/BMI Z-score unit) were 0.057 in males and 0.114 in females for FVC and 0.022 and 0.072 for FEV1, respectively, being significantly steeper among females in each age class. FEV1/FVC ratio was inversely correlated to BMI Z-score with similar slope values for male and female. FEF25-75/FVC ratio was negatively correlated to BMI Z-score: the slope values were steeper among females in each age group. In conclusion, despite both FVC and FEV1, are positively correlated to BMI, their disproportionate increase as BMI increases could cause a reduction of relative airway size as measured by the FEF25-75/FVC at higher BMI values. This could, at least in part, contribute to the reported association between overweight-obesity and asthma.

P3402 Effect of TGF-β on FoxO activity in airway smooth muscle cells
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Background: TGF-β is a mediator of abnormal airway smooth muscle (ASM) function in asthma and COPD. TGF-β triggers ASM cell (ASMC) hyperplasia and increases intracellular oxidants whilst reducing antioxidant enzyme expression. The O subfamily of forkhead box transcription factors (FoxO1, -3 and -4) activate CREB and CREM signaling, the MUC5AC expression in airway goblet cells was examined. Finally, the expression of FOXG1 in airway goblet cells was examined. Next, after transfection with pEFBOS-NIC (upregulating Notch signaling) or treated with γ-secretase inhibitor (downregulating Notch signaling), the MUC5AC expression in airway goblet cells was examined. Finally, the transcriptional regulatory mechanisms were analyzed.

Results: Notch signaling negatively regulates the expression of MUC5AC in airway goblet cells
Hai Feng Ou Yang, Respiratory Medicine, Xijing Hospital, Xian, Shanxi, China

Introduction and background: Goblet cell metabolism and airway mucus hypersecretion contributed to the pathogenesis of asthma and COPD. Evidence has shown that Notch signaling modulates the development of lung epithelial and the differentiation of intestinal goblet cells. Whether Notch signaling can regulate the expression of MUC5AC, a major component of airway mucus, is still unknown.

Aim and objective: To investigate whether Notch signaling can regulate MUC5AC expression in airway goblet cells.

Methods: Expression of Notch receptors and downstream molecules in airway goblet cells was examined. After transfection with pEFBOS-NIC (upregulating Notch signaling) or treated with γ-secretase inhibitor (downregulating Notch signaling), the MUC5AC expression in airway goblet cells was examined. Finally, the transcriptional regulatory mechanisms were analyzed.

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Aim and objective: To investigate whether Notch signaling can regulate MUC5AC expression in airway goblet cells.

Methods: Expression of Notch receptors and downstream molecules in airway goblet cells was examined. After transfection with pEFBOS-NIC (upregulating Notch signaling) or treated with γ-secretase inhibitor (downregulating Notch signaling), the MUC5AC expression in airway goblet cells was examined. Finally, the transcriptional regulatory mechanisms were analyzed.

Results: Notch signaling negatively regulates the expression of MUC5AC in airway goblet cells
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P3406
25-hydroxide-vitamin D induces TSLP expression in human bronchial epithelial cells via the VDUP1 pathway
Haijun Zhao, Dan Zhang, Cheng Hao Peng, Yang Xia, Shaoli Cai, Respiratory Unit, Nanfang Hospital, Guangzhou, China

Background: Airway epithelial cells (AEC) express 1α-hydroxylase and are able to convert 25-hydroxy-vitamin D (25(OH)D) to an active form that plays a role in mucosal immunity. Thymic stromal lymphopoietin (TSLP), a cytokine mainly produced by AECs during allergic asthma reactions, plays a critical role in the activation of Th2 inflammatory responses. Therefore, we hypothesized that 25(OH)D would enhance the expression of TSLP in airway epithelia (16HBE cell line) and that vitamin D3 upregulated protein 1 (VDUP1) could be involved in this process.

Methods: 16HBE cells were cultured with 25(OH)D, and TSLP and VDUP1 mRNA and protein expression were then determined by means of quantitative PCR, ELISA, and Western blot analysis, as appropriate. The role of VDUP1 on TSLP expression was assessed in untreated and 25(OH)D-treated 16HBE cells where VDUP1 levels were manipulated via overexpression or siRNA-mediated silencing. The effect of 10 μM triaracozole, a chemical inhibitor of 1α-hydroxylase, on the expression of TSLP was also determined.

Results: 25(OH)D significantly induced TSLP and VDUP1 mRNA expression in 16HBE cells. Silencing of VDUP1 dramatically inhibited 25(OH)D-mediated induction of TSLP, and overexpression of VDUP1 upregulated baseline TSLP expression and 25(OH)D-induced TSLP expression in 16HBE cells.

Conclusion: These data demonstrated that vitamin D increased TSLP expression in 16HBE cells via upregulation of VDUP1.

P3407
Acetylcholine leads to STAT-1 mediated oxidative/nitrosative stress in human bronchial epithelial cells
Missella Prodi1, Gianluca Daniela Albano1, Angela Marina Mentallano1, Caterina Di Santo1, Rosalia Gagliardou1, Giulia Anzalone1, Loredana Riccobono1, Anna Bonanno1, Michael Paul Pieper2, Mark Gjomarkaj1, IBIM, CNR, Palermo, Italy; 2Boehringer Ingelheim, Pharma, Biberach, Germany

The induction of nitric oxide synthase (iNOS) expression via the signal transducer and activator of transcription 1 (STAT-1) is involved in the mechanism of ox-idative/nitrosative stress in bronchial epithelial cells during airway inflammation of COPD and to evaluate the effect of the anti-inflammatory treatment. Therefore, we investigated whether ACh generates oxidative/nitrosative stress in bronchial epithelial cells via STAT-1 pathway activation in human bronchial epithelial cells (16HBE). We aimed to investigate whether ACh generates oxidative/nitrosative stress during airway epithelial cells and nitrotyrosine in the supernatants were evaluated by flowcytometry in 16HBE cells. Acetycholine leads to STAT-1 mediated oxidative/nitrosative stress in human bronchial epithelial cells.

P3408
TLR2 and TLR4 induced tolerance in alveolar macrophages: differential effect on TNFα and IL-8 release
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TLR2 and TLR4 signaling potentiates airway secretion from the swine submucosal gland via NO/cGMP/cGK pathway
Koji Murakami1, Tsutomu Tamada1, Masayuki Nara2, Koji Murakami1, Masahito Ebina1, 1Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; 2Department of Comprehensive Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Rationale: Airway secretion plays an important role in the airway defense as a part of innate immunity. A major fraction of the airway fluids appears to be derived from submucosal gland in response to ACh. Toll-like receptor 4 (TLR4) recognizes gram-negative bacteria and activates the innate immune systems. However, the biological role of TLR4 in the airway secretion is not well understood.

Methods: Freshly isolated swine tracheal submucosal gland cells were investigated their secretory activities as ion currents by applying a patch-clamp technique. LPS was used as a potent TLR4 ligand. The expression of TLR4 was estimated by both the immunofluorescent staining and R-PCR. The involvement of NO/cGMP/cGK-dependent protein kinase (cGK) pathway was investigated by applying both the NO synthase and GKI inhibitors. The synthesis of endogenous NO was estimated by an intracellular NO indicator, DAF-DA.

Results: LPS significantly potentiated the ACh-evoked ion currents. This potentiating effect was completely abolished by the pretreatment of anti-TLR4 antibody or the TLR4 antagonist. The immunofluorescent staining and RT-PCR revealed the abundant expression of TLR4 on tracheal submucosal glands. Two different inhibitors of each NOs and cGK completely abolished the LPS-induced potentiating effect, respectively. LPS further increased the ACh-induced synthesis of NO.

Conclusions: Our studies revealed that TLR4 signaling could potentiates the electrolyte and water secretions from tracheal submucosal glands via the activation of NO/cGMP/cGK pathway. These findings suggest that TLR4 takes part in the airway mucosal innate immune systems as one of important pathogen-specific secretagogue.
IL-33 is released rapidly and in large quantities following ALT exposure and a distinct IL33 expression and release from airway epithelium. In vivo IL-33KO BAL was confirmed the IL-33-ST2 axis was confirmed in ST2 and IL-33 KO mice which showed no detectable IL-33 in BAL followed by rapid clearance (below detection limit of 2pg within 4-5 hrs). Key downstream effects were an increase in IL-5 and 24 hours BAL IL-5 was significantly increased (both 10ng/ml) and the cytokine production was examined with proteome profiler antibody arrays (R&D) that detect the production of 40 cytokines simultaneously. Results: Basal and induced production of IL-1- alpha was similar in cells grown on collagen-1 and fibronectin but IL-1-beta could not be detected in cells grown on collagen-4. Low levels of G-SCF were detected in cells on collagen-1 fibronectin stimulated with cytokines, but when cell were grown on collagen-4 the levels were statistically higher. There were no difference in basal and induced production of GRO-alpha and IL-8 on cells grown on collagen-1 or fibronectin. The basal level of IL-8 was dramatically reduced on collagen-4 compared to collagen-1 and fibronectin. However cytokines triggered similar levels of IL-6 production regardless of matrix substrate. Conclusions: In this study we show that the extracellular matrix actively contributes to modify cell phenotypes. Cells grown on collagen-4 that represents a "homeostatic matrix" produced a different repertoire of inflammatory mediators than cells grown on "remodeled matrix proteins" collagen-1 and fibronectin.

**Inhibition of A. fumigatus growth by human respiratory cells**

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The innate immune response to fungi mainly involves macrophages and neutrophils. By contrast, the possible participation of respiratory epithelial cells has been poorly studied. In this study we observed that RENCROS display the property of inhibiting mycelium development of Aspergillus fumigatus (A.f) and that this activity is linked to PI3 kinase activation. Bronchial cells (BEAS-2B cell line) were incubated with A.f and the growth of the fungus was estimated by optical microscopy observation and measurement of galactomannan concentrations in the extracellular media. The role of PI3 kinase pathway was evidenced by the use of the specific inhibitor LY294002 (30 μM). Spore internalization in RENCROS was followed by epifluorescence. FITC-labeled spores (green) when outside of cells were further labelled with an anti-FITC antibody labeled with a red fluorochrome (Alexafluor 568). In the presence of REC, most of the spores do not germinate as opposed to spores incubated in the absence of cells. The growth quantification by galactomannan concentration measurements display a 4.5 lower concentration in the presence of cells. The anti-aspergillus activity is inhibited when cells are incubated with LY294002, indicating the involvement of the PI3 kinase pathway. Of note, inhibitors of p38 MAP kinase and ERK1/2 are inactive. We evidenced that the activity is directed against the spores and not against the hyphae but is not linked to the spore internalization.

In conclusion, as macrophages and neutrophils, REC play a role in the anti-aspergillus activity. They are able to prevent the mycelium development and as such potentially prevent its dissemination.

**Acknowledgements: Work supported in part by a grant from Vaincre la Mucoviscidose.**

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**Characterisation of endogenous IL-33 using a model of Alternaria-induced pulmonary inflammation**

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**Background:** IL-33 is a potential mediator of chronic inflammatory diseases including asthma. However, endogenous forms of IL-33 are poorly understood. Here we have used a model of Alternaria alternata (ALT) challenge to investigate in vivo mechanisms of IL-33 processing and release.

**Methods:** Cytokines were quantified in bronchoalveolar lavage (BAL) from BALB/C mice by MSD assay. Mast cells were differentiated from bone marrow over 5 weeks and stimulated with BAL or recombinant IL-33 for 24 hours. Results: Intranasal challenge with 50μg ALT to anaesthetised BALB/C mice caused a spike (∼2000 pg at 15-30min) of IL-33 in BAL followed by rapid clearance (below detection limit of 2pg within 4-5 hrs). Key downstream effects were an increase in 5 and 24 hours BAL IL-5 (∼400pg and ∼600pg, respectively) and eosinophilia at 24 hours. Conclusions: These findings suggest that IL-33 expressed in AT I cells, is involved in the transport of the airway epithelium.

**Results:** IL-33 conc. in post-lung transplant BAL trended towards an increase following diagnosis of BOS but did not reach statistical significance. However, elevated levels of IL-33 were associated with positive microbial culture (mean 178.107pg/ml±4.289pg/ml vs 71.31pg/ml±0.007). IL-33 was strongly expressed in airway epithelia with a predominant nuclear location IL-33 was not detected in response to epithelial cell damage. Conclusions: IL-33 is strongly expressed in the airway epithelium of chronic respiratory conditions but does not appear to be released as an alarmin in response to airway epithelial cell damage. Elevated IL-33 associated with infection in the post transplant population may contribute towards allograft dysfunction but further work is required to evaluate the cellular mechanistic pathways.
Activation of both transcription factors STAT5 and IRF-1 is insensitive to corticosteroid insensitivity in severe asthma. The long-acting β2-agonist, salmeterol (SA; 8) were obtained from endobronchial biopsies, cultured at passage 4-5. ASMC of the healthy (9), non-severe (NSA; 8) and severe asthmatics (SA; 8) were cultured at passage 4-5.

**Aims and objectives:**

- Compare protein/mRNA, phosphorylation, and nuclear expression in SA, NSA, and healthy (9).
- Compare with non-overweight subjects, obese subjects with asthma were less responsive to treatment. The aim of this study was to investigate the relationship between BMI and response to treatment in a group of patients that were referred for asthma control.

**Background:**

Increases in body mass index (BMI) are reported to influence asthma response to treatment. The aim of this study was to investigate the relationship between BMI and response to treatment in a group of patients that were referred for asthma control.

**Patients and methods:**

- Effectiveness measurements in this analysis included percentage of changes in forced volume in 1 second (FEV1), forced volume capacity (FVC), FEV1/FVC, and FEF25-75%.
- A total of 293 subjects with asthma of both genders and above 18 years of age were divided into the following BMI categories: 107 (36.5%) non-obese (BMI <25), 186 (63.5%) overweight and obese (BMI ≥25). Percentage of change was defined as change in variable between baseline and end-of-treatment.

**Results:**

- Analyses of non-overweight vs. overweight/obese asthmatics demonstrated non-significant differences in baseline FEV1 (1.62 ± 0.56 L vs. 1.63 ± 0.55 L, p = 0.89); FVC (2.58 ± 0.73 L vs. 2.47 ± 0.82 L, p=0.25); and FEF25-75% (1.04 ± 0.55 m/sec vs. 1.05 ± 0.50 m/sec, p=0.47) respectively.
- Compared with non-overweight subjects, obese subjects with asthma were less responsive to treatment than non obese asthmatic subjects. Percentage changes of FEV1, FVC, FEV1/FVC, and FEV1/FVC in non-obese versus obese patients were: 79.57 ±6.14% vs. 62.1 ± 6.14%, p<0.005; 47.7 ± 11.7% vs. 39.9 ± 28.3%, p=0.036; 151.98 ± 127.8% vs. 123 ±91.12%, p=0.041; 20.54 ± 15.63% vs. 15.63 ± 11.32%, p=0.005 respectively.

**Conclusion:**

Cigarette smoke extract treatments increased mTORC1 activity in U937 cells, and ramipril partially reversed corticosteroid insensitivity caused by cigarette smoke exposure.
Conclusion: Percentage changes of spirometric values to treatment in overweight/obese asthmatic patient were lesser in compared with non-overweight subjects.

P3421
Perceptions and factors affecting poor adherence to inhaled steroids among bronchial asthma patients in Kuwait
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Background: Poor adherence to regular inhaled steroids is a cause of poor asthma control.

Aim: To assess adherence to treatment, factors of poor adherence, perception on inhaled steroids among asthmatics in Kuwait

Design: Observational study

Subjects: 150 asthmatics (95 m,55) 15-60 years, were recruited and followed up for 12 consecutive months from January 2009 to December and asked to fill in a questionnaire of adherence, beliefs about asthma,treatment and reasons for non adherence.

Results: First 3 months, 66 (44%) were adherent to twice daily dosage, but at 12 months only 25%. More males were adherent at 3 months (63.6% vs. 36.4% p<0.05) and at 12 months (81.6% vs 18.4% P<0.05).Employed as compared to unemployed (p<0.05), educated to secondary school and above, as compared to the less educated (p<0.05) were more adherent at 3 and 12 months. At 12 months, younger asthmatics were more adherent than expatriates (p<0.05).

Logistic regression analysis of the beliefs for non adherence showed 52% did not consider asthma as a serious disease. 82% stopped medicine because of fear of side effects, 75% were influenced by the wrong advice by relatives or friends, that long term steroids are dangerous (p<0.05). 80 (51.6%) believed tablets are less dangerous than inhalers.

Conclusion: Adherence to inhaled steroids was poor. Factors were, females, fear of side effects, fear of side effects from inhalers and relatives with wrong information on steroids and poor understanding about asthma.

Since the employed and educated patients showed good adherence, asthma education is important in asthma management. In non-adherence, the clinician should find methods to overcome the barriers of non adherence.

P3422
Community-acquired pneumonia in pediatric patients: New diagnostic priorities
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Background: High incidence of childhood community-acquired pneumonia (CAP), changes in CAP manifestations, reduced significance of classical diagnostic criteria, leading to inadequate treatment, work against lowering risk of complications and mortality.

Aim: To study the features of actual clinical course of pediatric CAP.

Methods: 64 patients aged 1-18 years, with clinically and radiographically diagnosed CAP with detection of serum antibodies against intracellular pathogens, were followed up for 12 months. Patients were divided into two age groups: aged 1-4 (group A, n = 24) and 5-18 (group B, n= 40). All patients had numerous phenotypic signs of hematogenous infectious diseases.

Results: All patients had indistinct clinical manifestations. Recurrent course of CAP was in 54(84.4%) patients. CAP caused by Chlamydia pneumonia (Cp) was more frequent in group A – in 23 patients (95.9% of the group), by Mycoplasma pneumonia (Mp) – in group B, in 37 patients (92.5% of the group).

Asthma was diagnosed in 20(45.5%) patients mainly of group B, with recurrent CAP in 34.5% of asthmatic patients, 62.1% of them had pulmonary hypertension (PH), 6.7% - CT signs of bullous emphysema (BE).

Conclusion: 1. Close relationship between HCTD and CAP is revealed. 2. Cp-CAP was more frequent in pediatric patients up to 4 years old. Mp-CAP - in children 5 years and older. 3. Recurrent CAP was the cause of asthma exacerbation in one-third of patients with asthma and CAP. 4. Asthma in children with CAP and HCTD was more severe with development of PH, BE.

P3423
Strategy and implementation documents were published to improve outcomes in COPD and asthma in England
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Rationale: Despite three million people estimated to have COPD in the UK, only 900,000 currently have a diagnosis. Variation in care and outcomes is significant. Action was required to move from a reactionary service, treating those with moderate to severe disease, to prevention, earlier diagnosis and pro-active management.

Methods: A systematic evidence review was undertaken with the engagement of a range of healthcare professionals from primary and secondary care. Following wide consultation, consensus was reached on six high-level objectives to improve outcomes for patients which would require a collaborative approach involving public health, health and social care services.

Results: An Outcomes Strategy for COPD and Asthma was published in July 2011. This was accompanied by an implementation document specifically for the health service, which set out in more detail the actions to help meet the objectives. A baseline dataset of indicators for measuring and monitoring outcomes for improvements in the respiratory care have been established and benchmarking data produced to assess variation in models of service provision across England. This dataset is responsive to change at all levels of the provider system from local through to national and helps to identify areas and particular aspects of care for local action.

Conclusion: Through the Outcomes Strategy for COPD and Asthma, the NHS implementation document that accompanies it, and the regional clinical leadership, care and outcomes for COPD are improving through a shift in the burden of the disease to prevention, diagnosis and proactive management.

P3424
The directions of mild asthma evolution
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Mild asthma is the heterogenic cohort with low level of adherence and asthma control, so investigators curiously study it.

The aim was to study the results of evolution of the disease in mild asthma cohort among patients with available data for the period of 3 years.

We studied the history of 141 patients with a 3 year history of mild persistent asthma. Three groups were formed: 1st group – had actual controlled asthma (141), 2nd - had partially controlled asthma (n=74), 3rd - uncontrolled asthma (n=24).

E-data base collected the data of all the patients and includes information concerning educational level, passing educational asthma programs, lung function, Ig E level, treatment regimens, asthma control, measured by ACQ and ACT, cooperation index, life quality level and etc.

We observed in the 1st group – higher level of lung function and life quality level. Patients of this group more often took part in asthma educational programs, had higher cooperation index (p<0.05). Besides this 1st group didn’t get any therapy for 3 last months and 6.9% passed successfully allergen-specific immunotherapy. We have revealed difference in educational status and life quality level in other two groups. Patients of the 2nd group had significantly higher KCS, 269 (6.13±3.9 mg per day vs 108.9±4.19±5 mg per day in the 2nd group), Ig E level, low cooperation index, more rarely have made planned visits to their physician (p<0.05). Obvious difference in asthma control assessed by ACT between 2nd and 3rd groups was found.

Conclusion: The results of evolution of the disease finally demonstrate several interventions that could influence predictably on it: taking part in asthma educational programs, pass allergen-specific immunotherapy, making planned visits to the physician.

P3425
Current smoking and low HRQoL as strong predictive factors for acute care among elderly asthma patients
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Objective: To examine risk factors for emergency visits among elderly asthma patients in a well-organized asthma care setting.

Methods: The study population was a random sample of 344 patients visiting the Pulmonary Clinic of Helsinki University Hospitals (HUCH) with a diagnosis of asthma (A54.4-46) during the years 1995-2006. 95% asthma patients had at least one emergency visit and formed the active group. 227 patients without emergency visits formed the control group. Uni- and multivariate logistic regression was used to analyze the significance of several demographic and clinical variables for the need of emergency treatment.

Results: The study population was on average 56 (SD 13) years old and 72% of the patients were women. Follow-up among cases covered 799 patient-years and on average 0.4 emergency visits per patient-year was identified. Asthma, lower and upper respiratory infections were described as the discharge diagnosis in 45%, 17% and 6% of the visits, respectively. The cases were older, had suffered longer from asthma, had lower lung functions, and were more often ex- or current-smokers. In the multivariate analysis current smoking and low HRQoL (health related quality of life) remained independent risk factors for emergency room care (OR 3.9; CI 1.7-8.8 and OR 1.9, CI 1.2-3.0, respectively).

Conclusions: Current smoking is a risk factor for the need of emergency care. Also those with self-estimated poor HRQoL are in a risk for emergency treatment. In this study population, enrolled in the special care setting, the promotion of smoking cessation might play an important role in prevention of acute hospital care among elderly asthma patients.

6165
P3428  Which device for which patient? Criteria for selecting inhaler devices

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Inhalation is the preferred route of delivery for anti-asthma medications. Asthma management guidelines recommend inhalation choice, but they don’t provide specific guidance regarding devices selection.

Unless all asthmatic patients are able to use their inhaler devices correctly, poor inhalation techniques will continue to be one of the major obstacle of asthma management. Prescribing a suitable device for the patient will guarantee better inhaler technique and improves medication delivery to the airways and as a result will improve level of asthma control.

The ideal inhaler device is the device that is easy to be used by the patient and enable the desired medication to reach the airways. The selection of the device should be made after assessing patients abilities to ensure that they are able to understand the instructions and to perform the necessary steps correctly. However, in reality inhaler devices are often prescribed according to patient age, level of education, cost of the device, pharmaceutical companies recommendations or previous experience.

To guide our prescribers in selecting the best devices for their patients, we developed inhaler devices selection criteria according to patient’s cognitive, physical and inhalation abilities.

The aim of this presentation is to present the criteria assessment steps and inhaler devices choices.

References:

P3427  Methacholine challenge response in controlled asthma and correlations with other disease characteristics

Inna Stoicescu1, Ileana Stoicescu1, Diana Ionita1, Daniela Dospinoiu1, Felicia Cojocaru1, Camelia Nita1, Alina Croitoru1, Madalina Burecu1, Carmen Stroescu2.

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Aim: To assess methacholine challenge response in patients with controlled asthma and its correlations with other asthma characteristics.

Subjects and methods: Patients with controlled asthma performed methacholine challenge test (MCT) using ATS Guidelines (1999). Bronchial hyper-reactivity was considered severe for PC20 0.125 mg/mL and moderate for 0.125-2 mg/mL.

Spirometry, exhaled nitric oxide (NIOX) and blood eosinophils measurements were performed the same day prior to MC. A bronchodilator test was performed the next day and dFEV1 was calculated (difference and % from the baseline FEV1 value).

The allergic rhinitis history was noted. Correlations between parameters were calculated.

Results: Twenty-two patients were evaluated: mean age 47, 7 males.

The mean PC20 was 0.558 mg/mL (range 0.003-2). Nine patients had severe and 13 moderate hyper-reactivity.

Mean baseline dFEV1 was 84%, mean NIOX 35 ppb (range 5-108), mean dFEV1 0.46 L (0.04-1.35) and 23% (3-63), blood eosinophils 234/mmc (30-840) and 3% (0-6.9-4). Ten of the patients had allergic rhinitis.

The PC20 values correlated with dFEV1 post-bronchodilator value (r=0.429, p=0.046), but with no other parameters studied. The severity of hyper-reactivity was only associated with the dFEV1 values (p=0.017).

The bronchial response was similar regardless the presence of allergic rhinitis. The performed statistical evaluations show a statistically significant control.

Conclusions: Moderate/severe bronchial hyper-reactivity was seen in our patients with asthma considered controlled when using GINA 2011 criteria. NIOX values, eosinophil blood counts and bronchodilator response showed high variability. None of the studied characteristics correlated with the methacholine response, except for the bronchodilator response.

P3428  Exhaled nitric oxide correlations in patients with controlled and partially controlled asthma

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Aim: To assess NIOX values correlations with other disease characteristics in patients with controlled and partially controlled asthma.

Subjects and methods: Patients with controlled and partially controlled asthma performed exhaled nitric oxide (NIOX), spirometry, bronchodilator test and blood eosinophils measurements. The allergic rhinitis history was noted. Correlations between NIOX values and the other parameters were calculated.

Results: 42 asthma patients were evaluated: mean age 43, 14 males; 24 had controlled and 18 partially controlled asthma.

NIOX values varied between 5 and 151 ppb (mean 41) in the whole group of 42 patients.

All the tested parameters differ between the two groups. Significant differences were only seen in baseline FEV1 value (75% from predicted in the partially controlled, 85% in the controlled, p= 0.035) and blood eosinophils values (371/mmcc, 4.5% in the partially controlled, p=0.012; 155/mmcc and 2.3% in the controlled asthma patients, p=0.023).

In the whole group of 42 patients NIOX values correlated with blood eosinophils (r=-0.492, p=0.001), not with FEV1 values or the dFEV1 increase after the bronchodilator administration (p=0.05). The correlations were similar when the two groups were analyzed separately. NIOX values correlations with blood eosinophils values were r=0.577, p=0.012 in the partially controlled, and r=0.412, p=0.040 in the controlled group.

No correlations were seen related to the presence of allergic rhinitis.

Conclusions: Exhaled nitric oxide values showed high variability and only correlated with blood eosinophils values in our group of patients, regardless of asthma control.
The relationship between the serum YKL–40 level and severity of asthma
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Aim: The aim of this study was examined a relationship between the serum YKL–40 (chitinase-3-like-1) level and severity of asthma. Methods: In the study, 90 female non-smoker and without additional disease patients (ages 20–66) in a stable and exacerbation period for asthma were grouped as Group I: Stable mild persistent asthma (n: 30), Group II: Stable moderate and severe persistent asthma (n:30), Group III: Exacerbation period (n:30). The differences of the serum YKL–40 level among all the groups were examined with ELISA. Also, in the patient groups with asthma, the serum YKL–40 level was compared with age, age of asthma, body mass index (BMI), forced expiratory volume in first second (FEV1), peak expiratory flow (PEF), total IgE results. One-way analysis of variance was used to examine differences between groups.

Pearson’s correlation coefficient was used for correlation between variables.

Results: The serum YKL–40 levels during asthma exacerbation period were found the highest average (36.36±10.49 ng/ml) while the serum YKL–40 levels were found the lowest average (13.20±5.60 ng/ml) in stable mild persistent asthma have (p<0.05). There was a negative correlation the serum YKL–40 levels and FEV1, PEF, exacerbation period (p<0.05). There was no correlation between the serum YKL–40 levels and other variables in three groups.

Conclusion: Increased the serum YKL–40 may be a marker used to evaluate the level of asthma severity.

P3432 Heritable connective tissue disorders as factor modifying asthma symptoms in pediatric patients
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Background: High prevalence of heritable connective tissue disorders (HCTD) among children changes clinical manifestations of common childhood diseases, leading to diagnostic and therapeutic errors.

Aim: To study clinical features of asthma (A) in children with HCTD.

Methods: In 2005–2007, 186 patients with moderate allergic asthma (GINA Guidelines 2009) were followed up for two years. 33.4±1.6% patients had mild persistent A, 57.49±5% − moderate persistent A and 10.08% − severe persistent A. 55.68±3% patients clinically, serologically and immunologically diagnosed. All children had phenotypic manifestations of HCTD.

Results: CAP caused by Mycoplasma pneumonia was in 80% of asthmatic patients with CAP. By Cytomegalovirus – in 36.3%, by Chlamydophila pneumonia - in 29.1%. 47.3% of patients with A and CAP had recurrent episodes of CAP that caused A exacerbation. Pulmonary hypertension (PH) was in 28.8% of patients with A and in 32.7% of patients with CAP and A. 33.3% of the latter had severe persistent asthma. The EIT evidence of pulmonary fibrosis (PF) and emphysema bullae (EB). Patients with A exacerbation due to CAP received antibiotic treatment (macrolides) (ABT) besides controller therapy, and this provided the achievement of A control.

Conclusions: 1. A exacerbation in 80% of asthmatic patients was due to CAP caused by Mycoplasma pneumonia. 2. Recurrent episodes of CAP were in 47.3% of asthmatic patients with HCTD. 3. 28.8% of patients with A and HCTD, and 37.2% of patients with A, HCTD and CAP had evidence of PH, with PF and EB in 33.3% of the latter. 4. Basic therapy of asthmatic patients with CAP included ABT to achieve A control.

P3433 Relationship of body mass index and current asthma status among adult asthmatics presenting in the outpatient department
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Purpose: To determine whether a relationship between body mass index (BMI) and current asthma status among adult asthmatics seen in the outpatient departments of the Philippine General Hospital Asthma Comprehensive Care Unit, have better asthma control, decrease asthma severity, higher FEV1, and good response to bronchodilator.

Methods: All adult patients who fulfilled the inclusion criteria seen in the outpatient department (OPD) of the Philippine General Hospital from November 2010 to December 2011 referred by consultants, fellows in training and residents will be gathered and ask to complete a questionnaire after informed consent was obtained. If subject has no pulmonary function test, a free pulmonary function test will be done.

Results: BMI status was significantly associated with outcome measures. Majority of the obese patients have uncontrolled asthma. Results showed that, patients, regardless of their body mass index, who were enrolled at the Philippine General Hospital Asthma Comprehensive Care Unit, have better asthma control, decrease asthma severity, higher FEV1, and good response to bronchodilator. Obese asthmatics have more severe asthma, poorer asthma control, with more frequent attacks, more frequent use of relievers, and are overall less responsive to bronchodilators. Those asthmatics with proper education of their disease have better levels of control.

Clinical Implications: Proper weight management improves asthma control; prevent asthma attacks and better response to bronchodilators. Thus prevent hospitalization. Enrollment to asthma education program enhanced asthma management.

P3434 The role of the tracheal phonography in chronic obstructive lung disease and asthma diagnosis
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Obstructive lung diseases are the most common chronic diseases of bronchopulmonary system. According to epidemiological markers were identified more than 11 million people with chronic obstructive lung disease (COPD) in Russian Federation, and most common cause of population disability. In recent years, have been increasing the rates of asthma. The purpose of this study is to determine the role of tracheal phonography of forced expiration in the obstructive lung diseases diagnosis. This acoustical method is based on registration of forced expiratory noises which recording from laryngho-tracheal area. There were examined 59 patients with obstructive lung diseases at the age 46-58 years. It was diagnosed that 24 patients had bronchial asthma and 35 one had COPD. We compared spirometry grades and duration of the noise detected by tracheal phonography of forced expiration. All patients had lengthening of the acoustic value of 1.5-5 times the calculated norm. According to the correlation analysis between the acoustic value and FVC (r = 0.64, p<0.05), FEV1 (r = 0.46, p<0.05) and PEFR (r = 0.11, p<0.05). The result of our research is allowing us to recommend the acoustic method for chronic obstructive lung disease and asthma diagnosis.

P3435 Study of motivation in patients with bronchial asthma
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1Laboratory of Pernigilation of Non-specific Lung Diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration SB RAMS, Blagoveschensk, Russian Federation; 2Laboratory of Functional Research of Respiratory System, Far Eastern Scientific Center of Physiology and Pathology of Respiration SB RAMS, Blagoveschensk, Russian Federation

The disease leads to revaluation of personal values and motivation, that is why the patients are usually motivated to escape failures and are afraid of risk. The motivation of patients with bronchial asthma (BA) has not been studied enough.

Aim: To study motivation of BA patients.

Methods: 168 patients (78% of whom were women) with BA of different severity. The mean age was 47±11.9 years; the mean duration of the disease was 6.0±7.7 years. The test “Motivation to success” by T. Ehlers, method of diagnosis of the ability to risk by Schubert, Marlowe-Crowne Social Desirability Scale were used.

Results: The patients were divided into three groups. The 1st group included 37 patients with mild BA, the 2nd – 95 patients with moderate BA, and the 3rd group – 36 patients with severe BA. The patients of all groups had a motivation to success predominantly of medium and high level (the mean values are 3.14±0.66, 2.9±0.83, 3.05±1.24 points, respectively, at the maximum of 4 points). The patients of the 1st and 2nd groups were equally careful (low degree of readiness to risk: 2.4±0.63 and 2.36±1.03 points, respectively). By this criterion they significantly differed from the patients of the 3rd group who had medium values of the test (3.05±1.24, p<0.05). The level of approval motivation were low in the majority of the examined patients (in 78% of respondents it was within the range from 1.2±0.41 to 1.2±0.45 points).

Conclusion: BA patients have quite a high motivation to success achievement and a desire to get the result not depending on the disease severity. The low approval motivation appears due to the orientation to the personal opinion. The motivation have to be taken into account for effective doctor-patient communication.

P3436 Use of leukotriene modifiers promotes to decrease bronchial hyperreactivity in bronchial asthma patients

Background: Clinical studies proved, that leukotriene modifiers have mild and vari- able broncholytic effect, decrease symptoms, improve lung function and decrease asthma exacerbations.

6188
Objectives: This study aimed to investigate the influence of leukotriene modifiers (antagonists of Cys-LR1—montelukast) on bronchial hyperreactivity in steroid-naïve bronchial asthma patients.

Methods: A total of 58 patients (52 adults and 6 children) were included in the open-label study. Asthmatic patients were divided into three different age groups: 4-11 years (n=60), 12-64 years (n=62) and ≥ 65 years (n=52). COPD patients consisted of all ages groups (n=53).

Results: Clinically not controlled asthma with respect to Eosinophilic Lung Disease (EOL) questionnaire was present in 25% of patients. Moreover, the number of exacerbations in the previous year was reported by 37% of patients. Amongst COPD patients, 24% reported exacerbations of asthma.

Conclusion: The use of leukotriene modifiers (montelukast) in combination with inhaled steroids is an effective treatment for asthma and COPD patients with leukotriene receptor hypersensitivity.

P3437
ObSErVational study for thE monItoring of not controlled Asthma (SERENA)
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1Pulmonary Unit, University and General Hospital, Verona, Italy; 2Respiratory Intensive Care Unit and Thoracic Pathophysiology Laboratory, University and General Hospital Careggi, Firenze, Italy.

Background: International guidelines recommend control of asthma as a major goal of therapy. Patients with "well-controlled" asthma present no exacerbations. However, it is well known that implementation of guidelines in real clinical practice may be difficult. Objective: To assess the level of asthma control in real clinical practice in patients treated with inhaled steroids and/or bronchodilators following the GINA guidelines. Methods: This 6 months observational study was promoted by AIPO and was carried out in 16 Pulmonary Units. Consecutive patients with asthma, treated after GINA guidelines, attending the outpatients of each center were enrolled (2010). Data on exacerbations and treatments were collected by means of a web based Case Report Form, and control of asthma was assessed with the Asthma Control Test (ACT) questionnaire.

Results: The number and characteristics of the patients enrolled are reported in Table 1.

Table 1. Patients characteristics
N of patients Gender (MF) Age BMI Smokers Ex smokers Non smokers
584 200388 53 (19-88) 27 (16-341) 28% 72%

91% of patients were treated with LABA+ICS, while 9% with ICS and SABA. 60% of patients reported 1 exacerbation, 16% 1 Emergency Visit and 44% 1 non programmed visit in the year preceding the study. The data on control of asthma in the age groups is reported in Table 2.

Table 2. Control of asthma (ACT score)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N Obs</th>
<th>Mean</th>
<th>Median</th>
<th>10th Pctl</th>
<th>90 Pctl</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthmatic children</td>
<td>60</td>
<td>47.19</td>
<td>47.93</td>
<td>28.59</td>
<td>63.09</td>
<td>12.83</td>
<td>74.40</td>
</tr>
<tr>
<td>Adult asthmatics</td>
<td>62</td>
<td>66.14</td>
<td>69.11</td>
<td>52.99</td>
<td>76.47</td>
<td>19.99</td>
<td>87.01</td>
</tr>
<tr>
<td>COPD patients</td>
<td>53</td>
<td>58.51</td>
<td>58.19</td>
<td>48.97</td>
<td>74.63</td>
<td>38.35</td>
<td>74.63</td>
</tr>
</tbody>
</table>

Irrespective of age or the severity of disease, most asthma and COPD patients were able to inhale through the studied DPI device with an adequate PIF.

378. COPD: epidemiology and varia

P3439
Clinical pattern of COPD in South India—A global public health problem
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Chronic Obstructive Pulmonary Disease (COPD), among all noncommunicable diseases and chronic respiratory diseases, continues to be on the increase, mostly attributed to limited doctor/patient health education globally. Associated comorbidities are not often evaluated concurrently that a sizeable number of patients die of alternate disorders. Spirometry being the gold standard for diagnosis is forgotten that these patients are treated for few days as “Bronchitis”. The purpose of this communication is to highlight the clinical pattern of this disease as guidelines for the medical profession.

A total of 235 patients in the age group (35-77) were evaluated in the year 2011. The diagnosis was established by history, exposure to tobacco, atmospheric and/or industrial pollutants, clinical and laboratory examination and not the least, spirometry. EKG, imaging studies and eco were done as relevant.

The clinical observations include:
1. Majority were males and smokers.
2. 8 patients (4%) were not tobacco smokers.
3. Non tobacco smokers and those with comorbidities were symptomatic early.
4. Patients with echo based pulmonary arterial hypertension/cor pulmonale died early.
5. Majority of patients were elderly-60-70 years.
6. Common comorbidities were cardiovascular and musculoskeletal and related features.
7. Few of the patients initially presented with cardiac symptoms, diverting the attention of the primary disease, often forgotten.
8. Associated tuberculosis and diabetes mellitus were not uncommon.

Comments: There is still need for improved patient/doctor health education. All patients with smoking history for 5 or more years should be evaluated early before developing complications.

379. COPD: epidemiology and varia

P3440
Peak inspiratory flow rates through placebo dry powder inhaler device in various asthma and COPD patients
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Dry powder inhalers (DPIs) are inspiratory flow driven. We sought to characterise inspiratory flow parameters of placebo dry powder inhaler devices in asthma patients of various age groups and in patients with chronic obstructive pulmonary disease (COPD) in an open, randomised, multicentre study (SALIF). Preliminary data of the Easyhaler® test device will be presented.

The primary variable was the peak inspiratory flow (PIF) rate through the inhaler. Three inspiratory flow curves were recorded and the best of them was analysed. To ensure consistent dose delivery of the drug peak inspiratory flow rates for this device should be ≥ 28 L/min or higher.

A total of 227 subjects with documented diagnosis of asthma and/or COPD of various severities were included in the open-label study. Asthmatic patients were divided into three different age groups: 4-11 years (n=60), 12-64 years (n=62) and ≥ 65 years (n=52). COPD patients consisted of all ages groups (n=53).

Descriptive statistics of PIF values in different subgroups

<table>
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<tr>
<th>Subgroup</th>
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<th>Mean</th>
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619s
**P3440**

Course features of COPD in women and men
Mykola Ostrovskyy, Oleksandr Varunkiv, Iryna Savelikhina, Mariana Kulychny-Misnok, Internal Medicine #3, Ivano-Frankivs'k National Medical University, Ivano-Frankivs’k, Ukraine

**Background:** COPD is a leading among the present problems in Pulmonology. Epidemiological data indicate a greater prevalence of this nosology among men.

Prevalence of COPD in the world among men is 9.3%, and among women - 7.3%.

Given that COPD - a disease mainly of the second half of life, it should be noted that at this period women are characterized by a extinguishing of steroidogenesis function. This factor may be one of those that aggravating the course COPD in women.

**Aim:** To study the severity of breathlessness on a MMRC scale in women and men with newly diagnosed 2nd stage of COPD.

**Materials and methods:** The main inclusion criteria were: 1) age of patients ≥ 40 years; 2) Experience smoking ≥ 10 pack-years; 3) FEV1 ≤ 80% predicted; 4) FEV1/FVC ≤ 0.65; 5) Smoking ≥ 10 pack-years. All participants were treated at pulmonology department of Ivano-Frankivsk regional center of phthisiologhy and pulmonology. The average age of women was (58.5±2.8) years and men - (54.7±3.1) years.

**Results:** The level of FEV1 on average was 61.6±2.4% in women, and - 58.4±3.9% (p>0.05) in men. Index of breathlessness on a MMRC scale in women was 3.6±0.4, and 2.9±0.4 - in men. Thus, exploring the clinical course of 2nd stage of COPD among women and men aged 50 to 60 years, we can say that, despite the identical clinical manifestations of disease, there is a greater severity of breathlessness on a MMRC scale in women as in men.

**Conclusion:** The clinical course of COPD in women compared with men characterized with more severe shortness of breath on a MMRC scale with less ventilation violations, according to spirometry.

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**P3441**

Is high level of IgE an additional problem in smoking patients with severe and very severe chronic obstructive pulmonary disease (COPD)?
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Smoking is one of the greatest risks factors of COPD and it increases the risk of allergic sensibilisation.

The aim of the study was to estimate the level of IgE and its possible connection with COPD severity and sensibilisation to allergens in smoking patients with severe and very severe COPD and great length of smoking.

**Methods:** The 30 patients with very severe COPD were enrolled. It was estimated smoking history (body mass index (BMI), spirometric parameters (forced vital capacity (FVC), forced expired volume in 1 second (FEV1)) and level of total IgE.

**Results:** The skin prick test with local significant allergens (home dust, pollen of ambrosia, birch, fur of cat) was performed to patients with increased level of IgE.

**Conclusion:** The smoking patients with severe COPD has allergic constitution with increased IgE level and sensibilisation to different allergens. There is no strict correlative connection between the length of smoking and level of the IgE.

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**P3442**

Quality of COPD diagnosis in Ukraine: A phone survey
Ivan Voshnyevsky, Olga Khitrenko, Triana Kugler. Internal Medicine and General Practice - Family Medicine Department, Donetsk National Medical University, Donetsk, Ukraine

**Background:** Quality of COPD diagnosis remains poor in post-Soviet countries. There is limited information about beliefs and patterns of care of COPD in Ukrainian general practitioners (GP).

**Aim:** To explore the knowledge, beliefs and working stereotypes about diagnosis of COPD in Ukrainian GPs.

**Methods:** We performed a telephone survey of 85 GPs in Donetsk region, Ukraine. As criteria for selected GP diagnosis we answered on these questions:

1) "How many of COPD patients in your practice are both > 40 years old and smokers > 10 pack-years?" (correct was considered 80% and more); 2) "How many of COPD patients in your practice needed spirometry (SM) to confirm the diagnosis?" (correct was considered 100%); 3) "And how many of them actually asked for medical help to allergist. There is no significant connection between level of IgE and spirometric parameters. Allergic sensibilisation to home dust and the 3 patients had sensibilisation to fur of cat.

**Results:** The 24 patients had increased level of IgE (329,5 ± 88,9%) with increased level of IgE (> 8000) were present just in 20% (17 of 85) GPs.

**Conclusions:** Quality of COPD diagnosis is in very poor. 20% GPs demonstrate adequate knowledge and practice in correct COPD diagnosis.
Despite the significant differences in previously recognized and unrecognized COPD, there was no difference between the two in LOS (1.8±2.3 v. 1.9±2.3; p=0.09). LOS adjusted for procedure (actual/expected LOS) was also not significantly different (p=0.43 and 0.99±1.14 for recognized and unrecognized COPD, respectively; p=0.45).

Conclusion: The prevalence of unrecognized COPD among surgical patients is quite high and it appears to affect perioperative morbidity similarly to previously recognized COPD. The data suggests that spirometric testing of an at risk population for COPD may have value in preoperative assessment.

P3445
Clinical and functional characteristics of Italian and Spanish patients with alpha 1-antitrypsin deficiency
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Alpha-1 antitrypsin deficiency (AATD) is a rare genetic condition associated with pulmonary disease, for which national and international registries play a crucial role.

Methods: With the aim of providing a clinically better characterisation of AATD patients, we conducted an observational cross sectional study on adult patients affected by severe AATD enrolled in the Spanish and Italian national registries.

Results: We assessed 745 subjects, 416 enrolled in the Spanish and 329 in the Italian Registries with a mean age of 49.9 years (SD=13.8). The 57.2% of subjects were male and the 64.9% smokers or former smokers. The majority were index cases (81.2%), mostly with PI*ZZ genotype (73.4%), the mean diagnostic delay was 9 years (SD=12.1). Compared with PI*ZZ (n=547), PI*SZ (n=124) subjects had an older age at diagnosis and better preserved lung function despite a higher mean smoking consumption. Characteristics of PI*ZZ patients with chronic obstructive pulmonary disease (COPD) (n=412) were compared according to GOLD severity stages. Mean age was similar in GOLD I, III and IV, but subjects in GOLD II were older. In GOLD I women and non-index cases were prevailing. The rate of never smokers significantly decreased when severity of COPD increased. Augmentation therapy was administered to 19% of GOLD I, 48% of GOLD II, 59% of GOLD III and 51% of GOLD IV patients.

Conclusions: Early diagnosis of AATD is still an unmet need. PI*ZZ patients in both smoking and non-smoking groups had more severe respiratory disease than PI*SZ, despite less smoking consumption. Augmentation therapy is provided to similar proportions of patients with all degrees of severity of airflow obstruction from GOLD I to IV.

P3446
Bacterial airway colonization is not associated with increased procalcitonin in stable COPD
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1Clinic of Pulmonary Medicine, University Hospital, Aachen, Germany; 2Department of Pulmonary Medicine, Oslo University Hospital, Oslo, Norway; 3Department of Respiratory Physiology, Glittreklinikken, Hakadal, Norway; 4Institute for Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, Netherlands; 5Pneumology, Hospital Clinic, Barcelona, Spain; 6Pneumology, IRCCS Policlinico, Milan, Italy; 7Department of Respiratory Medicine, Belgrade, Serbia; 8Pneumology, Instituto de Investigaciones Biomedicas August Pi i Sunyer (IDIBAPS), Hospital Clinic, Ciber de Enfermedades Respiratorias (CIBERES), Barcelona, Spain; 9Pneumology, IRCCS Policlinico San Matteo, University of Pavia, Italy; 10Pneumology, University Hospital, Maastricht, Netherlands; 11Pneumology, Hospital Clinic, Barcelona, Spain; 12Clinical Diagnosis, Thermo Scientific Biomarkers, Hennigsdorf, Germany

Background: Bacterial colonization of the airways hampers the utility of sputum microbiology at exacerbation of COPD. We hypothesize that, in contrast to exacerbation, circulating procalcitonin remains low in chronic bacterial airway colonization in stable COPD.

Results: Despite the significant differences in previous colonization in patients with positive sputum cultures were similar (median 95% CI 0.080 [0.069-0.094] vs. 0.076 [0.064-0.091] vs. 0.080 [0.066-0.100]; p=0.312).

Conclusion: In contrast to acute exacerbation of COPD, procalcitonin values remain low in chronic bacterial airway colonization in stable COPD.

P3447
Air travel and COPD: A new algorithm for pre-flight evaluation
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The reduced pressure in the aircraft cabin may cause significant hypoxaemia and respiratory distress in patients with COPD. Simple and reliable methods for predicting need for supplemental oxygen during air travel have been requested.

Objective: To construct a pre-flight evaluation algorithm for COPD patients.

Methods: In this prospective, cross-sectional study of 100 COPD patients, sea level pulse oximetry at rest (SpO2_slt) and exercise desaturation (SpO2_o2max) were used to evaluate whether the patient a) is fit to fly without further assessment, b) needs further evaluation with hypoxia-altitude simulation test (HAST) or c) should receive in-flight supplemental oxygen without further evaluation. HAST was used as reference method.

Results: An algorithm was constructed using a combination of SpO2_slt and SpO2_o2max. Categories for SpO2_slt > 95%, 92-95%, and <92%, the cut-off value for SpO2_o2max was calculated to 84%. Arterial oxygen pressure <6.6 kPa was the criterion for recommending supplemental oxygen. When validated on a separate group of 50 COPD patients, this algorithm had a sensitivity of 100% and a specificity of 80%.

Patients with SpO2_slt > 95% combined with SpO2_o2max ≥ 84% may travel by air without further assessment. Supplemental oxygen is recommended if SpO2_slt 92-95% combined with SpO2_o2max < 84%, or if SpO2_slt < 92%. Otherwise, HAST should be performed.

Conclusions: The algorithm is a simple tool for pre-flight evaluation of COPD patients.

P3448
Indications of small airways disease in healthy smokers
Hid de Jonge1,2, Laurent Reulens1,3, Nick ten Hacken1,3, Dirkje Postma1,2
1Maarten van den Berge1,2,3, Dept of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, University of Groningen, University Medical Center Groningen, Netherlands; 2GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Netherlands

It has been well established that small airways disease is a risk factor for COPD development. Cigarette smoking is the main risk factor for COPD development. We investigated whether smokers, without COPD and an FEV1 > 80%pred, have indications of small airways involvement.

Healthy smokers and non-smokers (asymptomatic, FEV1 > 80%pred, FEF25-75 > 70%) were included. We performed spirometry, body plethysmography, and impulse oscillometry (IOS) in all subjects. Smokers were compared to non-smokers using Student’s t or Mann Whitney U test.

56 non-smokers (28 < 40 years and 28 > 40 years old) and 54 smokers (26 < 40 years and 28 > 40 years old) were included. Large airways parameters were comparable between smokers and non-smokers. In contrast, small airways parameters differed between smokers and non-smokers. Smokers had a lower FEF25-75 and R5-20, AX and Rf than non-smokers. No differences in RV or RV/TLC were found between smokers and non-smokers.

621s
Table 1: Differences between smokers and non-smokers

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers</th>
<th>Smokers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>m=56</td>
<td>n=54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>41.6 (21.4–57.6)</td>
<td>41.0 (23.2–51.3)</td>
<td></td>
</tr>
<tr>
<td>Males (n,%)</td>
<td>31 (55)</td>
<td>31 (57)</td>
<td></td>
</tr>
<tr>
<td>packyears</td>
<td>0</td>
<td>14.2 (2.9–27.8)</td>
<td></td>
</tr>
<tr>
<td>FEV1/s/predicted</td>
<td>3.6 (3.2–4.5)</td>
<td>3.6 (3.2–4.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>78.6 (75.1–83.7)</td>
<td>77.9 (73.8–82.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>FEV1/FVC (L)</td>
<td>3.7 (2.7–4.3)</td>
<td>3.3 (2.5–4.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV1/s/predicted</td>
<td>88.0 (74.8–99.0)</td>
<td>78.0 (68.5–94.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>R5 (pa/L/s)</td>
<td>0.28 (0.24–0.34)</td>
<td>0.32 (0.26–0.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>R2 (pa/L/s)</td>
<td>0.27 (0.22–0.31)</td>
<td>0.30 (0.22–0.34)</td>
<td>0.20</td>
</tr>
<tr>
<td>R0 (pa/L/s)</td>
<td>0.02 (0.00–0.04)</td>
<td>0.03 (0.01–0.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>X5 (pa/L)</td>
<td>0.07 (0.05–0.09)</td>
<td>0.08 (0.01–0.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>AX (pa/L)</td>
<td>0.14 (0.07–0.19)</td>
<td>0.19 (0.10–0.38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resonance frequency (Hz)</td>
<td>9.5 (7.8–10.7)</td>
<td>10.4 (8.8–14.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>RV/s/predicted</td>
<td>97.3 (20.7)</td>
<td>93.7 (15.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>RV/IC (%)</td>
<td>27.4 (6.3)</td>
<td>26.7 (5.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Alveolar NO (ppb)</td>
<td>4.2 (3.1–5.4)</td>
<td>4.7 (3.2–5.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Bronchial NO flux (no/L/s)</td>
<td>0.55 (0.39–0.72)</td>
<td>0.36 (0.18–0.53)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) and differences tested with Mann-Whitney U test, unless stated otherwise. * median (IQR), differences tested with Student’s t-test.

We demonstrate changes in small airways parameters in smokers with normal lung function. These changes are already present in smokers ≤40 years old. Whether this small airways disease in young smokers is a first step in COPD development, remains to be elucidated in further studies.

P3449
Usefulness of COPD assessment test (CAT™) for the management of COPD according to GOLD 2011
Takashi Motegi1,2, Takeo Ishii1,2, Kumiko Hattori1,2, Yuji Kurumoki1,2, Ryoko Futamata1,2, Koichi Yamada1,2, Akiko Gemma1,2, Koziro Kida1,2
1Respiratory Care Clinic, Nippon Medical School, Tokyo, Japan; 2Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

Background: The GOLD report (2011) proposes a new strategy for the management of stable COPD—the use of the CAT score. Is a CAT score >10 a useful borderline value for disease severity in a Japanese cohort?

Purpose: To determine the association between the CAT score of patients, and prior exacerbation frequency and usage of medical resources.

Method: A total of 180 patients recruited from a secondary COPD clinic. The CAT score was examines under stable conditions at least four weeks after any exacerbations. We investigated the association between the CAT score and various clinical parameters, including pulmonary function tests, 6-minute walking distance (6MWD), the St George’s Respiratory Questionnaire (SGRQ), the Hospital Anxiety and Depression score (HAD), a multidimensional assessment system (BODE index), exacerbation rate of the previous year, and the use of resources such as unscheduled visits and long-term oxygen therapy (LTOT).

Results: The mean age was 71.9, and %FEV1 was 59.3%. The CAT score was significantly associated with following parameters: %FEV1 (r= -0.42, p < 0.001), 6MWD (r= -0.26, p < 0.001), total SGRQ score (r= 0.74, p < 0.001), HAD-depression (r= 0.40, p < 0.001), HAD-anxiety (r= 0.32, p < 0.001), and BODE index (r= 0.46, p < 0.001). The patients with CAT score ≥10 was significantly associated with prescribed LTOT (p<0.001), frequent unscheduled visit (p<0.019), and frequent exacerbation of previous 1-year (p=0.006), but the subjects with CAT score ≥20 was not associated with exacerbation frequency.

Conclusions: We concluded that a CAT score ≥10 can be considered a reasonable borderline value for exacerbation frequency and usage of medical resources in a Japanese cohort.

P3450
COPD assessment test (CAT) in the evaluation of COPD
Virginia Almadina, Jesus Sanchez, Ana Gomez-Bastero, Agustin Valido, Maria Pavon, Alonso Montemayor. Pneumology, Hospital Universitario Virgen de la Macarena, Sevilla, Spain

Objective: To evaluate the correlation of CAT with other specific questionnaires and with clinical/functional parameters.

Methods: A prospective study analyzing DOSE, BODE and BODE index, GOLD stage, quality of life questionnaires (SGRQ, CRQ, and CAT), and number of exacerbations-year (no. ex-years), dividing patients into non-exacerbator (<2 exacerbations in the last year) and exacerbator (≥2) were done.

Results: No differences in general variables were found. Analyzing the correlation between CAT and CRC/SGRQ we found a significant correlation (r=0.70; CAT/CRC r= -0.66, p<0.001). The relationship of the questionnaires vs clinical/functional outcome is reflected in the table, where rates are moderate correlation with CAT, although improved with respect to SGRQ and CRQ, except in GOLD stages.

<table>
<thead>
<tr>
<th>m=104</th>
<th>VEF1</th>
<th>GOLD</th>
<th>BODE</th>
<th>BODEx</th>
<th>DOSE</th>
<th>CRQ</th>
<th>No. ex-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>0.23</td>
<td>0.44*</td>
<td>0.30</td>
<td>0.25</td>
<td>0.34</td>
<td>0.37*</td>
<td></td>
</tr>
<tr>
<td>SGRQ</td>
<td>0.27</td>
<td>0.30</td>
<td>0.42*</td>
<td>0.40*</td>
<td>0.34</td>
<td>0.37*</td>
<td></td>
</tr>
<tr>
<td>CRQ</td>
<td>0.29</td>
<td>0.29</td>
<td>0.52*</td>
<td>0.57*</td>
<td>0.50*</td>
<td>0.34*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05

No significant differences between stages of severity or prognosis and scores on CAT, except for GOLD stages, were found.

Figure 1. Relationship between CAT and clinical-prognostic parameters.

Conclusions: 1. Correlation of CAT with other quality of life questionnaires is moderate. 2. SGRQ and CRQ appreciate better clinical and prognostic variables. While CAT is more easily applied in daily practice, does not discriminate between different situations or serious prognosis, except in extreme stages of GOLD.

P3451
Relationship between COPD assessment test (CAT) and declines of lung function in COPD patients
Hyun June Kwak, Ji-Yong Moon, Tae Hyung Kim, Sang-Heon Kim, Jung Won Sohn, Dong Ho Shin, Sung Soo Park, Ho Joo Yoon. Internal Medicine, Department of Respiriology, Hanyang University College of Medicine, Seoul, Korea

Background: COPD assessment test (CAT) is a recently developed questionnaires used for assessing and monitoring chronic obstructive pulmonary disease (COPD). However, the relationship with CAT score and the other clinical parameters of COPD are not well determined yet. In this study, we aimed to investigate if CAT score is associated with the measures of clinical courses such as annual decline of lung function and acute exacerbation of COPD.

Methods: We enrolled the patients with COPD, who were followed for more than two years. CAT and St. George Respiratory Questionnaire (SGRQ) were performed and information of clinical parameters of COPD was collected in a retrospective manner.

Results: A total of 77 patients with COPD were recruited. CAT score showed a fair correlation with SGRQ score (r=0.42, P<0.001) and FEV1 (r=0.231, P=0.02). Higher CAT score was significantly associated with more rapid decline of FEV1 over 2 years (P=0.02) and acute exacerbation of COPD (P≤0.002).

Conclusions: CAT score showed good relationship with various clinical parameters of COPD, including FEV1, acute exacerbation and deterioration of lung function. These findings suggest that CAT reflects various features of COPD and could be used more widely in assessing and monitoring of COPD.
P3452 Evaluation of the quality of life with COPD assessment test
Alexandra Corlante1, Viktoria Simi1, Victor Bottoni1, Donna Ranu2,3
1Internal Medicine, State Medical and Pharmaceutical University “Nicolaic Testemianu”, Chisinau, Republic of Moldova; 2Respiratory Medicine, Institute of Phthisiopneumology “Chiril Dragusin”, Chisinau, Republic of Moldova

Background: COPD Assessment Test (CAT) is a short, simple questionnaire for assessing and monitoring chronic obstructive pulmonary disease (COPD) patients.

Methods: 60 consecutive COPD patients were enrolled into the study. We analyzed age, gender, anthropometric, pack years, spirometric data (FEV1, FVC, FEV1/FVC, BODE index (BMI, FEV1, MRC, 6 MWD)). Health-related quality of life was assessed by the CAT and the St. George Respiratory Questionnaire (SGRQ).

Results: COPD patients were studied, mean age was 60.2±7.5 years, mean FEV1, % was 34.6±11.3%. Patients across all stages GOLD/ATS/ERS classification had similar age and pack/year (p>0.01). Pearson correlation coefficient analysis demonstrates in COPD patients a significant positive correlation between the CAT and the total score of the SGRQ (r=0.59, p<0.01). Also correlations between CAT and MRC score negatively with 6 MWD (r=-0.52, p<0.01). The forward stepwise regression analysis shows that the age, dyspnoea and oxygen saturation are important predictors of HRQL in COPD patients which explains 58% of the CAT score.

Conclusion: COPD Assessment Test is a useful instrument to assess disease impact in COPD patients and sensitive to changes in patients with COPD independent risk factors for worsening of HRQL.

P3453 COPD care and management at nurse-led COPD-clinics in Swedish primary health care: A literature review
Eva Overland Eriksson, Eva Abeg Lennman, Aninka Nyberg, Dalarna University, School of Health and Social Studies, Falun, Sweden

Aim: The aim was to describe evidence-based knowledge regarding care and management of patients at nurse-led COPD-clinics in Swedish primary health care.

Methods: A literature review included ten studies, three qualitative, six quantitative and one both qualitative and quantitative. The search was carried out in PubMed/MEDLINE and CINAHL between year 1999 and 2012 with the search-words: COPD, nurse-led clinics, patient education, primary healthcare, quality of life, self-management, smoking cessation and Sweden. Two reviewers rated independently and extracted data from the articles.

Results: At nurse-led COPD-clinics in Swedish primary health care, nurses ran structured investigations including measurements according to medical guidelines, and gave information about self-management and smoking cessation. The COPD-clinics allotted sufficient time according to the guidelines: when the nurse had been trained in COPD care, more patients were diagnosed with COPD and fewer exacerbations were noted among COPD-patients. The structured programs for smoking cessation and self-management were used, an increased number of patients stopped smoking and patients’ quality of life was improved. COPD nurses showed shortcomings in self-management and smoking cessation concerning individualized care, the involvement of patients in shared understanding and responsibility and motivational dialogue. The prevalence of CB was 64% (622/974). Between groups (CB vs no CB), no significant difference was observed for age, sex, smoking habit and baseline FEV1. Patients with CB had higher HFEV1% predicted, 38.0±3.6 (p<0.001) and more prevalent current smoking, 42.4% vs. 31.2% (p<0.0001). Baseline SGRQ total and symptom scores were similar between CB and emphysema patients, 49.5 vs. 48.7 (p=0.46) and 56.1 vs. 53.7 (p=0.06) respectively, but SGRQ activity and impacts scores were higher in CB subjects, 64.2 vs. 67.2 (p=0.01) and 39.0 vs. 36.2 (p=0.02) respectively. In adjusted analyses, CB was not associated with more frequent exacerbations, 1.12, p=0.26. Cough and sputum scores are outlined in Table 1.

Table 1. Cough and Sputum Scores

<table>
<thead>
<tr>
<th>Cough</th>
<th>Sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cough score</td>
<td>1.20</td>
</tr>
<tr>
<td>Cough score ≥ 2</td>
<td>193 (22.8%)</td>
</tr>
<tr>
<td>Sputum score ≥ 2</td>
<td>160 (18.9%)</td>
</tr>
</tbody>
</table>

Conclusion: Physicians distinguished between subjects with CB who despite better FEV1, had worse SGRQ activity and impacts scores than emphysema subjects. However, subjects with physician identified CB actually differed on baseline cough but not sputum scores.

P3455 Predictors of mortality in a well-characterised group of patients with COPD
Saher B. Shaker1, Udo-Michael Goehring2,3, Fernando Martinez1
1Medical, Nycomed Belgium, Brussels, Brabant, Belgium; 2Pneumology, Centre Hospitalier Universitaire du Saart-Tilman, Liège, Belgium; 3Medical, Nycomed France, Antony, France

Objective: To identify clinical, physiological and radiological predictors of mortality in a well-characterised group of patients with COPD.

Method & material: Patients who participated in 3 clinical trials were included in this study. In these trials, patients were evaluated with clinical data, lung function tests and quantitative computed tomography (relatve area of emphysema < 910 HU [RA-910]). The date and cause of mortality were reported during 10 years, and the data of those who were still living by February 1st 2012 were censored at this time point. Data were analysed using Cox proportional hazard regression model first in a univariate model then in a stepwise multiple regression model.

Results: Data from 208 patients with moderate to severe COPD were available. A total of 104 patients died. The median survival time was 10.4 years (95% CI 9.4–∞). Age, packy years, FEV1, DLCO and RA-910 were significant predictors of mortality in a univariate model. In a multivariate model with a stepwise selection, age (p=0.005), packy years (p=0.02) and RA-910 (p=0.017) emerged as the significant predictors of mortality, whereas FEV1 (p=0.05) and DLCO (p=0.14) did not reach statistical significance.

Conclusion: In this population of smokers with moderate to severe COPD, age, packy years and the degree of emphysema on CT as RA-910 were the most important predictors of mortality.

P3456 Epidemiology of the “chronic bronchitis” phenotype of COPD-patients in Belgium and Luxembourg
Jean Louis Corhay1, Walter Vincker2, Marc Schlesser3, Pascale Bossuy3
1Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA; 2Internal Medicine, State Medical and Pharmaceutical University “Nicolae Testemianu”, Chisinau, Republic of Moldova; 3Respiratory Medicine, Institute of Phthisiopneumology “Chiril Dragusin”, Chisinau, Republic of Moldova

Background: Chronic bronchitis is a phenotype that has been associated with increased mortality, frequent exacerbations and disease progression. Aims and objectives: To investigate the prevalence of CB in a large cohort of COPD patients and identify features associated with CB.

Methods: Cross-sectional analysis of a multicenter cohort of COPD patients from Belgium and Luxembourg. The cohort comprised 974 patients (67.8±9.6 years; 72% males, FEV1 52.5±15.8% predicted). Results: The prevalence of CB was 64% (622/974). Between groups (CB vs no CB), no significant difference was observed for age, sex, smoking habit and prevalence of most comorbidities. However prevalence of cachexia and skeletal muscle wasting were higher in CB. The number of pack years was higher, and both FEV1% predicted and body mass index were lower in CB. The proportion of patients with CB increased with GOLD stage and was higher in emphysema phenotype and patients exposed to occupational risk factors. Patients with CB had increased numbers of mild (0.7±0.9 vs 0.3±0.9; p=0.002), moderate (1.1±1.4 vs 0.5±0.9; p<0.0001) and severe (0.3±0.8 vs 0.2±0.6; p=0.0185) exacerbations per patient per year. Frequent (moderate to severe) exacerbations (two or more per patient per year) occurred more frequently in patients with CB (62.7% vs 14.2% of patients; p<0.0001).

Conclusions: Prevalence of CB is high in COPD and increases with disease severity. CB is associated with occupational risk factors, occurrence of mild, moderate and severe exacerbations, frequent moderate or severe COPD exacerbations, and systemic co-morbidities such as cachexia and skeletal muscle wasting.

TUESDAY, SEPTEMBER 4TH 2012
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**P3457**

An old disease from a new perspective – GOLD 2011 recommendations for COPD

Rena T. Rubinsztajn, Tailuex Przybylowski, Marta Maskey-Wareczowska, Krszysztof Karwat, Ryszarda Chazan. Department of Medicine, Pneumonology and Allergology, Warsaw Medical University, Warsaw, Poland

The GOLD 2011 recommendations for chronic obstructive pulmonary disease (COPD) introduce a new classification system to optimize treatment in individual patients. Except for FEV1, this classification incorporates dyspnea severity or the CAT score and the number of exacerbations.

The aim of our study was to compare the GOLD 2010 and 2011 COPD classification.

The study group consisted of 128 patients. Based on the post-bronchodilator FEV1 only, as recommended in the GOLD 2010 report, there were 21 patients in stage I, 53 patients in stage II, 35 in stage III and 19 in IV, respectively. In all patients, the number of exacerbations per year was noted and dyspnea was assessed with the modified MRC scale. The patients were subsequently graded to group A,B,C, D as proposed in the combined COPD assessment in GOLD 2011.

<table>
<thead>
<tr>
<th>Patients characteristic</th>
<th>n</th>
<th>nMRC 0–1/2</th>
<th>Number of exacerbation 0–1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD I</td>
<td>21</td>
<td>12/9</td>
<td>19/2</td>
</tr>
<tr>
<td>GOLD II</td>
<td>53</td>
<td>21/11</td>
<td>40/13</td>
</tr>
<tr>
<td>GOLD III</td>
<td>35</td>
<td>8/27</td>
<td>14/21</td>
</tr>
<tr>
<td>GOLD IV</td>
<td>19</td>
<td>0/19</td>
<td>9/10</td>
</tr>
</tbody>
</table>

We had problems with grading of 37 (28.9%) patients according to the GOLD 2011 criteria; there were 14 patients in GOLD stage I/II with ≥ 2 exacerbations per year and 23 patients in GOLD stage III/IV with < 2 exacerbations per year.

**Patients classification with the GOLD 2011 staging system**

<table>
<thead>
<tr>
<th>GOLD 2011</th>
<th>n</th>
<th>GOLD 2010 (%): I / II / III / IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>28</td>
<td>39.2 / 60.8 / 0 / 0</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
<td>31.4 / 69.0 / 0 / 0</td>
</tr>
<tr>
<td>C</td>
<td>14</td>
<td>7.2 / 33.5 / 57.3 / 0</td>
</tr>
<tr>
<td>D</td>
<td>57</td>
<td>1.8 / 17.5 / 47.4 / 33.3</td>
</tr>
</tbody>
</table>

We conclude that despite the fact that the new GOLD 2011 combined assessment is aimed at optimizing therapy, in clinical practice, there may be problems with patient classification. This especially concerns patients with mild/moderate airflow limitation and frequent exacerbations and those with severe airway obstruction without frequent exacerbations.

**P3458**

Quantification of elastin fibre remodelling in COPD using probe-based confocal laser endomicroscopy (pCLE)

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COPD causes disruption of alveolar elastin and probable disruption of the elastin in the airway wall. pCLE can be used during bronchoscopy to image the elastin structure. A method for the automatic assessment of the directional distribution of the elastin fibres is presented. The structural disorder caused by the remodelling process can then be objectively quantified. Figure 1 shows examples of the analysis output, with detected elastin fibres in green, showing greater disorder in the case of mild COPD.

Figure 1

Table 1

<table>
<thead>
<tr>
<th>Healthy (standard deviation of angle)</th>
<th>Mild COPD (standard deviation of angle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.7912</td>
<td>48.6401</td>
</tr>
<tr>
<td>36.7107</td>
<td>49.8444</td>
</tr>
<tr>
<td>42.7017</td>
<td>55.0636</td>
</tr>
<tr>
<td>44.9255</td>
<td>50.3647</td>
</tr>
</tbody>
</table>

**P3459**

Effect of fluticasone propionate/salmeterol on exercise endurance in moderate-severe COPD

Wenlan Yang, Jinning Liu, Beilan Gao, Kebin Chong. 1Department of Pulmonary Function Test, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; 2Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Objective: To investigate the effect of Fluticasone Propionate/Salmeterol on exercise endurance and pulmonary function in patients with moderate-severe COPD.

Methods: 53 patients with moderate-severe COPD were randomly divided to two groups. Treatment group inhaled dry powder SFC(salmeterol 50ug, fluticasone Propionate 250ugs) twice daily for 24 weeks. Control group got symptomatic treatment for 24 weeks. Predose and postdose pulmonary and cycle cardiopulmonary exercise test evaluations were compared.

Results: There were no difference in predose pulmonary and CPET between two groups. In treatment group, With SFC treatment for 24 weeks, FVC, FEV1, IC were significant increased, ITGV, RV and TLV were significant increased(p<0.05); Peak WR increased, but had no statistically difference. Peak VO2, peak VO2/kg, peak VCO2, peak O2 pulse, peak VE were significant increased(p<0.05); VD/VT and lowest VE/VCO2 were decreased from (p<0.05); postdose improvement in IC was significantly correlated with the increase in Peak VO2. Peak VO2/kg, Peak VE, VD/VT and Lowest VE/VCO2 but not with FEV1. Predose and postdose pulmonary and CPET were no changes in control group.

Conclusion: Exercise tolerance in patients with moderate-severe COPD were distinguished impaired. After long term SFC treatment, lung hyperinflation at rest and exercise were decreased, exercise endurance were increased when compared with symptomatic treatment. CPET is useful in COPD patients as it allows objective measurement of the exercise tolerance and evaluation of the response to therapeutic intervention.

**P3460**

Roflumilast significantly decreased inflammatory biomarkers in induced sputum in current smokers patients with severe chronic obstructive pulmonary disease

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The aim our study was identify the impact of ROFLUMILAST to inflammatory biomarkers in induced sputum in current smokers patients with severe COPD.

All patients were divided in two groups: 124 patients have received BUDES-ONIDE/FORMOTEROL 640/18 mcg/day and ROFLUMILAST 500 mcg/day; 224 patients have received only BUD/FORM. 640/18 mcg/day. All patients were current smokers and observed during 6 months. In patients with severe COPD whom applied ROFLUMILAST together with BUD/FORM, the level of inflammatory biomarkers in induced sputum significantly decreased after 6 months therapy.
patients group with ROFLUMILAST therapy the number of neutrophils decreased importantly(39.1 + 9.8 vs 20.4+6.7%, p<0.001).This decreasing at the same time was accompanied with reducing the level of pro-inflammatory cytokins in induced sputum. IL-6 was decreased up to 15.7+4.2 pg/ml vs 29.6 + 6.9 pg/ml before treatment, p<0.001).The anti-inflammatory influence of ROFLUMILAST was accompanied with improving of lung function(_FEV1 increased up to 48.7+6.4 % vs 39.1% before treatment, p<0.05).Our study showed that, the added ROFLUMILAST to the therapy with BUD/FORM. significantly decreased the level of inflammatory biomarkers in current smokers with severe COPD.Summarized the followings we can conclude that,ROFLUMILAST as additional drug to the therapy with BUD/FORM. through reducing the severity of chronic inflammation may improve the lung function of the current smokers patients with severe COPD.

P3463 Long term oxygen therapy (LTOT) prescription in chronic obstructive pulmonary disease (COPD) patients in Wigan (northwest England) Sharada Gunar, Ayun Zubair, Andrew Cross, Imam Arze, Abdul Ashish. Department of Respiratory Medicine, Royal Albert Edward Infirmary, Wigan, United Kingdom

Background: LTOT has been shown to provide a survival benefit in severe COPD. In UK, since 2006, following a Royal college directive LTOT prescriptions were to be issued only by hospital specialists managing such patients after formal assessments (BTS working group report, January 2006). The directive aimed to standardise LTOT assessments, issue and follow up to hospital based practitioners and specialist services.

We audited the oxygen prescriptions for adult patients in Wigan between 2006-2011 to study concordance of Royal college directives with our oxygen prescriptions.

Methods: We analysed the oxygen prescription data provided by our suppliers (our products) for the patient details and prescriber source.

Results: There were 313 patients in whom oxygen was prescribed for COPD as the indication. The breakdown of prescriber source is as below:

<table>
<thead>
<tr>
<th>Health professionals prescribing LTOT in Wigan between 2006-11</th>
<th>N=313 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital COPD nurses</td>
<td>192 (62)</td>
</tr>
<tr>
<td>General Practitioners</td>
<td>71 (22.6)</td>
</tr>
<tr>
<td>Hospital doctors</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Other hospitals</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>Community respiratory nurses</td>
<td>8 (2.5)</td>
</tr>
</tbody>
</table>

Conclusions: There are still a substantial proportion of oxygen prescriptions issued at a community level by the general practitioners and community based nurses for patients with COPD. We are unsure regarding the assessments undertaken for the adequacy of such prescriptions. This could potentially lead to harm and is likely to lead to increased cost for the healthcare services. At the current times of austerity and duplication of services should be avoided to ensure the patients and NHS gets the maximal benefit from LTOT provision.

P3464 The occurrence of pneumonia in COPD patients treated with salmeterol / formoterol ADRS were reported in 181 patients. Most frequently reported ADRs were clinical bacterial pneumonia 4.9%, dysphonia 3.2%, bronchitis 1.2% and pneumonia (other) 0.8%. In 1,358 patients who were treated with SFC250 for any duration, diagnosis of pneumonia was reported as an adverse event in 8.4% of patients in the prior year, and 8.4% after starting SFC250. For the 922 patients were treated with SFC250 for 1 year, the diagnosis of pneumonia was made in 8.7% and 7.3% of patients in the year prior to and after starting SFC250, respectively. Pneumonia was more frequent in patients who had a hospitalization, lower BMI, longer duration of COPD, ex-smoker, severe COPD and patients with complication. The trend was the same in the year prior to and post SFC250.

Conclusions: In clinical practice setting, the frequency of pneumonia was comparable before and after starting SFC250.

P3465 Influence of tiotropium bromide and formoterol on bronchial hyperresponsiveness in COPD


Up to 60% of COPD patients can present bronchial hyperresponsiveness (BHR) which may be a pathophysiological feature of COPD rather than a surrogate marker of airway obstruction.

Aim: To evaluate an effect of single dose tiotropium bromide (TB) and formoterol on BHR in COPD patients.

Methods: 30 COPD II outpatients with BHR of mean age of 59 yrs were studied. The BHR level was analyzed initially and post-dose in 60 minutes after 18 mg TB (1-st group, n=11) and 12 mg formoterol (2-d group, n=19). BHR was assessed in methacholine challenge.

Results: A high level of BHR (provocative dose - PD_{20}=<0.04 mg) was at 40% of
COPD patients, medium (PD20 0.04-0.22 mg) at 43% and low (PD20 0.23 -0.47 mg) at 17% of the surveyed initially. Pre-bronchodilator PD20 in average were comparable in both groups: 0.10 mg for the 1-st and 0.12 mg for the 2-nd group (p=0.67). BHR levels after bronchodilators were significantly less in both groups. Thus, PD20 mean values increased in 2.4 times after formoterol (p<0.0007) and in 3.6 times after TB (p=0.0005). The number of negative tests (PD20 ≥ 0.47 mg, BHR < 15%) in the 1-st group was more than in the 2-nd: 54.5% of patients after TB and 21.1% after formoterol (p=0.06).

Conclusion: Long-acting bronchodilators – TB and formoterol after single administrations reduce BHR level in COPD patients. TB promotes more bronchoprotective effect than formoterol in COPD.

P3466
Influence of tiotropium bromide (TB) and carbocysteine (C) on mucociliary clearance (MCC) in patients with COPD
Tetyana Pertsueva, Oleyna Lykholyt, Oleyna Gurzhz, Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine

Aim: To compare the influence of TB alone and in combination with C on MCC. M&C: 27 smoking pts with severe COPD in stable condition were divided in 2 grs: gr.1=14, gr.2=13. All pts received TB 18 µg/d for 1 month. Gr.2 also received C 45 ml/d. Spirometry; biochemical parameters of sputum (medium weight molecules (MWM), trypsin, α1-proteinase inhibitor (α1-PI)) were researched for MCC evaluation.

Results: Dynamic of indices for gr. 1 in table 1, for gr. 2 in table 2.

Table 1
<p>|</p>
<table>
<thead>
<tr>
<th>Indices</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>% of changes</th>
<th>p-Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % of pred</td>
<td>38.6±1,15</td>
<td>46,5±2,23</td>
<td>20,3</td>
<td>0,002</td>
</tr>
<tr>
<td>MWM, mg/l</td>
<td>1351±534,52</td>
<td>1036,0±33,7</td>
<td>23,3</td>
<td>0,01</td>
</tr>
<tr>
<td>α1-PI, mcmol/sec L/g</td>
<td>5,1±0,3</td>
<td>6,4±0,4</td>
<td>25,7</td>
<td>0,02</td>
</tr>
</tbody>
</table>

Table 2
<p>|</p>
<table>
<thead>
<tr>
<th>Indices</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>% of changes</th>
<th>p-Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % of pred</td>
<td>37,2±1,14</td>
<td>46,4±1,6</td>
<td>24,7</td>
<td>0,003</td>
</tr>
<tr>
<td>MWM, mg/l</td>
<td>142±87,02</td>
<td>1197,9±48,1</td>
<td>19,2</td>
<td>0,008</td>
</tr>
<tr>
<td>α1-PI, mcmol/sec L/g</td>
<td>4,1±0,2</td>
<td>5,3±0,3</td>
<td>29,4</td>
<td>0,01</td>
</tr>
</tbody>
</table>

Conclusions: 1. TB demonstrated positive influence on MCC: broncholytic effect reduces damage influence of bronchial contents’ accumulation on cilia; activation of local trypsinolytic activity of sputum reduces of sputum viscosity; selective influence on M3-cholinoreceptors leads to bronchial secretion’s limitation and to anti-inflammatory effect, as a result – to decrease of MWM level, which leads to decrease of sputum viscosity. 2. Benefit of C addition to TB appeared only in greater increase of trypsinolytic activity of sputum reduces of sputum viscosity; selective anti-inflammatory effect, as a result – to decrease of MWM level, which leads to decrease of damage influence of bronchial contents’ accumulation on cilia; activation of local trypsinolytic activity of sputum reduces of sputum viscosity; selective influence on M3-cholinoreceptors leads to bronchial secretion’s limitation and to anti-inflammatory effect, as a result – to decrease of MWM level, which leads to decrease of sputum viscosity.

P3467
Microbiological screening infectious exacerbation of chronic obstructive pulmonary disease

Biological materials (sputum, swabs or swabs from the nose), obtained from 162 patients with AE of COPD. Microbiological examination of the material was carried out in accordance with the rules of GLP. Laboratory diagnosis of viral infection carried by rapid diagnosis (by enzyme immunoassay (ELISA), fluorescent antibody (IFA) and immunochromatographic assay.

The majority (84.1±3.3%) of patients with AE of COPD was caused by bacterial, and (31.8±1.4%) - viral pathogens, of which (9,8±4.1%) cases - only the bacterial pathogens in the (15.3±3.3%) - only viruses and (14.3±3.1%) - a combination. The greatest significance of bacterial pathogens were H. influenzae in 49.1% of cases, S. pneumoniae - in 22.6%, K. pneumoniae - in 9.4%. M catarrhalis - in 13.2%, E. coli - in 6.6%, S. aureus - 7.6%. Among the viral agents most frequently detected adenoviruses - in 31.6% of cases, influenza A and B - in 34.2%, para influenza - 26.3% and RS virus - at 7.9%

In patients with AE of COPD viral pathogens found: the influenza viruses A and B - Feb 7 (17,5±6,1%), Apr 5 (12,5±3,3%); Apr 37,5±4,2%; parainfluenza - May 3 (7,5±4,2%), Oct 7 (17,5±6,1%); adenoviruses - Feb 6 (15, 0±5,7%), Apr 1 (2,5±2,5%), Oct 5 (12,5±5,3%); RS virus - May 3 (7,5±4,2) %, which generally coincided with the seasonality of the disease to viral respiratory infections, caused by these pathogens.

The frequency of detection of viral pathogens of AE COPD also depended on the duration of the examination of patients from early relapse. In the first three days of exacerbation frequency detection of viral pathogens was (77,5±6,0%) ± 7.01; 4 - 7 day aggravation - (22,5±6,6)%; 8 days later and none of the patients viral pathogen was not detected.
Effects of endurance training on pulmonary and systemic levels of interleukin-8 in patients with stable COPD

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Background: Patients with Chronic Obstructive Pulmonary Disease (COPD) may show increased levels of interleukin (IL)-8 (CXCL8). Respiratory physiotherapy may reduce IL-8 induced sputum, but no information is available about the potential effects of endurance training on systemic or pulmonary levels of IL-8.  

Objective: To investigate the effects of endurance training on pulmonary and systemic levels of IL-8 in patients with stable COPD.  

Methods: Levels of IL-8 were quantified in plasma and induced sputum (ELISA) in a group of patients with moderate to severe stable COPD (study group [S]: n=64; 61±4 [mean±SD] years, FEV1: 49.5±14.2% pred. post-bd.) before and after an 8 weeks controlled endurance training program, and in a control group (C): n=5, 61±4 years, FEV1: 45.4±6.6% pred. post-bd., who did not perform such a program.  

Results: After 8 weeks, levels of IL-8 in plasma (from 4.2±4.3 to 3.9±4.4 pg/mL; C: from 4.4±4.2 to 6.5±6.2 pg/mL) and sputum (from 2217.1±1555.5 to 4153.2±3024.5 pg/mL; C: from 3012.8±1593.03 to 2599.9±1200.12 pg/mL) remained unchanged in either group, despite that S showed, respectively, an increase of peak oxygen consumption (from 1.1±0.3 to 1.2±0.3 L/min, p=0.04) and a decrease of lactate acid levels at peak exercise (from 5.5±1.0 to 4.2±0.7 mmol/L, p<0.05).  

Conclusions: In patients with stable COPD, a controlled endurance training program does not modify the pulmonary and/or systemic levels of IL-8. Hence, the beneficial effects of physical training cannot be attributed to the reduction of systemic pro-inflammatory cytokines.

Antielastin antibodies in chronic obstructive pulmonary disease

Belén Nuñez,1, 2 M. Rosa Julià,1 Jaume Sauleda,1, 2 Antonio Clemente,1 Judith García Aymérez,1, 3 Jose María Anto1, 2, 3 Álvar Aguait1, 3 PAC-COPD Study Group. 1Pneumologia, Hospital Son Espases, Palma de Mallorca, Spain, 2PAC, CIBER-Enfermedades Respiratorias, Banyoles, Illes Balears, Spain, 3Imunologia, Hospital Son Espases, Palma de Mallorca, Illes Balears, Spain.  

Aim: To optimize an anti-inflammatory therapy in COPD patients.  

Materials and methods: 24 pts in stable phase (age - 63±5.9 yrs), divided into two subgroups according to the stage of COPD. Measurements included clinical status, spirometry, serum levels of MMP-2 and MMP-9 by immune-fluorescent method (in conventional units).  

Results: Level of MMP-2 in all COPD pts was lower than in control (Table 1), besides it correlated with FEV1 (r=0.47, p<0.02). Level of MMP-9 in COPD pts in the whole was significantly higher than in control but regardless of FEV1 there were selected two phenotypes of COPD: 1st – with normal level of MMP-9, 2nd – with high one (Table 2).

Table 1

<table>
<thead>
<tr>
<th>Groups and subgroups</th>
<th>FEV1 (% pred.)</th>
<th>p-value</th>
<th>MMP-2</th>
<th>p-value</th>
<th>MMP-9</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=10)</td>
<td>1.76±1.19</td>
<td></td>
<td>101.3±6.4</td>
<td></td>
<td>254.4±9.4</td>
<td></td>
</tr>
<tr>
<td>COPD II-V (n=14)</td>
<td>1.4±1.67</td>
<td>&lt;0.05</td>
<td>45.1±3.6</td>
<td>&lt;0.05</td>
<td>127.8±4.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>COPD III (n=14)</td>
<td>1.4±1.67</td>
<td></td>
<td>45.1±3.6</td>
<td>&lt;0.05</td>
<td>127.8±4.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>COPD IV (n=6)</td>
<td>1.4±1.67</td>
<td></td>
<td>45.1±3.6</td>
<td>&lt;0.05</td>
<td>127.8±4.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Subgroups of COPD due to the level of MMP-9</th>
<th>FEV1 (% pred.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st – MMP-9 ≥ 140 (n=15)</td>
<td>56.3±7.1</td>
<td>0.01</td>
</tr>
<tr>
<td>2nd – MMP-9 &gt; 220 (n=9)</td>
<td>37.3±3.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusion: 1) low level of MMP-2 in all COPD pts reflects delay of tissues regeneration and intensification of inflammation because of degradation of monocytic chemotaxic protein-3 even starting with II; 2) high level of MMP-9
in some COPD pts reflects degradation of collagen, remodulation of tissues and intensification of inflammation; 3) MMP-9 may be used as a marker of COPD phenotypes and thus – to optimize an anti-inflammatory therapy.

P3475
Adenovirus IgG avidity – A marker of outcome in COPD-exacerbations
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Background: Adenovirus causes respiratory infections in healthy and chronically ill adult individuals. Virus replication, cell lysis and inflammation provoke pulmonary damage. Little is known about adenovirus infection, reinfection and reactivation in acute exacerbations of COPD (AECOPD).

Objectives: To evaluate effects of adenovirus infection during and after AECOPD.

Methods: 208 patients with severe AECOPD were tested for anti-adenovirus antibodies at exacerbation and after two weeks. Outcome parameters were measured for two years.

Results: Studied patients were predominantly male (54.8%), had an age of 70.9±8.9 years, a FEV1 of 41.2±17.2% predicted and smoked 45.2±27.9 pack years. At the time of exacerbation 39 patients (18.6%) had anti-adenovirus IgM and low-avidity IgG, indicating a present adenovirus infection. At exacerbation, patients with acute adenovirus infection were younger (p=0.031) and presented a lower hospitalization rate in the previous year (p=0.037). In contrast, they reported a poorer health-related quality of life at admission (p=0.003) and persistently impaired functional status 14 days after exacerbation (p=0.044). Patients with initial low-avidity adenovirus IgG who failed to convert to high-avidity adenovirus IgG within two weeks (n=13, 7%) had more recurrent AECOPDs within six months (1.23 vs. 0.63; p=0.032) and a shorter time to re-hospitalisation for AECOPD or death (p=0.018).

Conclusion: Adenovirus related severe AECOPD cases potentially have a more severe clinical course. In addition, patients who remain at low-avidity adenovirus IgG are at higher risk for subsequent AECOPDs and hospitalisation or death.

P3476
Impact of morning symptoms experienced by COPD patients on exacerbation risk, rescue inhaler usage and normal daily activities
Mark Small, Sarah Brownfield, Ryan Pollard, Steve Fermer. Respiratory, Adelphi Real World, Macclesfield, United Kingdom

Background: Patients consider the impact of COPD on morning activities to be substantial. Evidence of the association of morning symptoms and the impact on the entire day with poor breathing control contributes to the understanding of their importance for managing COPD patients.

Objectives: To quantify the impact of morning symptoms experienced by patients receiving inhaled corticosteroid plus long-acting f2agonist (ICS/LABA) by association with exacerbation frequency, rescue usage and impact on daily activities.

Methods: Data were drawn from a real world study of consulting COPD patients in the USA and Europe in 2011. Results were tested for significance (p<0.05) using Mann-Whitney and negative binomial regressions. Confounders included age, gender, BMI, comorbidities, severity, smoking status and adherence.

Results: Of the 3790 patients in the study, 593 were receiving ICS/LABA-only (+/- rescue). Of the 177 patients reported to experience morning symptoms, cough (65.5%) and excess sputum (53.1%) were the most common. Compared with patients without morning symptoms, these patients were associated with higher mean exacerbation frequency in the last 12 months (1.04 vs. 0.63; p<0.001), rescue usage per day (0.58 vs. 0.46 p=0.025) and daytime impact on a 7-point Likert scale where 7 represents a constant impact (3.61 vs 3.00 p=0.018).

Conclusion: Morning symptoms were associated with significantly more impaired breathing control for patients treated with ICS/LABA-only therapy. The association implies morning symptoms are an important indicator when assessing the impact of COPD and their presence suggests that further therapeutic intervention may be necessary.

P3477
Effect of melatonin on sleep quality of chronic obstructive pulmonary disease
Mark Small, Sarah Broomfield, Ryan Pollard, Steve Fermer. Respiratory, Adelphi Metro Centre for Respiratory Diseases, Macclesfield, United Kingdom

Introduction: Melatonin increases the sleep quality in certain COPD patients but its effectiveness is not yet clear.

Studies have shown that melatonin increases the sleep quality in certain COPD patients with poor sleep quality. The subjects received oral 3 mg melatonin (N = 27) or placebo (N = 27) in one dose 1 hours before sleep for a period of 30 days. The sleep quality was measured by Pittsburg Sleep Quality Index (PSQI) and daytime sleepiness was measured by Epworth Sleepiness Scale. Lung function and oxygenation was measured by spirometry and pulse oximeter.

Methods: Finally 48 patients completed the protocol and entered the final phase. Melatonin significantly resulted in improved global PSQI scores, especially sleep quality (P = 0.001), sleep latency (P = 0.001), sleep duration (P = 0.024) and sleep efficiency (P = 0.003). There was no significant difference in daytime sleepiness, lung function and oxygenation.

Table 1. sleep quality, daytime sleepiness before and after treatment with melatonin or placebo

<table>
<thead>
<tr>
<th>Melatonin (N=23)</th>
<th>Placebo (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>PSQI</td>
<td>11.6±3.96</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>2.6±0.95</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.2±0.95</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>2.30±1.06</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>0.91±0.85</td>
</tr>
<tr>
<td>PS</td>
<td>7.04±4.44</td>
</tr>
</tbody>
</table>

Conclusion: Melatonin results in improved sleep quality of moderate to severe COPD patients with sleep quality disorders.
Coagulation testing

<table>
<thead>
<tr>
<th>Coagulation testing</th>
<th>Significant bleeding</th>
<th>No bleeding</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% performed</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>93.8%</td>
<td>10.0 (10.5-11.3)</td>
<td>84.3%</td>
</tr>
<tr>
<td>aPTT</td>
<td>93.8%</td>
<td>26.2 (25.2-28.7)</td>
<td>84.3%</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>96.9%</td>
<td>324 (241-414)</td>
<td>94.6%</td>
</tr>
</tbody>
</table>

It was removed by rigid bronchoscopy. None of the cases had any risk factor for aspiration such as older age and altered mental status.

Unrecognized FB aspiration can result in obstructive pneumonitis, atelectasis, lung abscess, empyema, bronchectasis, hemoptysis, and pleural effusion. For that reason, patient with chronic cough, recurrent or unresolved lung infections even if no history of aspiration might be detected for FB aspiration.

P3480

Scar Grafting: An Infection Per 26 cases

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Inhalation of foreign bodies is rare in adults. Inhalation of scarpin is a phenomenon more frequent in the female population in Morocco. The aim of our study was to describe the characteristics of this particular foreign body and illustrate the circumstances and consequences of its inhalation. Twenty-six young patients all veiled, were hospitalized in the service of Respiratory Diseases University Hospital Ibn Rushd of Casablanca between January 2005 and July 2011 for inhaled scar pin. The mean age was 16 years. Inhalation was accidental in all cases, whereas patients initiated to wear the veil. The penetration syndrome was found in all cases. Clinical examination was normal in all patients. The chest X-ray showed the foreign body as a linear opacity, located right in 18 cases and left in eight cases. Flexible bronchoscopy was able to extract the pin in 21 cases. The pin was released spontaneously in three cases and two patients were operated on. The scar pin is a foreign body especially more common in women who wear the Islamic veil. Flexible bronchoscopy is an essential means of therapy, but the best preventive treatment is avoiding to put in the mouth sharp objects.

P3483

Chest drain fixation: How can we prevent drains from falling out? Lessons from an audit

Ali Al Ameri, Lucy Hcken, Steven Thomas. Respiratory, Calderdale Royal Hospital, Halifax, West Yorkshire, United Kingdom

Introduction and objectives: Chest drain displacement/falling out is the most common complication of small bore drains inserted by the Seldinger technique. This often necessitates repeat drain insertion, with resulting morbidity, delay in further procedures such as pleurodesis, and prolongs hospital stay. Varying techniques of securing chest drains have been described but limited data is available on which method is optimal. We compared two commonly used techniques which are currently in practice at our district general hospital: sutures, and sutureless dressing.

Materials and methods: A retrospective case note audit was performed of patients requiring chest drain insertion over a 12-month period in 2010. Seventy one small bore chest drains were evaluated according to the rate of displacement of those secured by sutures versus those with dressing alone. A prospective re-audit was then performed in 2011 over a period of 8 months, following recommendations to change practice to fixation with sutures. Fifty-four drains were evaluated, with sutures as the method of fixation in the majority.

Results: In the 2010 audit, the majority of drains were secured with dressing alone (47 v 24). Accidental displacement was observed in 37 of the total 71 drains (52%). Of those with dressing fixation only, 75% were displaced, compared to 4% of drains which were sutured in place. Twenty one patients required repeat drain insertion. During the 2011 re-audit, sutures were used in 48 out of 54 (89%). Only 6 drains were accidentally displaced (11%).

Conclusion: The results of this audit suggest that securing a chest drain with a suture, as compared to dressing alone, is more effective in preventing accidental displacement.

P3484

Surgical lung biopsy – Gold standard for diagnosis of idiopathic interstitial pulmonary fibrosis?

Olena Semendyayeva1, Nadiya Monogarova1, Vladimir Gavrysh2, Evgeniya Merenkova1, Sergey Leshenko1. 1Chair of Internal Medicine named after O.Y. Gavrysh, Donetsk National Medical University named after M. Gorky, Donetsk, 2Department of Interventional Lung Diseases, National Institute of Tuberculosis and Pulmonology named after F.G. Yanovskyy, Kiev, Ukraine

The current classification of idiopathic interstitial pulmonary fibrosis (IPF) is based on the account of the specificities of the clinical picture, radiological and pathological features. This raises the question of how much the necessity of verification of the diagnosis of IPF data pathologic study biopsy or autopsy lung material. To answer this question, we asked three highly-skilled pathologist with considerable experience in pulmonology, to conduct an independent analysis of the same histological lung tissue of patients with various forms of IPF. For the analysis of slides, presented 73 patients with IPF. Material for histological study was obtained during open and videotorakoskopich lung biopsy and at autopsy.According to clinical studies and results of computed tomography high-resolution was found clinical diagnosis of idiopathic fibrosing alveolitis (IFA) for the pathomorphological study,
non-specific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP) and respiratory bronchiolitis associated with interstitial lung disease (RB-ILD). Match the clinical diagnosis with the conclusions of three experts were only in 15 cases (20.5%), two experts in 33 (47.9%) and one - in 15 cases (20.5%). In most cases, differences in interpretation of histological data did not go beyond the group of IIP. Differentiated forms of IIP are very difficult. At the same time, identification of each form of IIP is not an end in itself, it is essential if accurate diagnosis determines the treatment tactics. In our opinion, surgical biopsy of the lungs is necessary in the differential diagnosis of IIP with other interstitial lung diseases.

P3485
Non-traumatic chylothorax – A retrospective analysis
Hang Siang Wong
1, Inês Neves 1, Fernando Coelho 1, Maria Teles 2, Anaabela Marinho 1
1 Pneumology, São João Hospital, Porto, Portugal; 2 Clinical Pathology, São João Hospital, Porto, Portugal

Introduction: Chylothorax (CL) is the presence of lymph in the pleural space. Diagnosis is based on lipoprotein profile of the pleural fluid (PF). The etiology is variable.

Aims: To characterize presentation and causes of non-traumatic CL.

Methods: Retrospective analysis of adults with CL (triglycerides ≥ 110 mg/dl) hospitalized in a central hospital between Jan/04 and Jun/11. A review, after computer supported search of hospital files of patients diagnosed with CL was made. Clinical, laboratory and image presentation, as well as treatment and outcome were analyzed.

Results: We identified 27 (43.5%) patients (pts) with non-traumatic CL; 19 (70.4%) were women. The median age was 62 years (33 – 96 years old). Dyspnea was present in 22 (81.5%), cough in 7 (25.9%) and chest pain in 6 (22.2%). Effusion was unilateral in 22 (81.5%), with milky appearance in 16 (59.3%); exudate in 7 (25.9%), chylous in 1 (3.7%). Mean ± sd of the triglycerides was 477 ± 443 mg/dL. Etiologies: Lymphoma in 14 (51.8%), metastatic cancer in 4 (14.3%), pulmonary tuberculosis in 2 (7.4%), liver cirrhosis in 2 (7.4%), lymphangioleiomyomatosis in 2 (7.4%), inconclusive in 3 (11.1%). Chest drain was needed in 11 (40.7%) pts, pleurodesis in 5 (11.1%). Infectious complications were seen in 13 (48.1%). Effusions solved in 16 (59.3%), persisted in 6 (22.2%), 5 pts were lost to follow up.

Conclusion: Our findings mirror those in the literature - CL may have no classic milky appearance, can be transudate, infectious complications are common and the most frequent cause was lymphoma.

P3486
Utility of closed pleural biopsy in a teaching hospital in Singapore
Hsiang Seng Wong, Respiratory Medicine, Changi General Hospital, Singapore, Singapore

Introduction: The yield of closed pleural biopsy is quoted in most studies to be around 90% for pleural TB and 70% for malignancy.

Objective: To determine the yield of closed pleural biopsy in our institution and the possible factors affecting the yield.

Methods: This was a retrospective study. All pleural biopsies done from 1/6/10 till 31/7/11 were included. Inclusion criteria were subjects with lymphocytic exudate pleural effusion who underwent closed pleural biopsy. All closed pleural biopsies were done under ultrasound guidance either by a respiratory trainee or an interventional radiologist.

Results: A total of 50 subjects underwent closed pleural biopsy. The positive yield of closed pleural biopsy in the cohort was 33/50 (66%). Out of the 33 positive yield, 17 (51.5%) were pleural TB, 6 (18.2%) were malignancy and 10 (30.3%) were other. The positive yield of pleural TB was 17/26 (65.4%), malignancy 6/13 (46.2%) and others 10/11 (90.9%). 32/50 (64%) pleural biopsies were done by respiratory trainees and 18/50 (36%) by interventional radiologists. The positive yield of pleural biopsies done by respiratory trainees was 18/32 (56.3%) and by interventional radiologists 15/18 (83.3%). No difference in the yield of closed pleural biopsy across the ages from 22 to 94 years old (p=0.85), male versus female (p=0.76), race (p=0.26), respiratory trainees versus interventional radiologist (p=0.067), TB versus malignancy (p=0.312).

Conclusion: The yield of closed pleural biopsy was lower compared to most studies in other centers. Age, gender, race, operator experience, TB versus malignancy did not show any significant difference in the yield.

P3487
Comparison of serum & pleural levels of NT-ProBNP in patients with acute dyspnea and pleural fluid referred to emergency department
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Background: Etiologic diagnosis of Pleural effusion is very important. Light criteria are sensitive for identifying exudates, but they misclassify 15% to 25% of transudates as exudates. N-terminal B-type natriuretic peptide is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload. This study compares serum and pleural levels of NT-ProBNP in patients with acute dyspnea and pleural fluid for diagnosis of heart failure.

Methods & materials: In an analytic-descriptive cross-sectional study, 43 patients with acute dyspnea and pleural fluid in two groups (15 patients with CHF and 28 patients with other pathology) were analyzed. NT-ProBNP measurement were performed by electrochemiluminescence immunosay method on admission. According to other biochemical analysis (albumin, total protein, cholesterol, triglyceride, amylase, LDH) were performed and gradient and ratio of this markers were accounted.

Results: The Mean±SD serum NT-proBNP levels in CHF and nonCHF patients were 15423±3351 pg/ml and 4751±1616 pg/ml, respectively, and plural NT-ProBNP levels in CHF and nonCHF patients were 14823±3249 pg/ml and 3569±1231 pg/ml, respectively.

Conclusion: NT-proBNP is a sensitive marker for the diagnosis of pleural effusions from heart failure.

P3488
Conservative pneumothorax management: How big is too big?
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Guidelines on primary spontaneous pneumothorax (PSP) management differ but commonly recommend intervention especially for larger PSPs. Evidence for recommending intervention over conservative management, even for large PSPs, appears scarce. We believe intervention is rarely required, that complications can and do ensue, and that conservative management of PSP has good outcomes without the risks associated with guideline-mandated intervention. Conservative management of large PSPs is outside current guidelines, despite a long international and local history of large PSPs being successfully managed in this way. We report to examine the evidence base for compelling reasons to change our current conservative practice. We are conducting a Cochrane Review of management of PSP; this is ongoing. We have performed a retrospective review of PSP patients admitted to our hospital and mostly managed conservatively, with good outcomes, no complications, and no increase in hospitalisation or readmission.

P3499
The influence of the patients’ participation in trials on the adherence to treatment in future
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The aim of the study was to estimate the influence of participation in trials on the adherence of the patients to the treatment of chronic obstructive pulmonary disease (COPD) and concomitant arterial hypertension (AH) after the trial finishing. 43 patients (average age 51.5±6.5 years) with severe and very severe COPD and concomitant moderate AH were enrolled. On the each visit patients received information about the necessity of the regular taking of the basis therapy of the main and concomitant disease. The duration of the trial visits were 160±32 minutes instead of 21±5 minutes in case of routine ambulatory visits. Patients filled diaries concerning their knowledge about COPD and AH, taking of the basis therapy of both diseases. The statistical program SPSS 16.0 used for working with the data of study. It was revealed that before the trial only 22 (51%) of the patients had basis therapy due to COPD and only 18 (42%) of them took antihypertensive therapy regularly. In the 6 months after the trial completing these data were 38 (88%) and 37 (86%) respectively. Patients answered that their knowledge about COPD and AH grows at 75±9%. The patients had 1,1±0.2 COPD exacerbations during the 6 months before the trial and during the next 6 months after the trial completing they had 0.7±0.1 COPD exacerbations (p=0.041). Perhaps, the improvement of the patients’ adherence to the treatment of COPD and AH connected with better cooperation between the patient and investigator than it was in routine clinical practice.

Conclusion: The participation in trial due to COPD improves the adherence of the patients to the treatment of COPD an AH connected with better cooperation between the patient and investigator but it is not effective in many cases, regardless of size. We continue to study PSP cases prospectively.
Patients with dyspnea is necessary for evaluating progression of the disease and MRC dyspnea scale and 6mw test. Since the assessment of level of function of P3491 Findings of our study showed that there are good correlation between subjects P3492 lung cancer, necrotizing pneumonia carried higher mortality. Active tuberculosis Surgery (n=48) 10 20.8 Levels of management vs mortality in hemoptysis Fariba Ghorbani, Shadi Shafaghi Shadi Shafaghi, Katayoun Najafizadeh. Lung transplantaion Research Center, National Research Institute of TB and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran Background: Since the description of dyspnea varies from patients to patient and also varies in various cultures, the aim of this study was evaluation of Persian version of MRC dyspnea scale and comparison of it with results of an objective test, 6 minute walking test (6mw).

Methods: In this cross-sectional study, 150 consecutive patients with chief complaint of dyspnea who referred to the physiotherapy department of Dr Masih Daneshvari hospital, Tehran, Iran for performing 6mw were selected. The severity of dyspnea was assested by MRC dyspnea scale. Results: 51% were male and the mean age of patients was 47 yr. 87.5% (n=287) had pulmonary diseases, 39 (26%) had cardiac diseases and 24 (16%) had dyspnea with unknown origin. The mean of disease duration was 8 yr and 23 (15%) used oxygen at home. Overall, 14% of patients were in level 1 MRC, 41% in level 2, 20% in level 3, 21% in level 4 and 4% in level 5. The mean (SD) of distance, decrease in oxygen saturation and increase in Borg dyspnea scale were 474±117 m, 8±8% and 2.2±, respectively. Levels of MRC dyspnea scale were negatively correlated with distance (r=0.500, P<0.001) and positively correlate with decrease in oxygen saturation (r=0.209, P<0.010) and increase in Borg dyspnea (r=0.387, P<0.001).

Conclusion: Findings of our study showed that there is good correlation between MRC dyspnea scale and 6mw test. Since the assessment of level of function of patients with dyspnea is necessary for evaluating progression of the disease and 6mw test needs skilled personnel and appropriate place, MRC dyspnea scale could be a good alternative.

P3491 Hemoptysis: Causes, interventions and outcomes – Indian single centre experience Deepak Talwar, Jitshu Chudraw, R.C. Jain, Sandeepan Kumar. Pulmonary and Critical Care Medicine, Metro Center for Respiratory Diseases, Noida, UP, India Introduction: Hemoptysis, requires multidisciplinary management & is lacking in tuberculosis hospitals. We evaluated profile of patients admitted with hemoptysis in tertiary respiratory care center. Methods: Retrospective analysis of 377 patients admitted with hemoptysis in Metro Centre for Respiratory Diseases between 2006-2011 done and results analyzed. All patients had active medical management and those suitable for surgery underwent elective or otherwise bronchial artery embolization (BAE) or bronchoscopic interventions (BI done).

Results: Mean age of patients was 49.5±16.52 years with 76.59% (n=287) being male. Mortality in male patients was significantly (59.6%Vs 40.4%; p<0.001). MN risk was also associated with a significantly longer length of stay (OR 1.054, p<0.001). A tumorous disease markedly increased MN risk (OR 2.33, p<0.001), while it was highly reduced in sleep-related breathing disorders (OR 0.04, p<0.001). MN risk was also associated with a significantly longer length of stay (10.2±6.9 5 vs. 5.4±6.0 days).

Conclusion: The application of a validated screening tool significantly contributes to detected patients at risk for malnutrition. Especially patients older than 65 as well as those with specific diseases need increased attention regarding MN risk. An early intervention could help to reduce length of stay.

P3494 Non-CF bronchiectasis: Correlation between body mass composition, lung function, inflammatory syndrome, gender and quality of life Adina Turcanu, Iulian Mihai, Roxana Aricescu, Traian Mihaescu, Pneumology, Clinic of Pulmonary Diseases, Iasi, Romania Background: The impact of bronchiectasis on health care’s costs and quality of life is important due to prolonged and repeated periods of hospitalization. Aim: Assess the situation of hospitalized patients diagnosed with non-CF bronchiectasis by studying the relationship between body mass composition, lung function and gender.to study how these parameters correlate with the inflammatory profile associated with acute recurrent respiratory infections.

Methods: 30 consecutive patients (15 male, 15 women) enrolled in 2011, evaluated through HRCT, bioimpedance, spirometry, inflammatory profile and Saint George Questionnaire.

Results: We observed that 70% of the patients (12 male and 9 women) had high percent of fat, the percentage of water was low at 60% of the patients (5 males, 6 females; also, the lean percentage was low at 28 patients (equal for both sex). Regarding the pulmonary function and the inflammatory syndrome we observed that 90% (27 patients) had abnormal values for CRP and ESR, and all patients had obstructive dysfunction syndrome (FEV1 between 34-45% from predicted values). 80% of the answers from Saint George Questionnaire indicated that the quality of life was medium to poor. We correlate this to low percent of lean and water, the presence of inflammatory syndrome and obstructive respiratory syndrome.

Conclusions: Body mass composition in patients with non-CF bronchiectasis is correlated with gender. Patients probably due to chronic lung disease and recurrent infections associated with the inflammatory syndrome. Obstructive lung condition
syndrome is present at almost all the patients and with the rest of parameters can be correlated with the decrease of the quality of life.

**P3495**

**Effects of inhaled saline and oxygen on noninvasive markers of airway and lung function**

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**Introduction:** Inhalation challenges have been shown to induce pulmonary effects, e.g. an increase in 8-isoprostanate levels in exhaled breath condensate (EBC) by hyperoxic air. The current study examined the sensitivity of noninvasive measures such as bronchial (FeNO) and alveolar (NOalv) nitric oxide, diffusing capacity for nitric oxide (DLNO) and carbon monoxide (DLCO), and hydrogen peroxide (H2O2) in EBC to detect alterations induced by oxidative or osmotic inhalative stress.

**Methods:** 20 healthy nonsmoking subjects aged 19-50y inhaled nebulised 3% hypertonic saline solution (HSS) over 20 min and 100% O2 at a flow of 50ml/min over 30 min on two days. Before and after inhalation spirometry, multifold exhaled NO, DLCO and DLNO were measured and EBC was collected and analysed for H2O2 using an optimised procedure with inhalation filter.

**Results:** HSS inhalation induced a median decrease in FEV1 of 3% (P<0.001) and in DLNO of 1.5% (P=0.05); no changes occurred for DLCO, alveolar volume, FeNO and H2O2. Results for NOalv were ambiguous in both inhalation groups. Hyperoxic air did not cause significant changes in any other parameter.

**Conclusion:** These results suggest that HSS inhalation not only causes slight airway obstruction but also induces alterations of fluid balance in the lung periphery that can be detected via DLNO but not DLCO. DLNO could thus be of clinical value in the diagnosis of mild pulmonary edema, e.g. related to cardiac dysfunction.

**Supported by** German Statutory accident insurance (DGUV), Berlin.

**P3496**

**Cytokine response in the lungs, pleural fluid and serum in children after thoracic surgery using one-lung ventilation**

**Davide Donnare, Oleksandr Katlov, Oleksandr Mazulov, Kateryna Dmytriieva. Anaesthesiology and Intensive Care, Vinntsa National Medical University, Vinnitsa, Ukraine**

Thoracic surgery mandates usually a one-lung ventilation (OLV) strategy with the collapse of the operated lung and ventilation of the non-operated lung. These procedures trigger a substantial inflammatory response. The aim of this study was to analyze the cytokine reaction in both lungs, pleural space and blood in patients undergoing lung resection with OLV.

**Methods:** Broncho-alveolar lavage (BAL) fluid of both the collapsed, operated and the ventilated, non-operated lung, respectively, pleural space drainage fluid and blood was collected and the concentrations of interleukin (IL)-6, IL-1RA were determined with enzyme-linked immunosorbent assays in 24 patients.

**Results:** Substantial inter-individual differences in the BAL fluid between patients in cytokine levels occurred. In the pleural fluid and blood these inter-individual differences were less pronounced. Both sides of the lung were affected and showed a significant increase in IL-6 (14.2±2.2 and 1.5±0.7 pg/ml, mean ± se) and IL-1RA (23.3±2.1 and 8.2±2.6 pg/ml, mean ± se) concentrations over time in the children with one-lung ventilation (OLV) and non one-lung ventilation (p<0.001). Except for IL-6, which increased more in the collapsed, operated lung, no difference between the collapsed, operated and the ventilated, non-operated lung occurred. In the blood, IL-6 and IL-1RA increased early, already at the end of surgery.

**Conclusion:** The inflammatory response of cytokines affects both the collapsed, operated and the ventilated, non-operated lungs. The difference in extent of response underlines the complexity of the inflammatory processes during OLV in contrast to the cytokines.

**P3497**

**Treatment effect of inhaled prolonged bronchodilator therapy (IPBT) combined with inhaled glucocorticosteroids (IGCS) on respiratory symptoms and external respiratory function in MDTR pulmonary TB patients with broncho- obstructive syndrome (BOS)**

**Galina Kuklina**, Vladimir Romanov 1, Department of Granulomatous Lung Disease, Central TB Research Institute, Moscow, Russian Federation; 2Department of Granulomatous Lung Disease, Central TB Research Institute, Moscow, Russian Federation

**Aim:** To study treatment effect of IPBT combined with IGCS on respiratory symptoms and external respiratory function in MDTR pulmonary TB patients with BOS.

**Methods:** We studied treatment effect of IPBT combined with IGCS on respiratory symptoms of 44 MDTR pulmonary TB patients with BOS: fibrotico-cavernous tuberculosis 16 patients, disseminated tuberculosis 8 patients, casesous pneumonia 6 patients, infiltrative pulmonary tuberculosis with cavities 14 patients. All patients were treated by standard TB chemotherapy on the base of WHO recommendations.

All patients were treated by one dose of 50/500 mcg of combined IGCS (including prolonged beta2-agonist-salmeterol and fluticasone propionate) twice a day during one month. Then this drug was not used during 5 months. Treatment effect was evaluated, first, at the beginning of the treatment and then at the end of treatment by this drug and, last, in 6 months, at the end of study. Respiratory symptoms were evaluated by 5-mark grading system and cumulative index (CI). FEV1 was shown in percents out of standard indications.

**Results:** We found that the use of combined bronchodilators CI decreased per 24.3% and dyspnea decreased per 37.5% during one month. And during the next 5 months CI decreased only per 10.3% and dyspnea per 13.3%. FEV1 increased from 63.3% to 85.4% during one month of inhaled broncholytic combined with IGCS use.

**Conclusion:** IPBT combined with IGCS significantly prompts dyspnea decrease and respiratory symptoms expression and, at the same time, it prompts FEV1 increase.

**381. The good clinical practice: useful case report**

**P3498**

**Transbronchial lung biopsy, our results in 1197 patients**

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**Background:** Transbronchial lung biopsy (TBLB) is routinely performed by pulmonologist to diagnose focal and diffuse lung diseases. Compared with open lung biopsy, TBLB has lower morbidity and mortality. The authors summarize the results of 1197 patients who underwent TBLB.

**Objective:** To evaluate the diagnostic yield of TBLB performed without any guidance during the procedure in various pulmonary affections.

**Methods:** Retrospective analysis of 1197 patients who underwent TBLB within the years 2008 to 2011. Patients were selected in groups according to a disease: focal lesion, suspected sarcoidosis, intestinal lung disease (ILD) other than sarcoidosis, pneumonia and bronchial asthma. No method of guidance during the bronchoscopy was used. The site for TBLB was chosen by a physician after revision of chest CT or chest radiograph. Results fulfilling the requested morphologic criteria of specific disease and leading to the final clinical diagnosis were judged to be true positive.

**Results:** The overall diagnostic yield of TBLB was 26.6%. Highest sensitivity was observed in sarcoidosis - 60.2%. In the subgroup of 302 patients with lung cancer, TBLB confirmed the disease in 142 (47.0%) cases. In the ILD excluding sarcoidosis group sensitivity, specificity, positive-predictive and negative-predictive value was: 12.4%; 92.9%; 91.4% and 14.8%, respectively. In 18 persons (1.5%) pneumothorax developed, major bleeding was observed in 7 patients (0.6%). There was no mortality.

**Conclusion:** We recommend TBLB for diagnosing focal pulmonary lesions and morphologic confirmation of sarcoidosis. For its safety TBLB is a convenient method even in other diseases mainly because numerous patients can avoid surgical lung biopsy.

**P3499**

**Intrapulmonary lipoma in children: A case report and literature review**

**Chunmei Zhig, Ling Cao. The Capital Institute of Pediatrics, Beijing, China**

**Objective:** To help early diagnosis of lipoma in children by reporting a rare case of intrapulmonary lipoma in a child.

**Case presentation:** A 13-month-old boy was hospitalized because of cough and fever. Physical examination revealed rales and wheezing over his lungs. Chest
Radiograph showed patchy infiltrate and consolidation near his left hilar. Chest CT scan showed patchy infiltration and round-shape, hypodense homogenious lesions located in the lower lobe of right lung without any calcification. After 19 days of antibiotics treatment, his clinical symptoms and signs disappeared, he underwent chest CT scan (Figure 1) again after treatment, and the result showed the patchy infiltration dissolved, however, the lesions in the lower lobe of right lung remained without any change. He was discharged. One month and one year later he was examined by chest MRI. The lesions were diagnosed as intrapulmonary lipoma by T2 weighted MRI images (Figure 2) with fat suppression.

Conclusions: Intrapulmonary lipoma can also be identified in children. Chest CT scan and MRI are very important for making correct diagnosis.

P3500
Munchausen syndrome by proxy presenting as unexplained hemoptysis: A report of two cases
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Hemoptysis is a serious symptom in early childhood and further investigation may be required in some cases. Munchhausen syndrome by Proxy (MSP) must be kept in mind particularly when suspicious behaviors of the supervisors are observed. Case 1: A thirteen-month-old boy was admitted with recurrent hemoptysis. He was hospitalized because of persisting symptoms for four months, however no reason was found and he was subsequently discharged. Detailed history revealed that hemoptysis had occurred only in times when he was alone with his mother. Despite comprehensive diagnostic evaluation including laryngoscopy, Computerized Tomography, bronchoscopy and endoscopy, no definitive etiology was diagnosed. During his hospitalization, the mother reported new bleedings of the child and blood stained clothes were noticed. Examination of security footage revealed that the mother was sneakingly obtaining the blood samples of another patient and deceiving medical staff. Case 2: An-eight-month old girl was admitted with a history of having vomited blood for two months. Reluctance of her mother was noticed by the physician during history taking. Upper endoscopic investigation revealed linear hemorrhagic lesions at pharynx and tonsils. No definitive etiology was diagnosed despite comprehensive investigations. During hospitalization, the doctor witnessed that her mother was injuring the child with her finger and making her bleed. She was warned about security footage of the room and her complaints resolved spontaneously.

Munchhausen syndrome by proxy is an unusual and difficult to identify cause of child abuse. It must be taken into consideration particularly in conditions with secondary gain of family members.

P3501
Thoracic splenosis – Case series and review of the literature
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Introduction: Splenosis is a rare finding of ectopic splenic tissue found within the thoracic cavity, abdomen or peritoneal cavity. In thoracic splenosis the splenic tissue most often grows in the form of a nodule and the auto-transplantation is usually caused by a previous penetrating or blunt trauma to the thoracic-abdominal region, resulting in splenic rupture.

Cases: We present three cases of thoracic splenosis. All the patients were Caucasian males aged 40-63 presenting with pleural masses that mimicked malignancy, who were eventually diagnosed as thoracic splenosis. All of them had a history of traumatic event to their upper abdomen which occurred 13-40 years ago resulting in splenectomy.

Methods: We made a Medline search in order to find all the cases of thoracic splenosis. We reviewed the cases in order to specify this rare condition.

Results: We found 39 case reports of patients diagnosed with thoracic splenosis. In the majority of the cases the patients are asymptomatic and are incidentally diagnosed with left hemithorax pulmonary lesions found via chest radiography or thoracic computed tomography. The average period of diagnosing thoracic splenosis from the time of trauma is roughly 21 years and ranges from 6 to 46 years. The diagnosis is challenging and the patients usually undergo extensive workup including surgical biopsy

Conclusion: We conclude that splenosis is a rare entity but one should think about this possibility in a patient with a left thoracic mass and a history of abdominal trauma, splenic rupture and splenectomy.

Abstract P3502 – Table 1: Diagnosis, location, origin of arterial vessel, and symptoms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Origin of Vessel</th>
<th>Follow up (yrs)</th>
<th>Exacerbations</th>
<th>Life threatening events</th>
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<tbody>
<tr>
<td>1</td>
<td>MDCTA, MRA, Gallium Scan, CT guided Biopsy</td>
<td>LLL</td>
<td>TA</td>
<td>11</td>
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<td>None</td>
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<tr>
<td>2</td>
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<td>LLL</td>
<td>TA</td>
<td>2</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>MDCTA, PET-CT</td>
<td>LLL</td>
<td>Abdominal Aorta/Celiac trunk</td>
<td>6</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
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<td>LLL</td>
<td>TA</td>
<td>4</td>
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<td>MDCTA</td>
<td>LLL</td>
<td>TA and Celiac Trunk</td>
<td>6</td>
<td>2</td>
<td>None</td>
</tr>
</tbody>
</table>

Conclusion: In asymptomatic or mildly symptomatic adult patient with lung sequestration, conservative follow up instead of surgery is a legitimate option.

P3503
Acquired tracheoesophageal fistula – A rare cause of chronic episodic cough
Anishesh Gupta1, Saurabh Kansal2, A.P. Kansal1, Bidhi Chand1. 1Chest and Tuberculosis, Govt. Medical College, Patiala, Punjab, India; 2ENT, Dayanand Medical College, Ludhiana, Punjab, India

Introduction: Acquired tracheoesophageal fistula (TOF) is a rare entity and occurs as a result of trauma, malignancy, granulomatous infection, any previous surgery of trachea and esophaogus. Symptoms include uncontrolled coughing after swallowing. The majority of acquired fistulas occur at cervico-thoracic junction.

Case report: We report a case of 55 yr female who presented to us with cough and regurgitation particularly after intake of liquids since two mths. There was no history of tuberculosis or malignancy. Patient was on antihypertensive agent for four mths but not on ACE inhibitors. On routine investigations TLC and ESR were raised but chest xray was normal. Sputum was negative for AFB. Patient was managed on lines of Gastro Esophageal Refux Disease with no improvement. CECT chest showed consolidative changes. Nothing significant found in upper GI endoscopy. Barium swallow revealed the losing of contrast into trachea and in bronchi, showing the presence of tiny fistula at C3-C4 vertebral level. Due to higher position of fistula, patient was advised to undergo surgery.

Discussion: An acquired TOF bypasses the laryngeal protection and leads to repeated aspiration. We are reporting a rare case of acquired TOF possibly of infective etiology which is a rare occurrence at such a age. It was also the cause of chronic episodic cough in this patient which was not relieved with various treatments. Malignant and traumatic causes have now superseded infection. Barium swallow will demonstrate the defect in 70% of lesions. The management of acquired TOF involves minimizing further aspiration to prevent pulmonary infections. Definitive management involves stenting or surgical repair with treatment of underlying cause.

Conclusion: Pulmonary sequestration in asymptomatic adults; a plea for conservative observation
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Background: Pulmonary sequestration (PS) is a rare congenital anomaly. Due to recurrent infections, the treatment in children is surgical removal of the sequestrated lung and this recommendation expands to adulthood.

Objective: To test if asymptomatic or mildly symptomatic adults with PS could be offered conservative follow up instead of surgery.

Methods: We conducted a case series analysis of all patients above 20 yrs old, with sequestration seen in our institute from 2000-2012. Diagnosis, symptoms, patient characteristics, natural course and treatment were reviewed.

Results: During a median follow up of 7 yrs, no major infection occurred and the lesion size remained unchanged in 4/5 patients while mild infection that resolved with oral antibiotics was noted in 1/5.
In this case, we report a newly categorized mediastinal cyst called Mullerian cyst, which was reported for the first time by Hattori et al in 2005. A 51-year-old female patient was admitted to our hospital with the complaint of dysphagia. T2-weighted chest magnetic resonance imaging (MRI) showed a cystic lesion attached to the vertebral column in the posterior mediastinum.

The patient underwent right thoracotomy. The cyst was tightly attached to esophagus and corpus of the 5th thoracic vertebra. The intact cyst was freed from posterior mediastinum.

It was lined by a ciliated tubal-type epithelium and had a thin wall composed of smooth muscle. The epithelium showed estrogen and progesterone receptor expressions immunohistochemically. Mullerian cysts arise from remnants of the Mullerian duct and can be located anywhere along the path of Mullerian duct regression. Pelvis is the most common localization and their occurrence in the mediastinum is extremely rare. However, mediastinal Mullerian cyst is newly known entity, it should be kept in mind for the differential diagnosis of posterior mediastinal cysts.

P3505
First presentation of a case of pulmonary alveolar microlithiasis with spontaneous pneumothorax
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Pulmonary Alveolar Microlithiasis (PAM) is a rare disease of unknown etiology. It is characterized by the presence of small calculi within the alveolar space. Clinical features vary and some patients may be asymptomatic for a long time with subsequent occurrence of dyspnea, dry cough, chest pain, and ultimately, respiratory failure. Recurrent spontaneous pneumothorax is a late complication of the disease. Herein we report a case of alveolar microlithiasis in a 42-year-old male whose first presentation was the symptoms of pneumothorax. He was admitted with sudden onset dyspnea and right sided pleuritic chest pain. After treatment of pneumothorax with insertion of chest tube, pulmonary function revealed normal indices. The chest radiograph demonstrated diffuse confluence of dense micronodular infiltrate. High-resolution CT scan revealed diffuse ground glass attenuation and calcifica-

tions along the interlobular septa and subpleural regions. A transbronchial lung biopsy confirmed the diagnosis of PAM.

P3506
Benign metastatic leiomyoma of uterus with lung damage
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Benign metastasizing leiomyoma of uterus is difficult to diagnose due to frequent location in the lungs. The characteristic manifestation is polygonal cells. The most common localization is pelvis. However, their occurrence in the lungs is extremely rare. We report a case of pulmonary metastasis of uterine leiomyoma in a 46-year-old woman with no previous history of gynecologic disease. The patient was admitted with sudden onset dyspnea and right sided pleuretic chest pain. After treatment of pneumothorax with insertion of chest tube, pulmonary function revealed normal indices. The chest radiograph demonstrated diffuse confluence of dense micronodular infiltrate. High-resolution CT scan revealed diffuse ground glass attenuation and calcifica-

tions along the interlobular septa and subpleural regions. A transbronchial lung biopsy confirmed the diagnosis of PAM.

Hyper eosinophilic syndrome (HES) is characterized by blood eosinophilic count 1500 or more for 6 months & eosinophil infiltrations of multiple organs like skin, heart, bone marrow, lungs. We report a unique case, rare in a female case report: 20 years old female had progressive dyspnea since 1 year. One report with her showed peripheral eosinophilia of 27% Respiratory system revealed signs of left pleural effusion with fluid eosinophilia. Eosinophilic pneumonia was diagnosed. Blood eosinophil count was 2750 cells. PTECG was normal. The thorax revealed RA thrombus & RV infarctions and cardiac MRI showed typical endomyocardial fibrosis in RV.

Echo showed RA thrombus & apical fibrosis. Hypereosinophilic syndrome (HES) is characterized by blood eosinophilic count 1500 or more for 6 months & eosinophil infiltrations of multiple organs like heart, bone marrow, skin. HES is a rare syndrome, rare in a female case report: 20 years old female had progressive dyspnea since 1year. One report with her showed peripheral eosinophilia of 27% Respiratory system revealed signs of left pleural effusion with fluid eosinophilia. Eosinophilic pneumonia was diagnosed. Blood eosinophil count was 2750 cells. PTECG was normal. The thorax revealed RA thrombus & RV infarctions and cardiac MRI showed typical endomyocardial fibrosis in RV.
A rare cause of hemoptysis: Munchausen syndrome

The authors report a case of a 65-year-old male patient, suffering of hypertension and permanent atrial fibrillation (treated with warfarin), with no previous history of pulmonary pathology, who presented with fever, wheezing, cough and hemopurulent sputum 4 days before. The chest radiograph showed middle lobe (ML) and lower right lobe (LLR) consolidation leading to the diagnosis of community acquired pneumonia as compared to normal subjects. The aim of our study was to assess pulmonary functions and the cardiopulmonary response to exercise in acromegalic patients. Ten patients who were followed by endocrinology department outpatient clinic were enrolled to study. Disease activity was evaluated by growth hormone (GH) and elevation of its peripheral mediator insulin-like growth factor-1. Acromegaly is known to significantly increase mortality rate. Cardiovascular diseases are the most common causes of death in acromegalic patients. Moreover acromegalic patients with cardiac hypertrophy have a decreased cardiopulmonary reserve compared to normal subjects. The main clinical symptoms were dyspnea in 20 pts (95.2%), cough in 19 pts (90.9%), fever in 17 pts (80.9%), pain in 5 pts (23.8%). AEP or CEP was the result of CD in 3 pts (teoplasmosis), in 1 pt. with sarcoidosis, rhinitis and in 2 with allergic bronchopulmonary aspergillosis. In 17 pts CD was identified. A statistical significance was found between the age of pts with AEP (56±12.2) and CEP (67±12.9) (p<0.05). There were no statistically significant differences between patients with AEP (614±279.3) and CEP (709±311.3) and in the groups of AEP (860.7±976.7) and CEP (579±429.3). 11 pts have been continually treated with corticosteroids, 8 pts temporarily. The longest treated patient has been receiving corticosteroid for more than 13 yrs.

Conclusions: EP is a very interesting disease. Treatment with antibiotics is unsuccessful, but corticosteroid treatment leads to a dramatic improvement. Dividing EP into AEP and CEP is not so clear cut.

Drug excipients allergy

P3512
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Introduction: Because of its rarity, drug excipients allergy is often unsuspected by the doctors. Some times the active drug is blamed and discontinued unnecessarily when the real culprit is drug excipients. This was suspected when patients reported exacerbation of urticaria with anti histaminic which are actually used for treating urticaria. After suspecting drug excipient as the cause of allergy.

Material: To know actual cause it was decided to do patch testing with common drug excipients. The common excipient selected were Yellow Tartrazine, Titanium Dioxide, Sunset Yellow, Brilliant Blue, Quinoline Yellow, Talcum, and Ponceau 4R.

Method: Patch testing material were prepared by using the basic material and suitable vehicle. 24 patients were selected for patch testing. Patch was put on patients back after 48 hrs reading were taken to confirm the skin sensitivities. Results: Out of 24 patients 15 patients were positive for Yellow Tarrtazine only, 3 patients showed positive to Titanium Dioxide. 2 patients were positive to Quinoline Yellow and Talcum. 2 were positive with Brilliant blue. 3 patients were positive Yellow Tarrtazine, Sunsets Yellow and Talcum.

Conclusion: Drug excipients play an important role in causation is required to be standardised for patch testing. This type of patients should be treated in view of such investigations and preferably treated with drug without excipients.

Rosai-Dorfman disease: Presentation of a clinical case

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Introduction: Rosai-Dorfman disease (RDD) is a rare histiocytic proliferative process, infrequent and idiopathic benign with painless cervical or systemic lymphadenopathy, fever, leukocytosis, polyclonal hypergammaglobulinemia and accelerated erythrocyte sedimentation. In a low percentage, there are extranodal manifestations. The historical diagnosis consists of filling of sinusoids in ganglia with linfocytes, plasmatic cells and histocytes positive for S100, CD68, glia with linfocytes and histiocytes positive for S100, CD68, edema of face, neck and arms. The erythrocyte sedimentation was accelerated (90 mm/hr). Chest x-rays showed mediastinum widening and tumor in the pulmonary right hilum. The computed tomography showed right hilum hypervascular of 7 cm. The bronchoscopy with biopsy showed right bronchi infiltrate with tumoral edema of face, neck and arms. The erythrocyte sedimentation was accelerated (90 mm/hr). Chest x-rays showed mediastinum widening and tumor in the pulmonary right hilum. The computed tomography showed right hilum hypervascular of 7 cm. The bronchoscopy with biopsy showed right bronchi infiltrate with tumoral
aspect. The histopathological findings revealed histiocytic proliferation and others with eosinophilic cytoplasmic features and lymphoid cells. Emperipoliseis and plasmatic cells where identified, with Russell bodies. With the diagnosis 120 mg a day of interferon-alpha was initiated, continuing with 40 mg daily over 6 months with favorable response reducing the size of the lesion. **Discussion:** In this case, the manifestation of the disease was dyspnoea produced by the bronchial obstruction and compaction of the superior vena cava due to the hilar infiltrative histiocytic mass, so our initial probable diagnosis was a bronchogenic cancer. This extranodal manifestation is infrequent, but it is to be taken into account as part of the pulmonary and mediastinal pathology.

**P3514**
Three tumors in a young woman with Cushing's syndrome

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**Case:** A 38-year old female with no relevant medical history was referred to internal medicine with clinical features compatible with Cushing’s syndrome. Laboratory results suggested ectopic adrenocorticotropic hormone (ACTH) production. The pituitary gland had a normal aspect on magnetic resonance imaging but computed tomography of the chest showed a smooth, oval mass in the posterior mediastinum and a nodule in the left upper lobe. Diffferential diagnosis consisted of carcinoid, small cell lung cancer or neuroendocrine tumor. Bronchoscopy showed no endobronchial lesions but both lesions could not be reached with fluoroscopic guidance. On 18F-deoxyglucoson positron emission tomography (18FDG-PET) increasing 18FDG uptake was seen in the mediastinal mass and in the right gluteal region, but not in the left upper lobe. Somatostatin scintigraphy showed uptake in the left upper lobe, but not in the other masses. Histological biopsy of the gluteal mass showed a desmoid type fibromatosis. Wedge resection with peroperative frozen section resulted in a benign tumor and a type 1a (TAa) was found. For treatment and staging resection of the left upper lobe with mediastinal lymph node sampling and resection of the mediastinal mass followed in the same session. The resections were complete but one lymph node (N2) was positive for carcinoid metastases. The mediastinal mass appeared to be a schwannoma.

**Conclusion:** Cushing’s syndrome caused by ectopic ACTH in a TAaN2M0 typical carcinoid. Furthermore, the two PET-positive lesions appeared to be a schwannoma and a desmoid type fibromatosis. This case stresses the importance to link presenting condition with imaging features and to obtain histological confirmation.

**P3515**
The treatment of a non-Lagrenhans-cell histiocytosis, Erdheim-Chester disease: A case report

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Erdheim-Chester disease (ECD) is a rare, non-Langerhans histiocytosis with multi-system involvement. Pulmonary involvement is uncommon. We present a 46-year-old woman who presented with chronic cough, dyspnea and yellowish plaques in the peripheral area. She was previously diagnosed as diabetes insipidus. Chest radiographs showed bilateral diffuse interstitial infiltrates. Symmetric sclerotic bone lesions, dural nevve thickening were defined on imaging studies. Histopathologic examination of the skin lesions revealed infiltration of CD-68 positive foamy histiocytes. She was diagnosed as ECD with pulmonary, pituitary, skeletal, orbita, central nervous system and skin involvement. Following first-line treatment with corticosteroids her syptoms worsened. Treatment with interferon-alpha was started. She had an marked improvement in symptoms, radiologic findings and skin involvement under this treatment.

**Conclusion:** ECD should be considered in the differential diagnosis of interstitial lung diseases. As there is no standard treatment for this disorder, interferon-alpha can be effective in the treatment of Erdheim-Chester disease.

**P3516**
High grade laryngeal stenosis caused by an extramedullar metastasis of plasmacytoma

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We report the case of a 69-year-old woman who was presented to our department with rapidly progressive hoarseness, stridor and dyspnea for week. The patient had a history of multiple myeloma for 3 years and resected breast cancer for 1 year. On fiberoptic bronchoscopy a high grade (>80%) right sided laryngeal submu- cosal mass, affecting both supra- and infraglottic parts of the larynx, was found for the reason she has symptoms. We performed a surgical tracheostomy considering it the only viable option of airway managament. An MRI scan of the neck revealed a right sided cervical mass of 7x3cm, as well as an enlarged lymph node in the right supravaculariauricular region (I1). Biopsy was performed both of the lymphnode (core needle biopsy) and the laryngeal mass (EBUS-TBNA). The histological and immunohistochemical findings were consistent with metastasis of the known multiple myeloma. Extramedullar metastasis of multiple myeloma is a rare complication of the disease occurring. Laryngeal stenosis due plasmacytoma has been described in pediatric patients, but never in adult patients before.

**P3517**
Urinary incontinence in adult bronchiectasis patients: Common but treatable

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**Background:** Patients suffering from urinary incontinence (UI) often avoid seeking medical attention, due to embarrassment, consequently remaining untreated. UI negatively impacts of quality of life, psychological health and relationships.

In patients with non-CF bronchiectasis, it may also reduce adherence to chest physiotherapy. UK Physiotherapy Guidelines (2009) suggests screening for UI in patients with non-CF bronchiectasis.

**Methods:** Screening at new specialist bronchiectasis clinic for symptoms of UI, with referral onto Continence specialist services.

**Results:** Of the initial 116 patient referred to the bronchiectasis service, 76 were female. 55% of female patients had UI (UI-Br). 87.5% of UI-Br patients reported symptoms for over 5 years, with 40% of patients describing symptoms of over 10 years duration. 37% reported UI as having a terrible impact on quality of life. Patients were assessed by a Continence Nurse Consultant. A personalised UI management plan was formulated, including education on pelvic floor strengthening, urge suppression and voiding techniques. Other treatments used included bladder retraining (40%) and toilet resheduling (40%). Over 60% of patients have been discharged by the Continence Service, following symptom improvement.

**Conclusions:** In asking about UI, in line with UK guidelines, we identified symptomatic patients and referred them onto an appropriate specialist service. We identified a high prevalence of UI in female patients with non-CF bronchiectasis. Patients suffered symptoms for a prolonged period with a significant impact on quality of life. Through appropriate specialist input, these distressing symptoms have been improved in the majority of our patient group.

**P3518**
Hypogammaglobulinemia, reduced B cell count and recurrent sino pulmonary infections: Good’s syndrome

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A 62-year-old woman with a history of thyroidectomy for capsule-invasion-free, type AB thymoma, presented with cough, dyspnea and fever. She had frequent respiratory tract infections for 9 months. Her initial physical examination was normal. Abnormal laboratory studies on admission were anemia, leukocytosis, proteinemia, elevated erythrocyte sedimentation rate, C-reactive protein and procalcitonin levels. On chest tomography, multiple mediastinal and hilar lymph nodes, bilateral traction bronchiectasis and miliary nodules were seen. E-Coli was isolated in bronchoalveolar lavage. TBNB and TBB were negative for probable thymoma metastasis.

For the probability of Good’s Syndrome, serum immunoglobulin levels were measured and found normal for lgA, low for lgG and high for lgM. Flow cytometry demonstrated 8% of CD19+, 12% of CD56+, 14% of CD57+, 30% of CD4+, 37% of CD8+ cells in total lymphocytes; consistent with B-cell immunodeficiency. With the diagnosis of Good’s Syndrome, intravenous immunoglobulin treatment was started. During her follow-up, she was hospitalized twice for respiratory tract infections. Now she is on ciprofloxacin profilaxis.

Good’s syndrome is a rare cause of combined B or T cell deficiency. Its main characteristic are hypogammaglobulinemia, reduced or absent B cells, reduced serum levels of IgG, IgA and IgM. Recurrent sino pulmonary infections caused by encapsulated microorganisms. Management of syndrome includes surgical resection of thymoma, treatment of infections and immunoglobulin replacement therapy. Good Syndrome is a rare but treatable condition and it should be considered in patients with the diagnosis of thymoma and frequent respiratory tract infections.
P3519
Expiratory muscle activity and nasal expiratory pressure during reverse sniff
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The evaluation of expiratory muscle strength is of clinical importance in patients with neuromuscular respiratory disease. Maximal expiratory pressure (MEP) has achieved wide acceptance as a simple non-invasive measurement of expiratory muscle strength. However, MEP measurement is difficult for neuromuscular disease patients. In this study, we measured expiratory muscle activity during reverse sniff, a maneuver akin to “blowing your nose”, and we analyzed the relationship between expiratory muscle activity and reverse sniff nasal expiratory pressure (RSNEP).

In 5 healthy subjects, mean age 21.2 yrs, weight 69.2 kg, height 176.6 cm, we inserted fine wire electrodes into transversus abdominis muscle (TA) using high-resolution ultrasound. RSNEP was measured through a catheter that occluded one nostril, while the contralateral nostril remained open. Subjects performed short, sharp, maximum and variable intensity of reverse sniff, beginning from FRC, while standing. TA EMG activity was expressed as percent of maximum EMG (%EMGmax) throughout respiratory and non-respiratory maneuvers. Mean MEP was 80.8±36.0 cmH2O. Mean maximum RSNEP was 34.9±18.7 cmH2O, and mean TA EMG activity at maximum RSNEP was 73.9±23.6%EMGmax. TA EMG activity increased with stepwise increments in RSNEP. In every subject, the linear relationship between RSNEP and TA EMG activity was significant (r = 0.56, p<0.05).

We conclude that RSNEP corresponds to the activity of the expiratory muscle transversus abdominis, and that this simple maneuver may be useful for assessment of expiratory muscle strength.

This study was approved by Kitasato university human ethics committee. This work was supported by MEXT of Japan KAKENHI (2350061).

P3520
Inspiratory muscle training (IMT) as an adjunct to pulmonary rehabilitation (PR) in patients with severe COPD
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Background: Up to now there is insufficient evidence for IMT as an adjunct to PR in patients with COPD.

Method: From November 2011 until January 2012 in our clinic 198 COPD patients underwent a 3-week inpatient PR, including 90 with COPD III-IV. Of these patients the control group (CG, n=38) received standard PR, consisting among other things of physical training, education, breathing therapy and psychosocial support. The intervention group (IG, n=52) underwent an additional IMT with at home training. Subjects performed short, sharp, maximum and variable intensity of reverse sniff, beginning from FRC, while standing. TA EMG activity was expressed as percent of maximum EMG (%EMGmax) throughout respiratory and non-respiratory maneuvers. Mean MEP was 80.8±36.0 cmH2O. Mean maximum RSNEP was 34.9±18.7 cmH2O, and mean TA EMG activity at maximum RSNEP was 73.9±23.6%EMGmax. TA EMG activity increased with stepwise increments in RSNEP. In every subject, the linear relationship between RSNEP and TA EMG activity was significant (r = 0.56, p<0.05).

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This study was approved by Kitasato university human ethics committee. This work was supported by MEXT of Japan KAKENHI (2350061).

P3521
Predictive factors of survival in amyotrophic lateral sclerosis patients with respiratory dysfunction
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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that causes severe respiratory dysfunction which is the major cause of death. Early management of respiratory symptoms may improve outcomes and survival.

Aim: Describe survival of patients with ALS and respiratory dysfunction and identify predictive factors of survival.

Methods: Retrospective analysis of patients with ALS evaluated in an outpatient setting. Ventilatory support data was screened. Kaplan-Meier survival analysis was performed and predictive factors were evaluated by Cox multivariate regression.

Results: 60 patients (25 females) with a median age of 64.5 years (range 34-80) were analyzed. At presentation, 33 patients (55%) had initial slow bulbar-onset and 27 (45%) rapid bulbar-onset. Non-invasive ventilation (NIV) was initiated in 52 patients (86.7%), with a mean vital capacity of 1699±678 L and 22±40.8 months after diagnosis. Mean duration of NIV was 19.6±23.7 months. Mechanical assisted cough was used in 23 patients (38.3%). Gastrostomy was performed in 21 patients (17 rapidly bulbar) and tracheostomy in 10 (9 rapidly bulbar) after a mean time of 13.6±17.0 months under NIV. The 5-year survival was 48%. The median overall survival and survival after respiratory muscle aids initiation was significantly higher in slowly bulbar patients compared with rapidly bulbar (p=0.03 and p<0.01, respectively). In multivariate analysis, predictive factors of survival were younger age, slow bulbar-onset, and early NIV initiation.

Conclusion: Survival may be prolonged in patients with ALS and respiratory dys- function with early NIV initiation. Age and bulbar onset have significant negative impact on survival.

P3522
Short-form Sun-style Tai Chi as an exercise training modality in people with COPD: A randomised controlled trial
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The aims of the study were, in people with COPD to: determine the effect of short-form Sun-style Tai Chi (sSCT) compared to usual medical care on exercise capacity, balance and quality of life (Part A) and investigate the exercise intensity of sSCT (Part B).

Method: Part A was a single blinded, randomised controlled trial with concealed, random allocation of participants to either the Tai Chi Group (TCG) or Control Group (CG) (usual medical care only) after confirmation of eligibility. Participants in the TCG training for one hour, twice weekly for 12 weeks at a moderate dyspnoea or exertion level (score = 3 in a 10 point scale). Part B was a repeated measures design where participants who had completed training in TCG performed incremental shuttle walk test and sSCT while wearing a portable metabolic system. Exercise intensity of sSCT was determined by the percent of oxygen consumption (VO2) reserve.

Results: Of 42 participants (mean (SD) age 73 (8) years, FEV1% 59 (16)% predicted), 38 completed Part A of the study (19 in each group) and 15 completed Part B. Compared to control, S SCT significantly increased incremental shuttle walk distance (mean difference, 95% CI 55 metres, 31 to 80) and endurance shuttle walk time (384 seconds, 186 to 510); reduced medial-lateral body sway in semi-tandem stand (-12.4 mm, -21 to -3); and increased total score on the chronic respiratory disease questionnaire (11 points, 4 to 18). The exercise intensity of S SCT in COPD was 53 (18)% of VO2 reserve.

Conclusion: Short-form Sun-style Tai Chi was an effective training modality in people with COPD and the exercise intensity was moderate which met the recommendation for training in COPD.
Twenty-three participants completed the survey, mean (SD) age 74 (8) years.

**Methods:** The Cochrane Airways Group Specialised Register of trials and the PEDro database were searched to identify randomised controlled trials comparing breathing retraining to no breathing retraining or another intervention in COPD.

**Primary outcomes** were dyspnoea, exercise capacity and quality of life; secondary outcomes were QoL.

**Results:** 16 studies involving 1104 participants with mean FEV1 30.5% predicted were included. Few studies reported allocation concealment, assessor blinding or intention to treat analysis. Two studies showed improvement in 6-minute walk distance after 3 months of yoga involving pranayama timed breathing techniques (mean difference 45m, 95% CI 29.6-61m), with similar improvements in single studies of pursed lip breathing (mean 50m) and diaphragmatic breathing (mean 35m).

Effects on dyspnoea and quality of life were inconsistent. Two studies reported that addition of ventilation feedback (VFB) to exercise training did not improve dyspnoea, exercise tolerance or quality of life more than exercise training alone. One study showed that VFB alone was less effective than exercise training for improving exercise capacity. No adverse effects were reported.

**Conclusion:** Breathing retraining in COPD is safe and improves exercise capacity when compared to no intervention; however there are no consistent effects on dyspnoea or quality of life. Breathing retraining may not have additional benefits beyond that offered by exercise training for people with COPD.

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**P3524**

Tai Chi, like it or not? The COPD experience

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**Aim:** To determine the experience of people with COPD to Tai Chi. Methods: Participants, who finished 12 week short-form Sun-style Tai Chi (SSTC) training program, completed a survey of eight questions. Each question was answered by putting a stroke on a 10 cm Visual Analogue Scale with anchors at either end, ranging from the negative of the question on the left to the positive of the question on the right. The number of supervised training sessions attended and the number of days unsupervised home training practised was reported.

**Results:** Twenty-three participants completed the survey, mean (SD) age 74 (8) years, mean FEV1% predicted 59 (17%). Participants attended 21 (2) supervised training sessions out of a possible 24 sessions and performed 4 (1) days per week of unsupervised home training. The Table below indicates the results of four survey questions.

<table>
<thead>
<tr>
<th>Tai Chi survey questions (score out of 10 cm)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How enjoyable was your Tai Chi exercise program</td>
<td>8.9 (1)</td>
</tr>
<tr>
<td>How helpful was the Tai Chi program at improving</td>
<td></td>
</tr>
<tr>
<td>a) Physical fitness</td>
<td>7.9 (2)</td>
</tr>
<tr>
<td>b) Balance</td>
<td>7.9 (1)</td>
</tr>
<tr>
<td>c) Shortness of breath</td>
<td>7.0 (2)</td>
</tr>
<tr>
<td>How hard were the following parts of the Tai Chi program</td>
<td></td>
</tr>
<tr>
<td>a) Remembering the movements</td>
<td>5.3 (3)</td>
</tr>
<tr>
<td>b) Balancing during Tai Chi movements</td>
<td>6.5 (2)</td>
</tr>
<tr>
<td>c) Coordinating your breathing and the Tai Chi movements</td>
<td>7.0 (2)</td>
</tr>
<tr>
<td>Would you continue Tai Chi training as your regular exercise regimen</td>
<td>8.4 (2)</td>
</tr>
</tbody>
</table>

**Conclusion:** Participants reported that SSTC was a highly enjoyable exercise which they perceived improved their physical fitness, balance and shortness of breath. Compliance with supervised and unsupervised training was high. Importantly, participants indicated that they would continue Tai Chi as their regular exercise regimen.

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**P3525**

Effects of Tai Chi Qigong exercise training on asthma control

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**Background:** Though exercise training increased exercise capacity in asthma, its effect on asthma control has not been well described. This study aims at exploring the impact of Tai Chi Qigong(TCQ) exercise training on asthma control.

**Methods:** This prospective, case-control study recruited adult asthmatics with pre-bronchodilator FEV1 of ≤75% predicted. In addition to the self-monitored peak-expiratory flow rate (PEFR) and Asthma Control Questionnaire (ACQ), patients in TCQ and control groups were assessed at 0, 4 and 10 weeks. These included 6-minute walking distance(6MWD), pre and post-6MWD spiroometrics and dyspnea indices(Borg), transitional dyspnea indices(TDI), Saint George Respiratory Questionnaires(SGRQ) and maximum inspiratory pressure(MPI). TCQ exercise trainings were provided to the TCQ group during week 4-10.

**Results:** There were 29 and 8 patients in TCQ and control groups respectively. After TCQ training, the TCQ group demonstrated significant improvements in PEFR and Asthma Control Questionnaire(ACQ), patients in TCQ and control groups were assessed at 0, 4 and 10 weeks. These included 6-minute walking distance(6MWD), pre and post-6MWD spiroometrics and dyspnea indices(Borg), transitional dyspnea indices(TDI), Saint George Respiratory Questionnaires(SGRQ) and maximum inspiratory pressure(MPI). TCQ exercise trainings were provided to the TCQ group during week 4-10.

**Conclusions:** TCQ exercise training improved asthma control. This finding and the associated improvements in exercise capacity, muscle strength and dyspnea signalled that TCQ training could be considered an effective, adjunctive asthma-therapy.
tended to reach greater improvements in ACT (especially in items 2, 3 and 4, i.e. shortness of breath, asthma symptoms at night, rescue inhaler) and NQ than the CG, but these trends weren’t significant between groups.

Conclusion: BT could be a promising adjunct to PR.

P3528
Speech and language therapy effectiveness in vocal cord dysfunction management
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Introduction: Vocal cord dysfunction (VCD) “paradoxical vocal cord adduction” is misdiagnosed as asthma, resulting in over medication and increased hospital admissions. There is anecdotal evidence of the benefits of Speech Therapy (SLT) in management of VCD. This study explored the impact of SLT on symptom control and hospital admission prevention.

Method: One hundred consecutively referred patients (mf ratio=1:5, mean age 45yrs, range = 16-77) underwent detailed assessment at a tertiary VCD clinic with nasendoscopy confirmed VCD. No 81/100 (81%) had physician-diagnosed asthma, 45/81 (56%) required oral steroids. Patients received four sessions of SLT. Treatment effectiveness was assessed pre/post therapy, using in-house self-rated, VCD symptoms score (range 0-25). N=21/100 (21%) patients reported hospital admission with dyspnoea in the year prior to assessment. Data were analysed to determine number of hospital admissions one year pre/post SLT intervention.

Results: Differences pre/post therapy were assessed using Wilcoxon Signed Ranks Test. Significant reduction in patient reported symptoms was noted post SLT pre vs. post therapy; mean (SD) = 17.88 (3.10), 8.16 (4.13) respectively, p<0.0001. Reduction in hospital admissions was noted in the year post SLT intervention; pre vs. post therapy mean (SD) = 10.7 (8.8), range = 2.3-15, 1.2 (2.2), range = 0-6, p<0.0001. Conclusion: SLT significantly improves symptom control and reduces hospital admissions in VCD. The availability of effective therapy prompts the need to increase awareness of vocal cord dysfunction.

Reference:

P3529
The long-term effect of ambulatory oxygen (AO) in normoxaemic COPD patients who participate in pulmonary rehabilitation (PR) and desaturate during exercise. A randomised study
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Introduction: The long-term benefits of AO in combination with PR in COPD patients experiencing exertional desaturation have not been studied.

Patients and methods: Normoxaemic COPD who participated in PR and desaturate >4% and below 90% during endurance shuttle walk test (ESWT) were randomised to control (n=23) or AO 2 L/min. from a portable oxygen concentrator (n=22) to be used during physical activity.

PR consisted of supervised training 20 wks + unsupervised daily training at home and then 13 wks without supervised training.

Results: Only 45 of 165 eligible patients wanted to participate. Mean FEV1=32% and MRC=4.5 (3.5).

Supplemental oxygen improved satO2 during ESWT by 2.3% (p<.001). In the study period of 33 wks, 10 and 6 patients withdraw from the AO group and control group, respectively. Patients spent in average 7.9 hours/week on oxygen.

Conclusion: AO greatly reduces hypoxaemia in COPD patients undergoing PR and can be used as a supplementary therapy during physical activity.

P3530
Preliminary results of noninvasive ventilation during a pulmonary rehabilitation program in patients with COPD
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Introduction: Exercise training at higher intensities seems to result in a better training effect. However, in some patients with COPD this intensity is limited due to decreased ventilatory pump capacity. Noninvasive ventilation (NIV) relieves the work of breathing, so higher intensities are reached and could result in a better exercise tolerance.

Objective: Analysis of the effects of Bi-pap during an exercise training program in COPD on lung function and maximal exercise capacity.

Methods: 8 patients were randomized in a NIV (n=5) or control group (n=3). Patients trained with or without NIV for a period of 6 weeks. Lungfunction and exercise tests were started before and after 6 weeks. NIV was set on IE pressure of 4/1 and 2 leakage valves were added for patients comfort.

Results: Ventilation at maximal tolerated load (VE max) changed significantly in the experimental group and did not reach significance in the control group compare to baseline (p>0.043). In the same test setting there was no significant drop in heart rate.

Conclusions: Noninvasive ventilation during exercise training may change ventilation at maximal tolerated load and heart rate after 6 weeks. This allows patients to train at a higher level and achieve better training results because of a better ventilatory adaption during exercise.

P3531
Benefits of a new device for inspiratory muscle training in COPD
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In chronic obstructive pulmonary disease (COPD), inspiratory muscle weakness may occur as a result of the combined effects of increased work of breathing, malnutrition, hypercapnia/hypoxemia and others. The benefit of inspiratory muscle training (IMT) depends on patients phenotype but also on the type exercise methods.

The aim of the study was the evaluation of medium (3 months) and short-term (at the end of a pulmonary rehabilitation program, PRP) effects of IMT using the TrainAir® electronic system.

47 patients with COPD (GOLD stage III, IV) without previously PRP were divided in 2 groups. Both groups followed one month a comprehensive PRP, but the group of patients that initially presented lower values of the respiratory maximum pressures IMT was added. Patients’ assessment consisted of: spirometry, maximum inspiratory and expiratory pressures (MIP, MEP), 6-minute walk test (6MWT), body composition, MRC scale, and COPD Assessment Test (CAT).

Our results demonstrated in both groups the increase of exercise capacity on short and medium term (p<0.025) measured by the distance expressed in meters walked to 6MWT as compared to the initial value (500±173 and 488±146 vs. 457±51 for the IMT group, 492±99, and 479±87 vs. 452±105 for the control group). IMT significantly reduced the difference between groups for MIP (kPa) (from 2.9±1.0 to 2.3±0.75, p=0.002), and the effect had been maintained over the medium term (p=0.016). Also, CAT score reduces more significantly on medium term in the presence of IMT (from 21.27±4.13 to 16.91±2.21 vs. from 22.5±2.19 to 19.50±1.85 in control group, p<0.001).

In conclusion, in COPD patients, in addition to the improvement of MIP, IMT was beneficial for patients’ symptomatology.

P3532
The impact of PEEP, CPAP and BiPAP in post-exercise recovery from dyspnea in COPD patients
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Dyspnea is the chief complaint of COPD patients limiting their ability to perform activities of daily living reducing quality of life. To relieve dyspnea, patients may try short acting bronchodilators, pursed lip breathing or physically stop activity.In this study we evaluated different types of positive airway pressure (PAP) therapies to help COPD patients recover from dyspnea following activity.

639s
The aim of this study was to determine if PAP therapies would reduce the patient’s recovery time from a Borg of 7 to their baseline Borg following a standardized exercise regimen. 10 COPD patients classified as Gold Stage 2, 3 or 4 with an FEV1 less than 55% were evaluated. These patients were subjected to a baseline test where they recovered without any device to the baseline Borg. During 2 successive visits, during the recovery phase, patients were asked to try 6 different types of PAP therapy. This included 2 levels of PEEP, CPAP or BiPAP therapy. Borg scores were measured every minute during exercise & every 30 seconds during recovery phase. Time to recover was measured with other physiological parameters. Results indicate that all forms of PAP therapy tested aided the patients to recover faster. Among the 3 tested therapies, BiPAP provided the shortest recovery time improving the time to recover to baseline by 40±9%. CPAP was 2nd best at 27±16.6%. PEEP provided 26±1.3% improvement. These findings indicate that PAP therapy helps COPD patients recover from shortness of breath following activity. The impact of these therapies on other physiological endpoints (Heart Rate, Respiratory Rate & SpO2) are being analyzed. These are being further tested to confirm the findings.

P3533 Efficacy of Nordic walking in rehabilitation of patients with COPD: 
Preliminary data
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Background: Nordic walking is a well-known activity which combines sport and physical training and is widespread in Scandinavia as summer training for Nordic ski athletes and it is extremely simple to perform. However, there are very few studies which evaluated the use of Nordic walking in the field of physical rehabilitation. The aim of the study is to assess the efficacy of Nordic walking in patients with COPD. 
Methods: We enrolled 11 patients with COPD (mean age 64.2±1.3) in a stable phase of their disease and randomized them into two groups. The study group was composed by 5 patients who performed a daily 30 minutes session of Nordic walking for 5 days a week for a total period of 3 weeks. The control group was composed by 6 patients who were treated with traditional rehabilitation (selective training of arms and legs) for the same period as study group. Both the groups performed educational intervention and exercises for respiratory coordination. The two groups of patients performed spirometry, blood gas analysis, 6 minutes walking test, MRC, BDI/TDI, EuroQol, and Saint George test before and after the rehabilitation period. 
Results: Patients in the study group had a significant improvement in terms of post training 6 minutes walking test, MRC, EuroQol, and Saint George (p < 0.05) whereas patients in the control group had only an improvement in MRC (p < 0.05).
Conclusions: This preliminary study shows the efficacy of nordic walking in reducing dyspnea, improving physical performance and quality of life in a small group of patients with COPD. If confirmed in larger studies nordic walking could become part of the training schedules for COPD rehabilitation.

P3534 Effectiveness of pulmonary rehabilitation including occupational therapy (OT) on the prognosis of patients with COPD 
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Aim: We reported that the appropriate pulmonary rehabilitation including OT according the pathophysiology of patient with COPD improved his or her prognosis in the historical control study. In this prospective observational study, we investigated the effectiveness of our pulmonary rehabilitation program on the survival prognosis of COPD patients with long-term oxygen therapy (LTOT).

Method: The subjects were 72 patients with COPD (male: female, 65:7, 69±6.8 years old, FEV1 0.7±0.20 L, 96 predicted 36±14.0%, FVC/FVC 38±10, who underwent LTOT between 1995 and 2005. All patients were on medication and underwent CPET before pulmonary rehabilitation program. We decided the safe range using the data of CPET, and it was represented by each patient's SpO2 and underwent PLB using a portable sleep recorder (PSR: SAS2100 by NIHON KOHDEN).

Results: Forty-six patients died during the follow-up period. Causes of death were the respiratory failure in 20 cases (43.5%), malignant diseases in 10 cases (21.7%) and other diseases in 16 cases (34.8%). The overall 50% survival time was 9.0 years. The 50% survival time in patients with less than 30% of FEV1 predicted, 11ml/kg/min of peak oxygen uptake were 8.7 years and 8.1 years after PLT, respectively.

Conclusion: The appropriate pulmonary rehabilitation including OT according to the pathophysiology of each individual patient with COPD decreased the number of death caused by respiratory failure and greatly improved the prognosis of patients with very severe COPD as compared to the previous studies.

P3535 Respiratory muscles trainings as physical rehabilitation in patients with chronic obstructive pulmonary disease and myoccardial infarction 
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Background: Patients with MI and concomitant COPD often can’t take part in physical trainings as a part of cardiac rehabilitation.

Purpose: To study the effect of respiratory muscles trainings (RMT) in patients with acute MI and COPD.

Methods: 87 patients were randomized to either an exercise training group (EG) or to a control group (CG). Patients were on their 5-7 day of MI. The EG participated in a RMT with gradual increase of inspire and expire resistance. RMT were held with the use of Threshold IMT and PEP devices. RMT were started at the hospital on the 5-7th day after MI and were continued for 1 year at home by patients themselves.

Results: In 1 year the distance of 6 minute walk test increased significantly in EG (285±8.7 m vs 275±3.4±9.28, p < 0.01). VO2peak also increased significantly in EG (68.4±1.55 vs 46.6±1.16 ml/kg/min, p < 0.01). RMT helped to stabilize mean pulmonary pressure (MPP) (35.4±4,7 mm Hg in TG vs 40.7±6.9 mm Hg in CG, p < 0.05). There was a statistically significant increase in the maximal inspiratory mouth pressure in most of patients (0.6 kPa ± 0.8 vs 4 kPa ± 1.1, p = 0.01). Health related quality of life (HRQL) increased in both groups, but in EG patients it grew significantly higher according to SQRQ and SF-36. In a year there were no lethal outcome in both groups. EG patients had significantly less hospitalizations because of HF progression (7.8% in EG vs 14.6% in CG) and pneumonias (2.1% vs 15.3%).

Conclusion: RMT in patients with MI and COPD can be started at their acute period. It improves physical capacity, stabilized MPP, increase HRQL and decrease number of hospitalizations during first year after MI.

P3536 Comparison of the effects of the diaphragmatic breathing exercise in rehabilitation to COPD subjects with normal and high body mass index 
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Background: COPD rehabilitation is a coordinated program of exercise, disease management training, and counselling that can help COPD patients to stay more comfortable and improve to carry out patient’s day-to-day activities. COPD is an heterogeneous disease with a mixture of clinical and functional phenotypes, hence individualization of action strategies, such as pulmonary rehabilitation is very important.

Aim: To compare the effects of diaphragmatic breathing exercise technique in improving quality of life in COPDs with normal and increased BMI.
week for 8 to 56 days. We evaluated the breathing pattern by PSR, respiratory rate (RR), 6-minute distance (6MD), and oxygen saturation (SpO2) before and after these programs.

Case A: Vital Capacity (VC) 0.94L (%VC 44.8%), Forced Expiratory Volume in one second (FEV1) 0.52L (%FEV1 37.4%).
Case B: VC 2.34L (%VC 80.1%), FEV1 0.65L (%FEV1 37.4%).
Case C: VC 1.73L (%VC 61.0%), FEV1 0.57L (%FEV1 34.3%).
Case D: VC 2.17L (%VC 75.9%), FEV1 0.58L (%FEV1 35.6%).
Case E: VC 1.37L (%VC 61.6%), FEV1 0.96L (%FEV1 73.2%).

Results: The average height of waveforms of the breathing pattern increased about 3 times. 6MD in 2 cases and SpO2 in 3 cases increased in this study; however, the 3 other cases of 6MD and 2 other cases of SpO2 remained unchanged. Additionally, RR decreased in 4 cases. Since the start of the program, changes in the breathing pattern from mouth to nose breathing were observed.

Conclusions: This study revealed that BAT and PLB resulted in a decrease of RR and a change in the breathing pattern; furthermore, after this program, changes from mouth to nose breathing were observed.

P3538
Consumed by breathlessness – A critical interpretative synthesis
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Background: COPD is characterised by acute exacerbations (AE) often prompting hospital admission. The application of The Common Sense Model suggests that scrutinising the reported experiences of AE and constructing understanding of appraisals of AE may suggest ways to target interventions.

Methods: A systematic review was conducted. The terms: exacerbate* OR hospital* AND Chronic obstructive* OR emphysema OR bronchitis AND interview* were used to search electronic databases. Inclusion criteria included: primary research published in English of the patient’s experience of an AE, COPD, using qualitative methodologies. 8 full text papers were included.

Data were extracted by 3 researchers and constructs elicited by 3researchers via Reciprocal Translational Analysis.


Conclusions: Patients are fearful of their symptoms, this prompts constant vigilance and increased passivity. Targeted interventions that acknowledge intense fear and shape appraisals and acceptance may reduce distress and improve focus of self-management messages.

P3539
Effect on prevention of readmissions of a home-based education and exercise program implemented early after a severe exacerbation of COPD
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Introduction: Exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease COPD) represent a major health burden and the impact of early education and rehabilitation programs on readmission after an exacerbation are open to debate.

Objectives: To assess the effect of a two-month, home program (HP) based on education and exercise, implemented just after a severe exacerbation of COPD, on future hospital admissions and number of outpatients visits.

Methods: Following a case-control design, COPD patients who had just undergone treatment of an acute exacerbation were enrolled on to a multidisciplinary intervention HP that included education sessions and exercise training from the second day after discharge (1 group), for a period of 8 weeks, and were compared with a non-intervention group which received usual care (UC group). Primary outcome was the rate of severe exacerbations and secondary outcome outpatients visits during a 6-month follow-up period.

Results: 10 patients underwent the program and 12 patients were included in the control group (1 group mean [SD] age 72[7] years, 45[17%] predicted, m) 7 patients were readmitted to hospital with an exacerbation in the UC group (58%) and 1 in the 1 group (10%) (p<0.05). The difference in the number of outpatients visits in both groups was not statistically significant (1 group [IQR 0.2]; UC group [IQR 0.1]).

Conclusions: A post-exacerbation multidisciplinary HP in COPD may reduce re-exacerbation events that require admission over a 6-month period, without a significant increase in the number of outpatients visits.

P3540
Effectiveness of an additional tobacco-dehabitation-coaching (TDC) through nursing staff during inpatient pulmonary rehabilitation (PR)
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Background: Tobacco dehabitation (TD) is an essential component of PR. The nursing staff could be able to make an important contribution to TD. We studied the effectiveness of additional coaching from the nursing staff to an already existing comprehensive TD programme (TDP).

Methods: From February until July 2011 717 patients were admitted (3-week inpatient PRs) of which 26% were smokers. The classification of “smoker” was made in data consolidation served by patients, the physician’s estimation and biomonitoring (COHb). Intervention group (TDC + coaching through nursing staff = TDC): All smokers within the observed ward were invited to short supportive conversations by the nursing staff (in the first week twice a day, in the following weeks twice a week). In the observed time span 336 patients (95 of which smokers) were assigned to the ward with the associated pilot study. 63 smokers participated in the offered TDC voluntarily (78% male, 53.9 ± 8.1 y). 61 patients regularly used NRT. The control group consisted of 381 consecutive patients from a different ward, observed within the same time span, of which 90 were smokers (59% male, 52.9 ± 9 y). These patients took part in the same TDP, but without TDC.

Results:

Discussion: Those smokers who took part in the TDC refrained from smoking significantly more often than those who did not obtain this support.

P3541
Retrospective survival of COPD patients according to disease stage and pulmonary rehabilitation program
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The aim of this study was to examine the retrospective survival of patients with chronic obstructive pulmonary disease (COPD) according to type of pulmonary rehabilitation (PR) program and Global Initiative for Obstructive Lung Disease (GOLD) stage.

Retrospectively, 193 patients (mf 92/101, mean age 69.2 ± 8.6 SD) receiving PR were studied with lifetable analyses. FEV1 % pred was significantly different in the in-patient (n = 72), out-patient (n = 72), and maintenance group (n = 49) [mean 54.5 ± 21.8 SD, 52.2 ± 17.7, and 42.9 ± 15.0, respectively (p < 0.001)]. The evaluated impact of variables on survival in the three groups was significant for age, FEV1, and the use of long-term oxygen therapy (LTOT) (p < 0.001, HR 1.06, p < 0.01, HR 0.98, and p < 0.005, HR 2.18, respectively). Mean survival was eight years in GOLD stage 4 (n = 22), six in stage 3 (n = 79), and >10 in stage 1 (n = 18) and 2 (n = 74). The impact of the evaluated variables on survival in the GOLD stages was significant for age, LTOT and stage 3 (p < 0.005, HR 1.05, p < 0.01, HR 2.33, and p < 0.02, HR 4.24, respectively). For the in-patient, out-patient and maintenance group days of PR were mean 30.3 ± 20.4 SD, 18.9 ± 10.4 and 30.6 ± 20.3, respectively (p < 0.001), stays in hospital 0.35 ± 0.85, 0.86 ± 1.46, and 1.17 ± 1.60, respectively (p < 0.003), and days in hospital 2.90 ± 8.89, 4.78 ± 8.26, and 9.04 ± 15.69, respectively (p < 0.010).

In conclusion, patients with GOLD stage 4 lived significantly longer than stage 3. Older age, decreased pulmonary function and LTOT predicted poorer survival in all PR groups. In addition to older age and LTOT, stage 3 predicted significantly poorer survival.
P3542 Pulmonary rehabilitation affects lung hyperinflation and cardiovascular response in exercise in COPD
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Background: Pulmonary rehabilitation (PR) including exercise training has been reported useful for idiopathic pulmonary fibrosis (IPF) patients. The aim of this study was to compare the characteristics of five exercise measurements in evaluating the efficacy of PR in IPF patients.

Methods: Twenty-three COPD patients (9F; age 70 yrs ± 8; BMI 28 kg/m² ± 5) with moderate to severe airflow obstruction (FEV₁/FVC range: 65-36%) admitted to a 6-week PR course performed a pre-to-post evaluation of lung function test and symptom-limited cardiopulmonary exercise test (CPET). Inspiratory capacity (IC) manoeuvres, VO₂ dyspnoea (D) and leg fatigue (F) were assessed during the CPET. Cardiac response was also assessed by means of oxygen pulse (VO₂/H), product of systolic blood pressure and heart rate normalized for the maximum workload (DP/W), and heart rate recovery at the 1st min (HRR).

Results: Workload (W) and Maximum oxygen uptake (VO₂max) increased from 61.2 W ± 23.7 to 74.5 W ± 33.4, p= 0.002, and from 23.7 to 74.5 W ± 33.4, p= 0.002, respectively) following PR. The IC for a given W significantly changed from 0.03 L/W ± 0.01 to 0.02 L/W ± 0.01 (p=0.01). VO₂/H increased from 4.1 L/min/bpm ± 2.7 to 9.8 L/min/bpm ± 2.7 (p=0.006). DPW decreased from 352.2 ± 103.3 to 288.7 ± 113.2 (p=0.002), and HRR changed from 8.6 bpm ± 6.7 to 13.3 bpm ± 8.8 (p=0.007) at peak of exercise. Moreover, D (from 1.3 ± 0.5 to 1.3 ± 0.6, p=0.005) and F (from 1.3 ± 0.6 to 0.98 ± 0.56, p=0.005) reduced at peak/W.

Conclusions: Our study shows that training effect during rehabilitation course in COPD is associated with significant reduction of lung hyperinflation and improved cardiovascular response to exercise.

P3543 Endurance time is the most sensitive exercise measurement for evaluating pulmonary rehabilitation efficacy in patients with idiopathic pulmonary fibrosis
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Kensuke Kataoka3, Tomoya Ogawa1, Fumiko Watanabe1, Jun Hirasa1, Kazuyuki Tabira3, Jun Hirose1, Fumiko Watanabe1, Jun Hirasa1, Kazuyuki Tabira3

Objective: Pulmonary rehabilitation (PR) has been reported effective for improving exercise capacity and HRQoL in patients with idiopathic pulmonary fibrosis (IPF). It is unknown which exercise measurements are more suitable for evaluating PR efficacy in IPF patients. The purpose of the present study was to compare the characteristics of five exercise measurements in evaluating the efficacy of PR in IPF patients.

Methods: We performed a case-control study in which 53 IPF patients were divided into the PR group and the control group (C group). The PR group underwent a 6-week PR course performed a pre-to-post evaluation of lung function test and symptom-limited cardiopulmonary exercise test (CPET). Inspiratory capacity (IC) manoeuvres, VO₂ dyspnoea (D) and leg fatigue (F) were assessed during the CPET. Cardiac response was also assessed by means of oxygen pulse (VO₂/H), product of systolic blood pressure and heart rate normalized for the maximum workload (DP/W), and heart rate recovery at the 1st min (HRR).

Results: Workload (W) and Maximum oxygen uptake (VO₂max) increased from 61.2 W ± 23.7 to 74.5 W ± 33.4, p= 0.002, and from 23.7 to 74.5 W ± 33.4, p= 0.002, respectively) following PR. The IC for a given W significantly changed from 0.03 L/W ± 0.01 to 0.02 L/W ± 0.01 (p=0.01). VO₂/H increased from 4.1 L/min/bpm ± 2.7 to 9.8 L/min/bpm ± 2.7 (p=0.006). DPW decreased from 352.2 ± 103.3 to 288.7 ± 113.2 (p=0.002), and HRR changed from 8.6 bpm ± 6.7 to 13.3 bpm ± 8.8 (p=0.007) at peak of exercise. Moreover, D (from 1.3 ± 0.5 to 1.3 ± 0.6, p=0.005) and F (from 1.3 ± 0.6 to 0.98 ± 0.56, p=0.005) reduced at peak/W.

Conclusions: Our study shows that training effect during rehabilitation course in COPD is associated with significant reduction of lung hyperinflation and improved cardiovascular response to exercise.

P3546 Early versus late pulmonary rehabilitation on anxiety and depression in chronic obstructive pulmonary disease patients with acute exacerbations
Liv Karin Vesteng1, Anne Edvardsen, Karianne Spetaas Henriksen, Siri Skumlien.

Objective: To study the effect of a cost and home based PR program & to compare the improvement in outcome in non PR group.

Results: The mean 6MWD showed an average increase of 75.72 meters in the study group, while an average decrease of 2.1 meters in control group. Mean value of study group was higher for 6-MWD results and difference between the two groups was statistically significant (p<0.05). AQ-20 showed a mean decrease of 6.12 in study group and 1.5 in control group which is also statistically significant (p<0.05).

Conclusion: A simple outpatient-based PR can improve health status, quality of life and exercise capacity in patients with COPD.

Clinical implications: This can be promoted on a wide scale & can benefit a lot of COPD patients in resource poor setting.

P3547 Role of low cost pulmonary rehabilitation programme in COPD in rural area of India
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Background: Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the world (WHO 2000). COPD patients appear to benefit from Pulmonary Rehabilitation (PR) & maintenance of physical activity, improving their health status, decreased dyspnoea & fatigue (Berry MI et al, AJRCCM 1999; 160:1248-53). PR is done with exercise equipment, supporting staff & follow up. In resource poor areas this is not possible. We evaluated the effect of home based PR programme in COPD patients in rural areas of India.

Methods: COPD patients in stable state who were ready to follow up for 12 weeks at 2 weeks interval were included, 40 patients who completed the PR formed the study group while 20 patients who were not included in PR formed control group. The Airways questionnaire-20 score (AQ-20) and the 6 minutes walk distance (6-MWD) were analysed in both groups, who continued on a similar drug management.

Objective: To study the effect of a low cost and home based PR program & to compare the improvement in outcome in non PR group.

Results: The mean 6MWD showed an average increase of 75.72 meters in the study group, while an average decrease of 2.1 meters in control group. Mean value of study group was higher for 6-MWD results and difference between the two groups was statistically significant (p<0.05). AQ-20 showed a mean decrease of 6.12 in study group and 1.5 in control group which is also statistically significant (p<0.05).

Conclusion: A simple outpatient-based PR can improve health status, quality of life and exercise capacity in patients with COPD.

Clinical implications: This can be promoted on a wide scale & can benefit a lot of COPD patients in resource poor setting.
P3547 Pulmonary rehabilitation in patients referred for lung transplantation
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The purpose of this study is to prospectively examine efficiency of Nordic Walking, a low cost, accessible and proven beneficial form of physical exercise as form of pulmonary rehabilitation in patients referred for lung transplantation.

Material and methods: 22 patients, referred for LT in Dyrt of Lung Diseases and Tuberculosis were invited to take part in the study. The PR program, which conducted for 18 weeks, was based on Nordic Walking exercise training. Lung function tests (FVC, FEV1), mobility (6 minute walking test (6 MWT)), rating of dyspnea (Borgs scale, MRC and Baseline Dyspnea Index) and quality of life (SF-36 and SGRQ) were performed before and after the complete exercise program.

Results: No adverse events were observed after completed the PR program in patients referred for LT. After 18 weeks of PR with Nordic Walking programme we observed significant (p<0.05) increase of mean results of 6 MWT (310.2 vs. 372.1). Also results of lung function test showed improvement (FVC, FEV1) but without statistical significances. No statistical significant differences were observed in perception of dyspnea (MRC, OGD, Borgs scale) before and after completed the study. SGRQ showed significant (>4 pts) improvement in activity score. General health quality of life questionnaire (SF-36) showed improvement in domains: Physical Functioning, Role-Physical, Bodily pain, General Health and Social Functioning but only in Role-Physical domain the improvement was statistically significant (p<0.05).

Conclusion: Pulmonary rehabilitation with Nordic Walking programme is safe, cost-effective and easy to use in end stage lung disease patients referred for LT resulting improvement in mobility and quality of life.

P3548 Home-based pulmonary rehabilitation program following a severe exacerbation of COPD
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Introduction: Pulmonary rehabilitation (PR) is an effective intervention for patients with chronic obstructive pulmonary disease (COPD) and is recommended by clinical guidelines. Timing of referral for rehabilitation, immediately after exacerbations of COPD, to later on while the patient is in a stable state, however, is open to debate.

Objectives: To evaluate the effects of a two-month, home-based PR program on dyspnea, exercise capacity, muscle strength and activities of daily living in COPD patients after a severe exacerbation.

Methods: COPD patients who had just undergone inhospital treatment for a severe exacerbation were enrolled on to a multidisciplinary home PR program within 48-72 hours of discharge. The program consisted of twice-weekly sessions for a period of 8 weeks. Lung function, oxygen saturation, exercise capacity (six-minute walk distance test), quadriceps strength, sedentary index and London Scale Scoring were recorded at hospital discharge and after 2 months. Body weight and muscle mass measurements were compared to determine the change in the measured variables after the program (paired t test).

Results: 10 patients underwent the program (mean [SD] age 71.90 [7.1] years, baseline FEV1 42.71[11] % predicted). Significant improvements were attained after the program in exercise capacity (pre 280m and postprogram 354m p<0.05), oxygen saturation (pre 91.4%, and postprogram 94.4% p<0.001) and London Scale Scoring (pre 22.1 and postprogram 14.9 p<0.001). No statistically significant improvements in lung function, BODE index and quadriceps strength were observed.

Conclusions: Post-exacerbation PR improve exercise capacity tolerance in COPD patients with a significant impact on activities of daily living.

P3549 Dry sodium chloride aerosol in rehabilitation of patients with COPD
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Aim of the study: The main objective was to estimate the efficacy of inhaled dry sodium chloride aerosol (DSCA) in rehabilitation therapy (RT) of patients with COPD.

Objects and methods: It was double blind placebo study. 72 patients (pts) with moderate and mild stage of COPD were recruited. They were randomized in 2 groups - interventional group (IG) (21 m, 18 f, 60.3±10.8 yrs) and control group (CG) (22 m, 11 f, 58.5±8.9 yrs). All patients received RT. daily procedures of chest massage, light radiation, physical exercises. Pts of IG were treated with the DSCA (45 min twice a day for 14 days). DSCA containing particles with size of 1-5 μm and level of mass concentration in the room of 10-15 mg/m3 was produced by ultrasonic generator GBA-01.17 (Haimone, Lithuania). CG received placebo inhalations (inhalations with room air) instead of DSCA. Clinical, functional parameters and measures of health-related quality of life (HRQL) by SF-16 and LCQ (10 items) were estimated before and after the complete RT procedures and in 3 months.

Results: Improvements of clinical symptom scores were observed in the both groups after the course of RT (p<0.05), but in 3 months positive effect was noticed only in IG (before-13.5±4.4; after-9.1±4.3; in 3 months-9.6±4.3; p<0.05). Measures of LCQ were changed significantly after RT only in pts of IG, received DSCA (3.5±2.5 and 5.2±4.6; p<0.05). Positive changes of physical functioning measures (SF-16) were observed in IG and CG groups after RT, but they have been kept till 3 month only in IG.

Conclusions: Application of inhalations of DSCA on the background of the RT in pts with COPD renders to positive effect.

P3550 Pulmonary rehabilitation and the association of anaemia with clinical and functional parameters in patients with COPD who referred to a pulmonary rehabilitation programme
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Polycytemia is commonly associated with COPD but recent reports suggest that anaemia is also prevalent. Aim: The aim of this study was to determine the prevalence of anaemia in patients with COPD who referred to PR programme and to explore the clinical and functional associations between anaemia.

Materials and methods: 398 COPD patients who referred to Atatürk Chest Disease and Chest Surgery Training Hospital PR Center between January 2008 and December 2011 were evaluated retrospectively and 176 patients were included. Patients were classified as anaemic,polycthyemic or normal. Dose was assessed with the MRC and EQ-5D dyspnea, quality of life assessed with SGRQ. Exercise capacity was measured using the ISWT, ESWT, body composition was assessed with BMI, FM% and depency were assessed with the HADS. Results: Anaemia was present in 14 (3.5%) patients and polycythaemia in 24 (6.1%) patients with COPD. Exercise tolerance and health-related quality of life (HRQL) by SF-16 and LCQ (10 items) were calculated. No statistically significant differences were observed in any the domains: Physical Functioning, Role-Physical, Bodily pain, General Health and Social Functioning but only in Role-Physical domain the improvement was statistically significant (p<0.05).

Conclusion: Anaemia is associated with poor clinical and functional outcomes in patients with COPD who referred to PR programme and provide support for the evaluation and monitoring of anaemia in these patients.

P3551 Outcomes of pulmonary rehabilitation according maintenance treatment in real life COPD patients
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Pulmonary rehabilitation (PR) improves health status as well as exercise tolerance in symptomatic patients with chronic obstructive pulmonary disease (COPD).

Maintenance bronchodilator (BD) therapy is recommended to improve symptoms and could enhance ability to train and augment benefits of PR.

We aimed to evaluate if the modality of inhaled medication therapy could improve exercise tolerance and health-related quality of life (HRQL) in real life patients with COPD who were referred to PR.

We compared HRQL (Saint George Respiratory Questionnaire; SGRQ) and six minute walk distance (6MWD) after PR according to maintenance treatment: no long-acting bronchodilators (N); long-acting β2-agonist or anticholinergic BD (LABD); combined treatment with long-acting β2-agonist plus inhaled corticosteroid (double therapy; DT); or DT plus long-acting anticholinergic BD (triple therapy; TT). All groups used short acting bronchodilators as needed.

One hundred forty five COPD patients (64% males) who attended PR and classified according their treatment. Twenty nine received no maintenance therapy; TT). All groups used short acting bronchodilators as needed.

No difference was found related to baseline spirometric, 6MWD and SGRQ values. The whole sample presented significant improvements in total and specific domains of SGRQ (p<0.05) as well as 6MWD (53.1±65.7; p<0.01) with no difference among treatment groups.

In conclusion, in a real life cohort of COPD patients the specific maintenance therapy did not interfere in clinical PR outcomes.
**P3552**

**Influence of pulmonary rehabilitation in patients with COPD in respiratory hospital admissions (Rha) and emergency department visits (EDv)***

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**Introduction:** Pulmonary Rehabilitation (PR) provides significant clinical benefits to patients with severe and very severe COPD

**Objectives:** To verify the effect of PR on COPD patients in our Hospital, not only in terms of Lung Function Tests but also in Rha and EDv.

**Methods:** 148 patients were studied, 106 started PR from January 2009 to October 2010 and 42 did not.

We compared EDv and Rha of patients for one year before and after receiving PR and also with the patients who did not participate. Changes in FEV1 and in 6MWT (6-minute walk test) were also studied.

**Results:**

<table>
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<tr>
<th>Table 1. Data of 106 patients who followed PR</th>
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<tr>
<td>Before PR</td>
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<td><strong>EDv</strong></td>
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<td>FEV1*</td>
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<td>6MWT*</td>
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*Statistically significant.

Both EDv and Rha show a decrease, being statistically significant in the case of EDv. Also FEV1 and 6MWT show a statistically significant improvement.

**Conclusions:** PR is an effective intervention in treating COPD patients, as it shows significant clinical improvements by increasing capacity to perform physical exercise and by lowering EDv and Rha rates.

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**P3553**

**Six months and one year follow up of COPD patients who had oral nutritional supplement therapy as a part of pulmonary rehabilitation program**

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We evaluated long term efficacy of oral nutritional supplement (ONS) which was indicated according to body composition abnormalities in patients with COPD. 41 patients who were given ONS were enrolled. Pulmonary function tests, quality of life, exercise capacity, dyspnea sensation, and body composition data were recorded before and after PR program, at 3, 6 month and in 20 patients 1 year follow-up visit.

Table1 summarizes parameters of patients that were grouped according to ONS duration. In all groups ONS lead to sustained improvements of exercise capacity, dyspnea, symptom management, and body composition at 3 and 6 month. Quality of life was protected in group 1, in other groups it was over baseline values despite loss at 6 month. Both exercise capacity and quality of life decreased at the end of the first year, exercise capacity was lower than baseline. Improvements in symptom control, dyspnea, body composition were protected in one year follow up.

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<td><strong>Group 1</strong></td>
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<tr>
<td>Patients numbers</td>
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<td>Age (years)</td>
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<tr>
<td>Tobacco pack/years</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>FFMI (kg/m²)</td>
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<td>MIP (cmH₂O)</td>
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<td>1RM</td>
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<td>ISWT (meters)</td>
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<td>SGRQ Symptom</td>
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<tr>
<td>SGRQ Activity</td>
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<td>SGRQ Impact</td>
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<td>SGRQ Total</td>
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</table>

As the changes of body composition are correlated with prognosis and survival in COPD, all patients who are scheduled to receive a PR program should be evaluated and be given ONS if necessary.

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**P3554**

**Intensity of training and physiologic and clinical changes after pulmonary rehabilitation programme in patients chronic obstructive pulmonary disease***

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The aim of the study was to evaluate the efficacy of a pulmonary rehabilitation programme (PRP) in relation to the intensity of exercise training achieved during PRP in patients with Chronic Obstructive Pulmonary Disease (COPD). We performed a retrospective analysis on 92 COPD patients (FEV1% 54) who participated in a PRP between 2007 and 2009. All subjects did an outpatient training exercise programme lasted 2 months. The training sessions were 20 and each session consisted in 30 min of cycleergometer exercise associated with 30 min of upper limb exercise. Before and after the PRP the following measurements were done: Changes in 6MWT and cardiopulmonary exercise test (CPET), upper and lower limb endurance (UELLLE), MRC, MMIP and MEP, quality of life by SGRQ. Patients were divided into two groups based on the achievement (Group 1) or not (Group 2) of high intensity training, meaning the intensity of 75% of Wmax reached in CPET pre PRP, sustained for as long as 25 - 30 minutes for 8 final sessions of the PRP.

After PR changes from baseline were significant for all measurements in Group 1, but not in Group 2. Therefore, reaching and maintaining high intensity of exercise training is associated with better results obtained by PRP in COPD patients.

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**P3555**

**Two-years of a community maintenance follow-up program in patients with COPD***

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**Introduction:** Benefits of short-term outpatient rehabilitation programs (RP) have been showed in patients with COPD that decline gradually over one year after discharge. Moreover, the capacity of maintenance follow-up programs to preserve the benefits of pulmonary rehabilitation programs is controversial. Therefore, the objective of this study was to examine the efficacy of a two year, supervised, community maintenance follow-up program to maintain the benefits of an initial 12-week outpatient RP.

**Methods:** Eight patients (moderate to severe) COPD men (GOLD), dyspnea 2-3 (MMRC) were included. All patients performed a two years, supervised, community maintenance program (CMP) (twice a week) following a 12-week outpatient rehabilitation program (twice a week). Maximal dynamic resistance (IRM) of the upper limb (chest press and dorsal) and lower limb (leg press and leg extension), and peak power output at 70% of IRM in leg press were measured. Analysis of variance with repeated measures was used for statistical analysis.

**Results:** Initial data from the RP were used as a baseline for all outcomes. IRM in leg press increased (P <0.001) by 20% in RP and 22% in CMP from baseline. IRM in chest press increased (P <0.001) by 32% in RP and 45% in CMP. IRM in knee extension and dorsal increased (P <0.001) by 36 and 55% in RP and 38 and 35% in CMP, respectively. Power output of the lower limb at 70% of IRM increased by 33% in RP and 30% in CMP (from 55±1.08 to 73±4.12 to 72±25.8 W, P <0.05) from baseline.

**Conclusions:** A low volume, supervised, CMP is able to maintain and improve the benefits of a short-term RP in COPD patients. Supported by Ministries of education of Spain and Health Department of Navarre.
Attendance vs prescription: Exercise attendance rates for people with COPD: Systematic review

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The duration, frequency, mode and intensity of exercise programs for people with COPD are recommended by international consensus statements. The question for this review was: How consistently are a priori criteria and attendance rates reported for people with COPD participating in exercise programs? A systematic search of CINAHL, Embase, and CENTRAL (Cochrane), was undertaken in October 2011. Studies were eligible for inclusion if published in English, included people with COPD, assessed the effects of rehabilitation as the primary intervention (+/- adjunctive strategies) and included at least 2 weeks exercise training (+/- education). There were no limits placed on intervention site (hospital, community, home) or publication date. Data extraction processes were confirmed prospectively for consistency (>80% agreement), with pairs of reviewers extracting data independently and disagreements resolved by consensus. The search returned 752 citations (497 citations excluded from title and abstract) with 255 full text articles retrieved for review. Of the 174 articles reviewed to date, a further 21 citations have been excluded. Of the 153 studies, 100% report the at training sessions (n = 83) and less than a third of these report a priori criteria for attendance (n = 23, 28%). These preliminary analyses suggest that reporting of attendance rates in COPD exercise trials is low, which makes it difficult to calculate dose-response relationships between exercise participation and improvements in health outcomes.

P3556

The effectiveness of a home-based pulmonary rehabilitation program (PRP) in people with COPD

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Background: PRP has been shown to be one of the most effective interventions for COPD. However several barriers have limited participation. To overcome some of these barriers a Home-Based PRP was offered to people who were unable to attend the Hospital-Based PRP.

Aim: To assess the effectiveness of a Home-Based PRP in improving exercise capacity and quality of life in people with COPD unable to attend the Hospital-Based PRP.

Methods: A retrospective review of patients recruited to a Home-Based PRP at Liverpool Hospital between January 2009 and November 2010. 6MWT and SGRO were used. Data analysed by SPSS using the Paired T Test.

Results: 67 patients were recruited with an average age of 72 years of these 33% completed the PRP and post PRP assessment, and 30% completed the 12-month post PRP follow up. At post-PRP 6MWT improved by 36.7m P=0.001 and SGQRI improved by 9.5% P=0.003. At 12-months (compared to baseline) post-PRP 6MWT was -12.6m P=0.5 and SGQRI improved by 3.5% P=0.4. Difference in outcomes between males and females were also noted as outlined in the table.

Conclusions: A Home-Based PRP can be a suitable alternative for patients who are unable to attend a Hospital-Based PRP. However, a CTR with appropriate sample size would be required.

P3558

Referral to pulmonary rehabilitation amongst patients admitted to hospital with COPD

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Background: Pulmonary rehabilitation (PR) is recommended in the management of patients with COPD. However, little information is available about the incidence of referral to PR amongst COPD patients.

Aim: This study prospectively examined consecutive patients admitted to hospital with a primary diagnosis of COPD, to determine the incidence and characteristics of patients referred (versus not) to PR.

Method: Demographic, disease and admission characteristics were collected using prospective and retrospective medical record review, and patient interview at the end of hospital admission. Information about referral to and attendance at a PR program in the past, and referral to PR from the current admission, were obtained from patient interview and confirmed in medical records.

Results: From 190 patients, 64 were recruited to interview (77 excluded due to insufficient English language, cognition, or missed; 43 were repeat admissions and 6 declined). Included patients were aged 72(12) years (mean(SD)), with FEV1%predicted=44(19)%; 61% had a respiratory physician involved in their ongoing care. Of the 64 patients interviewed, 39 (61%) had been referred at some point since diagnosis to PR, but only 15 (24%) had attended. During the current admission, 20% (n=13) had been referred to PR. In 12 cases (19%), PR had been discussed but no referral made, and in 39 cases (61%) PR had not been discussed.

Conclusion: A proportion of COPD patients admitted to hospital had not been referred either in the past, or at the time of the index admission, to PR. Further analysis of this data to determine characteristics associated with referral (or not) will help direct strategies to implement PR in more people with COPD.

384. CT findings: educational posters

P3559

The evaluation of pulmonary involvement pattern in high resolution computerized tomography of patients with rheumatoid arthritis in Iran from 2010-2011

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RA is a chronic systemic disease Pulmonary involvement is the most frequent manifestation of rheumatoid arthritis. The goal of this study was to assess pulmonary involvement pattern in patients with RA by HRCT Scan in Bandar-abbas.

Methods: In this prospective study fifty patients with RA referred to rheumatology clinic in Bandar Abbas were evaluated. Data were obtained included: age, sex, duration of disease, methotrexate usage, smoking, pulmonary chronic disease, clinical symptoms of pulmonary involvement and patient self assessment. After clinical and laboratory investigations, HRCT were performed.

Results: Mean age of 49.3 years. Three patients with respiratory symptoms and 47 patients without pulmonary complaint. The most frequent pulmonary involvement in HRCT findings sub pleural fibrosis (26%) and followed by air trapping and mosaic pattern (20%), pleural thickening (14%), honey combing (10%), pulmonary nodules (8%), oblong bronchial thickening (8%), ground glass pattern (8%). Bronchectasis (8%), Alveolar (2%) and reticular pattern (2%). There was no statistically significant relationship between lung involvement pattern and, rheumatoid factor positivity. Anti CCP and methotrexate usage but correlation between HRCT findings and age, duration of the disease, disease activity (DAS 28) and respiratory symptoms was significant (P<0.05).

Conclusion: The results of our study indicate HRCT was useful for evaluation of pulmonary involvement in patients with RA although these patients had no respiratory symptoms. Larger and prospective studies are needed to assess of lung involvement pattern in HRCT in asymptomatic RA patients.
Computerized tomography findings of pulmonary nocardiosis at diagnosis
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Background: Nocardiosis is a rare chronic respiratory infection with varied clinical presentations. The aim of the present study was to analyze the radiographic features of pulmonary nocardiosis at diagnosis.

Methods: Ten consecutive patients with pulmonary nocardiosis were evaluated. The findings on chest CT scans and the CT manifestations of the disease were retrospectively reviewed.

Results: Three radiologists (H.I. and M.I.), who were board-certified by Japan Radiological Society, diagnosed and standardized the radiographic features present in the 10 patients. The findings of high-resolution CT (HRCT) imaging in patients with pulmonary nocardiosis were as follows: ground-glass opacity (GGO) (100% of cases), consolidation (60% of cases) and nodules (50% of cases). Among these, 8 patients (80% of cases) showed bilateral findings. The nodules were predominantly unilateral in 2 patients (20% of cases). The nodules were predominantly unilateral in 2 patients (20% of cases). The nodules were predominantly bilateral in 2 patients (20% of cases). The nodules were predominantly unilateral in 2 patients (20% of cases). The nodules were predominantly bilateral in 2 patients (20% of cases). The nodules were predominantly bilateral in 2 patients (20% of cases).

Conclusion: Pulmonary nocardiosis tends to cause bilateral GGO and consolidation at diagnosis. At least 80% of cases showed bilateral findings. These findings may be useful for the diagnosis of pulmonary nocardiosis.
Background: The study of the normal ageing process is becoming more important as life expectancy increases. To our knowledge, no studies reporting chest HRCT findings in asymptomatic, non-smoking elderly subjects with both normal echocardiogram and PFTs were conducted. **Objectives:** To describe chest HRCT findings in a population of asymptomatic, non-smoking elderly subjects with normal echocardiogram and PFTs. **Methods:** After institutional approval, patients over 65 years old recruited from the Geriatrics outpatient clinic were studied and compared with normal volunteers under 50 years old. Written consent was obtained. Participants were submitted to a questionnaire, echocardiography and PFTs for assessing absence of disease, and afterwards submitted to chest HRCT. Scans were interpreted and findings were scored, including pulmonary nodules, cysts, parenchymal bands, interlobular septal thickening, reticular opacities and bronchiectasis. Non-parametric tests were used for the statistical analysis, with P < 0.05 representing statistical significance. **Results:** The HRCT findings of 53 asymptomatic subjects over 65 years old (mean age 74.6 y) were compared with those of 24 volunteers under 50 years old (mean age 35.7 y). The prevalence of abnormal scans was higher in the elderly (84.9% vs 12.5%, P < 0.001). Comparing both groups, significantly more elderly subjects had scans with parenchymal bands (35 vs 3; P < 0.001), interlobular septal thickening (12 vs 0; P = 0.014) and lung nodules (10 vs 0; P = 0.026). **Conclusion:** Parenchymal bands, interlobular septal thickening and lung nodules are present in asymptomatic elderly subjects and may represent normal ageing of the lungs.

P3566 Thoracic manifestation of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease: CT findings in 149 patients

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**Objective:** The purpose of this study was to assess pulmonary CT findings in patients with myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease. **Materials and methods:** The pulmonary CT scans of 149 patients with elevated MPO-ANCA levels (77 with microscopic polyangiitis, 8 with Churg-Strauss syndrome, 12 rapidly progressive glomerulonephritis and 42 with unclassified disease) were retrospectively assessed with regard to parenchymal and mediastinal abnormalities. **Results:** The CT findings consisted of ground-glass attenuation in 110 Patients (74%), consolidation in 67 patients (45%), traction bronchiectasis in 46 patients (31%), and honeycomb in 46 patients (31%). Consolidation, thickening of bronchovascular bundle, interlobular septal thickening, and pleural effusion were more frequently observed in patients with classified disease than in those without an unclassified disease. Honeycombing was more frequently observed in patients with unclassified disease than in those with classified disease. **Conclusions:** The CT findings in patients with MPO-ANCA consisted mainly of ground-glass attenuation, consolidation, and traction bronchiectasis. Consolidation, thickening of bronchovascular bundle, interlobular septal thickening, and pleural effusion were more frequently observed in patients with classified disease than in those with unclassified disease. In contrast, honeycombing was more frequently observed in patients with unclassified disease than in those with classified disease.

P3567 Sarcoidosis; the great mimicker: A CT study

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**Purpose:** Assessing manifestations of sarcoidosis in chest CT to make clinicians and radiologists consider this disease in daily practice. **Material and methods:** CT and HRCT scans of 59 patients with biopsy-proven sarcoidosis were reviewed. **Results:** Many of the classical findings including bilateral hilar and paratracheal adenopathy and other forms of parenchymal involvement like bronchovascular bundle thickening, nodularity, fibrobronchiectatic and fibrocavitary changes affecting upper and middle zones as well as pleural thickening were noted as previously mentioned by many authors. But what highlights our study is the interesting uncovering of 30.5% unilateral and bilateral asymmetric parenchymal involvement, also scattered parenchymal metastasis-like nodules (20.3%), Patchy ground glass opacities mimicking BOOP (33.9%), the galazy nodular pattern (11.9%) and enlargement of main pulmonary artery (23.7%).

Parenchymal manifestations are shown in Fig. 1. In addition to the usual widely known mediastinal lymphadenopathy stations, we found a considerable amount of hilar involvement (55%), paraseptal ophthalmic (22%), and 6.8% intraaparenchymal lymph nodes and the least common pulmonary ligament lymph nodes (1.7%).

**Conclusion:** Sarcoidosis can present with unusual findings in uncommon sites so whenever looking at a pulmonary CT we should ask: “Am I dealing with sarcoidosis?”

P3568 MDCT differences between cardiac edema, viral pneumonia and ARDS

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**Purpose:** Acute respiratory distress syndrome (ARDS) is a type of severe, acute lung dysfunction affecting all or most of both lungs that occurs as a result of illness or injury. The main radiological problem is to see differences with cardiac edema or viral pneumonia. Main purpose is to show possibilities of MDCT in detection of important differences. **Methods:** We examined 356 patients with ARDS, 656 with viral pneumonia and 456 with cardiac edema. Patients were examined by 16/64 MDCT using virtual bronchoscopy, perfusion and pulmonary angiography. There were 194 male and 162 female patients from 13 to 82 years with ARDS, 303 male and 353 female with viral pneumonia, 9 to 54 years; 201 male and 255 female, 54 to 76 years old. **Results:** ARDS was caused by injury in 204 cases and with acute illness in 148 cases. 6 cases were without known cause, probably drug abuse. Patients were with hypoxia, PF ratio was less than 200 and all had bilateral x-ray changes. The usual diagnostic approach is to perform standard x-ray of the lung but in cases of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease the main problem is to see differences with ARDS and from pneumonia; also if patients have cardiac problems in history it is not necessary that they do not have ARDS. There are 2 major radiological differences: first is quality of alveolar fluid and second is condition of alveolar wall. Also important differences are in condition of airways and blood vessels.Different diagnosis was made in 18.9% of patients. **Conclusion:** Fast diagnoses for patients in critical care units are vital to patient life. MDCT with virtual bronchoscopy, perfusion and pulmonary angiography can give us fast answer and prediction. MDCT can be performed in patients with mechanical ventilation.
Pharmacology, Gifu University School of Medicine, Gifu, Japan

1Second Department of Internal Medicine, Gifu University School of Medicine, vascularity of sarcoidosis

In cases with aberrant vessels going up to the diaphragm a seques-

the celiac trunk to a lung sequester in the right lower lobe.

Endoscopic narrow-band imaging-quantitative assessment of airway

microvessel network that could be seen hardly with the ordinary filter. This com-

Intensive care unit physicians are often confronted with patients who have a per-

It was our aim to investigate the ability of narrow-band

In vivo

P3571

In vivo visualization of endobronchial tumor cells using an endocytoscopy system

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Background: Endocytoscopy system (prototype, BF-Y0005, Olympus Medical Systems Co., Tokyo, Japan) is a bronchocytoscope visualizing at a high magnification of 450 times on a 14-inch video monitor. Cellular structures can be visualized in real-time during bronchoscopy.

Objectives: To evaluate the diagnostic utility of endocytoscopy on endobronchial tumors.

Methods: Between July 2009 and April 2011, 19 cases with endobronchial tu-

Patients and methods: The study included 65 patients with suspected lung cancer scheduled for bronchoscopy. After identification of endoscopically visible tumor patterns visualized by NBI as described by Shibuya and histology of lung cancer. Broad spectrum of diagnostic bronchoscopy

P3570

Endoscopic narrow-band imaging-quantitative assessment of airway vascularity of sarcoidosis

Koumei Yanase1, Yasushi Ohno1, Fumihiko Kamiya1, Junki Endo1, Fumita Ito1, Norihiko Funagachi1, Hiroshi Ishara2, Shinya Minatoguchi1, 1Second Department of Internal Medicine, Gifu University School of Medicine, Gifu, Japan; 2Pharmacology, Gifu University School of Medicine, Gifu, Japan

Introduction or background: Various changes of subepithelial vessels of the bronchial mucosa occur in some respiratory diseases. NBI is a new technology that improves the image contrast of the surface structure by adjusting the spectrum feature regarding the wavelength dependency of the light penetration depth into the tissue and the hemoglobin absorption. We have observed in sarcoidosis patients of subepithelial vessels using a narrow-band imaging of bronchofiberscope.

Aims and objectives: It was our aim to investigate the ability of narrow-band imaging in combination with computerized image analysis to quantitatively assess airway vascularity in sarcoidosis patients.

Methods: In consecutive sarcoidosis patients, the routine procedures, optical analysis of the main carina and the upper lobe carina were performed. From every site five representative pictures were chosen.

Results: A total of 16 sarcoidosis patients were analyzed. Increased numbers of vessels were found and these vessels were also observed in areas of cartilage. Angiogenesis or mucosal thickening was observed.

Conclusion: High magnification view with NBI revealed a clear fine subepithelial microvessel network that could be seen hardly with the ordinary filter. This com-

Figure 1: Abdominal ultrasound (CCDS) and MRI. Angiography showing an aberrant vessel from the celiac trunk to a lung sequester in the right lower lobe.

Conclusions: In cases with aberrant vessels going up to the diaphragm a seques-

385. The broad spectrum of diagnostic bronchoscopy

P3572

Follow-up using fluorescence bronchoscopy for the patients with photodynamic therapy treated early lung cancer

Handy Ali Mohammadien Mahmoud, Kazuya Kondo. Chest Department &

Tumor cavitary defects, such as cavity wall erosion, exhibited 100% correlation with pathological findings. The first side effects were recorded after 48 hours of photodynamic therapy.

Conclusions: Our results confirm that SAFE - 3000 allows accurate assessment of the quality and efficacy of PDT.

P3574

Relation between vascular patterns visualized by narrow band imaging (NBI) videobronchoscopy and histological type of lung cancer

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Introduction: Narrow Band Imaging (NBI) videobronchoscopy is a new technique for visualization of bronchial mucosa. It has shown to be efficient in lung cancer detection. The primary aim of this study was to evaluate relation between vascular patterns visualized by NBI as described by Shibuya and histology of lung cancer.

Patients and methods: The study included 65 patients with suspected lung cancer scheduled for bronchoscopy. After identification of endoscopically visible tumor NBI was used to determine predominant type of pathological vascular pattern (dotted, tortuous, abrupt-ending blood vessels – Shibuya descriptors). Pearson’s chi-square test was used to test statistical significance between vascular pattern and histological type of cancer.

Results: Lung cancer was confirmed in all patients.63.1% was diagnosed with squamous cell lung cancer (SCLC);24.6% had adenocarcinoma;9.2% had small cell (SCLC) and 3.1% large cell lung cancer(LC). Dotted blood vessels were significantly(p<0.000) associated with adenocarcinoma, identified in 68.4% adeno-

nocarcinoma and 31.6%SCLC. Tortuous blood vessels were identified in 72% SCC,8% adenocarcinoma,12%SCLC and 8% of LC. Tortuous blood vessels were significantly(p<0.000) associated with SCLC. Abrupt ending vessels were identified in 81% SCC, 14.3% SCLC and 4.8% adenocarcinoma, this type of blood vessels was also significantly associated(p<0.000) with SCC.

Conclusions: Dotted visual pattern of blood vessels identified during NBI video-

bronchoscopy is highly suggesting adenocarcinoma histology of lung cancer, while tortuous and abrupt ending blood vessels significantly suggest squamous cell histology of lung cancer.

P3575

Safety profile, efficacy and patient comfort with propofol sedation in outpatient fiberoptic bronchoscopy

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Introduction: Procedural sedation is suggested in outpatient bronchoscopy to
improve tolerance & patient satisfaction. Propofol, a short acting intravenous hypnotic, offers advantages over benzodiazepines/opiates.

Objectives: We analyzed the feasibility, efficacy & safety profile of propofol administered by a trained nurse for outpatient bronchoscopy.

Methods: A total of 276 flexible bronoscopies performed between 2009 & 2011 using propofol sedation only without premedication were retrospectively reviewed. Patient demographics, indications, type of procedure, procedure time, medication doses, comfort level on 10cm verbal analogue scale (VAS, 0-10) & adverse events were analyzed from procedure records.

Results: Of the 276, two-thirds (182, 66%) of patients were male with an average age of 56 years (range 18–92). An average weight of 73 kg. Indications included diagnostic BAL (127, 46%), TBLB (68, 25%), TBNA (41, 15%) & EBB (22, 8%). Average procedure time was 36 minutes (range 12–145). Average propofol dose was 1.86 mg.kg−1 (range 0.12–2.23 mg) while 37 received combined sedation (mean 2.74mg). No sedation related complications were reported. Increased duration of FB and age of 56 years (range 18–92) were attributed to hypoxia & bronchospasm. There were no procedure-related deaths. A majority (196, 71%) of patients reported VAS of 4-6 with good amnesia, while 56 (20%) had VAS > 6 & 24 (8.6%) had VAS < 3.

Conclusions: Propofol is an easy to administer, safe, & effective procedural sedative for outpatient bronoscopies providing acceptable comfort.

P3576 Lidocaine administration to the laryngopharynx for inducing anesthesia before bronchoscopy: A comparative study of Jackson’s spray method and ultrasonic nebulization

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Objectives: To compare the degrees of pain experienced by patients and additional intraoperative amounts of lidocaine required when lidocaine is administered using Jackson’s spray and an ultrasonic nebulizer.

Methods: Patients who were given laryngopharyngeal anesthesia before bronchoscopy were divided into 2 groups of 20 patients each: group A, which was given 4% lidocaine 5 mL by using Jackson’s spray, and group B, which was given 2% lidocaine 10 mL by using an ultrasonic nebulizer. The degrees of pain in group A were significantly higher than those in group B (A: 3.5 ± 1.2 vs. B: 2.2 ± 0.9, p = 0.03). An analysis based on patient age and smoking history showed that the rate of lidocaine use in group A was significantly high in elderly persons (less than 70 years of age) and smokers (p = 0.05).

Conclusions: Laryngopharyngeal anesthesia before bronchoscopy, the Jackson spray requires a large amount of lidocaine at the time of bronchoscopic examination for bronchoscopic time, compared with the ultrasonic nebulizer.
were used in ≥50%, and floroscopy systems were used in 99.8%. Biopsies were performed after discontinuation of therapy in patients receiving antipatecl clot drugs and anticoagulants in 96.7% and 97.4% of the facilities, respectively. Atropine was administrated for premedication in 67.5% of the facilities, a decrease from previous surveys. Intravenous sedation was given in 36.1% of the facilities. In 21.9% of these, the procedure was conducted in the outpatient clinic for ≤70% of patients. A bronchoscope was orally inserted in ≥70% of patients in 95.7% of the facilities. Intravenous access was maintained during the examination in 92.5% of the facilities, oxygen saturation was monitored during examinations in 99.0%, oxygen was administered in 97.6%, and resuscitation equipment was available in 96.6% of the facilities. Bronchoscopes were disinfected using an automatic washing machine, but glutaraldehyde was used in 42.2%.

**Conclusions:** Japanese-specific characteristics in bronchoscopic practice were identified. Whether procedures used in Japan meet international guidelines with respect to safety should be monitored continuously. In addition, a Japanese evidence-based consensus is needed.

P3580

The ratio of HBsAg, anti-HCV and anti-HIV positivity in patients indicated for fiberoptic bronchoscopy before the procedure

Seyfettin Günsel, Mehmet Aydogan, Omer Deniz, Alper Gundogan, Gurkan Metin, Ergun Topkapan, Hayati Bilgic

Introduction: Performing fiberoptic bronchoscopy has many risks for the bronchoscopy personnel. May be the most important risk is the transmission of tuberculosis bacilli from the patient to the bronchoscopy personnel. In addition, transmission of blood-borne viruses such as hepatitis B, HCV and HIV might be the other important risk for the bronchoscopy personnel particularly for the bronchoscopist. Splash of bronchial secretions to conjunctiva might be considered as the main route of transmission. Non-inact skin exposure might be the second route.

Aim: The aim this study was to investigate the ratio of the patients having positive results for blood-borne viruses undergoing bronchoscopy before the procedure.

Methods: We retrospectively screened the medical files/records of the patients undergoing bronchoscopy procedure between May 2011 and January 2012.

Results: There were 183 patients with a bronchoscopy indication. Mean age was 55±17 years. 123 patients had HBsAg, anti-HCV and anti-HIV test results. HBsAg was positive in five patients (4%). Anti-HCV and anti-HIV test results of all the patients were negative.

Discussion: In our country, different results for HBsAg positivity, between 2%-10%, were reported in different studies. Our results are similar the results of these studies. A ratio of 4% HBsAg positivity should not be seen as a small ratio. Absence of anti-HCV and anti-HIV positivity might be attributed to the small number of study group.

Conclusion: This study suggests that bronchoscopy personnel are under the risk of hepatitis B transmission. Large studies are needed to indicate the transmission risk of blood-borne viruses for the bronchoscopy personnel.

P3581

Verucous carcinoma of the tracheobronchial tree – An underdiagnosed entity?

Claas Steppen, Joseph Alhana, Juergen Schubbert, Jens Kruppmann

Herren: We retrospectively screened the medical files/records of the patients undergoing bronchoscopy procedure between May 2011 and January 2012.

Results: There were 183 patients with a bronchoscopy indication. Mean age was 55±17 years. 123 patients had HBsAg, anti-HCV and anti-HIV test results. HBsAg was positive in five patients (4%). Anti-HCV and anti-HIV test results of all the patients were negative.

Discussion: In our country, different results for HBsAg positivity, between 2%-10%, were reported in different studies. Our results are similar the results of these studies. A ratio of 4% HBsAg positivity should not be seen as a small ratio. Absence of anti-HCV and anti-HIV positivity might be attributed to the small number of study group.

Conclusion: This study suggests that bronchoscopy personnel are under the risk of hepatitis B transmission. Large studies are needed to indicate the transmission risk of blood-borne viruses for the bronchoscopy personnel.

P3582

Hemangiopericytoma – An extremely rare bronchial tumour, a difficult diagnosis

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Background: Hemangiopericytoma is a rare mesenchymal tumour originating from the capillary pericytes (about 1% of vascular tumors). Its primary localization in the lung is extremely rare.

Case presentation: A 52-year-old man, smoker (60PY), is diagnosed two months ago by bronchoscopy and chest CT scan with the main left bronchus tumour with subsequent negative biopsies. He was admitted to our hospital for re-examination and clarification and endoscopic diagnosis. "Encéfaloidal" endoscopic tumour that stenoses left bronchi from the beginning by 65%, but without bronchial wall infiltration around the tumor.

1. We performed rigid bronchoscopy and "Jet" ventilation with snare electroresection of tumour in three stages. Histopathological examination of a biopsy specimens - non-small carcinoma. Follow bronchoscopy intervention, persist only distal total obstruction of left main bronchus.

2. Radical left pneumonectomy with mediastinal lymphadenectomy and intrapericardial atriocephalic anastomosis. Postoperative chemotherapy that combined carboplatin and taxol were performed.

Conclusion: Hemangiopericytoma is a rare vascular slow-growing tumor with high local recurrence and poor prognosis because the recurrence of disease. Preoperative diagnosis is difficult. Surgical radical excision is the treatment of choice, although the criteria for determining the area of resection have not been established.

P3583

Pulmonary-alveolar microtheliosis (PAM) as a rare differential diagnosis of diffuse lung diseases diagnosed by transbronchial cryobiopsy

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Introduction: PAM is a rare pulmonary disease of unknown origin. Microscopically, it is characterized by diffuse alveolar calcification. Chest x-ray usually presents a "sandstorm" image. Diffuse lung diseases are typically diagnosed by computed tomographic imaging; histological validation is won by surgical lung biopsy. Current studies show a more important role of transbronchial cryobiopsy for histological diagnosis.

Case report: A 26-year-old male presented with dyspnea. The radiographic images (chest x-ray, computed tomography) showed interstitial pulmonal changes without radiological guidance; the cryoprobe was cooled for five seconds and then retracted after bronchoscopy intervention, persist only distal total obstruction of left main bronchus. The specimen were rared between two experienced lung pathologists.

Results: Histologically the cryobiopsy showed only few hints for PAM, whereas in the cryobiopsy a pulmonary-alveolar microtheliosis could be proven due to big amount of alveolar tissue with concentric calcification. In respect to untypical radiographic signs this was determining.

Conclusion: There is a huge variety of diffuse lung diseases. The diagnosis of PAM was surprising because the radiographic images showed an untypical morphology. The histological diagnosis of PAM was proven by transbronchial cryobiopsy. This shows the potential impact of transbronchial cryobiopsy in different entities of interstitial lung disease.

P3584

Management of video capsule bronchial aspiration

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A 74-year-old patient with of occult gastrointestinal bleeding was referred for a small bowel exploration using video capsule endoscopy. Medical history revealed...
left hemiparesis and swallowing disorders as sequel of stroke. A video capsule endoscopy was scheduled after the advice of the ENT specialist. Within minutes after the capsule ingestion, the patient developed a typical choking episode. Real-time visualization of the video-endoscopic “bronchial tree” images by the gastroenterologist quickly assisted by the pulmonologist enabled locating the capsule at the level of the main carina/left main bronchus. Immediate bronchoscopy under general anaesthesia allowed the pulmonologist to gently catch the video capsule and to readily place it within the gastro-intestinal tract (stomach). Small bowel exploration could then be performed “as scheduled” and revealed duodenal and jejunal angioomas as the source of the bleeding. Pictures as well as short video sequences of the choking episode and of the gastro-intestinal placement of the capsule with the bronchoscope are presented. Based on this experience and on the literature (about 9 reported cases of tracheobronchial video capsule aspiration) two recommendation can be made:

1. Caution should be taken in patients with swallowing disorders
2. Immediate tracking by of the capsule initial path is recommended

The present case also shows that a combined approach (gastroenterologist + pulmonologist) permits to replace the video capsule in the right way during the same procedure.

**P3585**

A case of primary tracheal B cell lymphoma leading to obstruction of central airway

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Primary malignant tumors of the trachea are rare, and they follow up such as asthma, chronic obstructive pulmonary disease incorrect diagnoses. Tracheal tumors are rare and the incidence less than 0.01% and the majority of squamous cell carcinoma. Very few cases of primary lymphoma of the trachea have been reported so far. 72 years old male patient admitted to our clinic with complaints of shortness of breath, bronchoscopy showed a mass obstructing the tracheal lumen of the almost complete. Dioxide laser and coring was performed for emergency debulking.

There was no another focus of the patient's systematic screening whose pathological result is B-cell lymphoma. Reported due to a rare tracheal tumor.

**P3586**

Foreign body aspiration by a 31 years old female patient, mimics diaphragmatic hernia

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Introduction: We present a case of food aspiration by a 31 years old female patient, masquerading as diaphragmatic hernia. Aims and objectives: Our aim is to show that food aspiration is a life threatening condition and it can easily escape detection.

Methods: A 31 years old female presented at the emergency department with shortness of breath. Her past history was unremarkable. The chest X-ray demonstrated total collapse of the left lung and herniation of the stomach and large intestine into the left pleural cavity. Chest CT- scan demonstrated the presence of stomach and large bowel in the left chest suggesting a postero-lateral diaphragmatic hernia. The patient was subjected to an postero-lateral thoracotomy. To our surprise there was only local evagination of the left hemidiaphragm. Atelectasis of the left lung persisted despite ventilation with high pressures. The patient subjected in intraoperative flexible bronchoscopy and there was presented a large quantity of mucus surrounding a soft mass adhered at the wall of the bronchus. Rigid bronchoscopy was performed the following day and a piece of meat was extracted. Results: Atelectasis soon dissipated and the patient had normal breath again, after the extraction of the food mass. Conclusion: Foreign body aspiration is unusual in adults, except those who are debilitated or have neuropsychiatric disorders. The doctors must be suspicious about this condition even in young healthy patients and bronchoscopy must be used as diagnosing and therapeutic step before the patient subject a thoracotomy.

**P3587**

Endoscopic resection of airway benign tumors by argon plasma coagulation

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Benign airway tumors with central airway obstruction require immediate intervention for symptoms relief. Argon Plasma Coagulation (APC) is a cheap tool readily available in hospitals. Four patients presented for obstructing tracheal or bronchial tumor (2008 to 2011). Initial investigations included fiberoptic bronchoscopy and CT imaging of the chest. Argon plasma was set to 35 Watt and delivered in non-contact fashion through a large fiber during rigid bronchoscopy. Initially tumor coagulation was done followed by mechanical resection and finally APC was applied to tumor base. Patients were discharged next day and followed clinically by CT imaging and bronchoscopy. All patients were reevaluated one year after ablation to eliminate recurrence.

Case1: 24 years old female presented for uncontrolled asthma. Endoscopic resection with APC revealed tracheal schwanna.

Case2: 35 years old female, 6 month pregnant, intubated for respiratory failure due to obstructive tracheal tumor. Endoscopic resection yielded low-grade muco-epidermoid carcinoma of the trachea.

Case3: 60 years old male, smoker, with concomitant sarcomatous carcinoma of the kidney presents for dyspnea, persistent cough and obstructive lesion of the right main bronchus. Ablation by rigid bronchoscopy and APC unraveled bronchial hamartoma.

Case4: 57 years old male, smoker, presents for persistent cough. Rigid bronchoscopy and APC resection of right bronchial obstruction uncovered a hamartoma.

APC is an effective and efficient tool to use during resection of benign bronchial tumors, it’s safe to use in pregnant patient and provides immediate airway relief. Swannamara, hamartoma and low-grade muco-epidermoid tumors can be treated with this modality.

**P3588**

An unusual approach to manage a bronchopleural fistula following carinal pneumonectomy

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A 52-year-old lady was referred with a T4N0M0 lung adenocarcinoma in the right main bronchus with protrusion into the trachea. She was an exsmoker with COPD and hypothyroidism.

She had a right carinal pneumonectomy with anastomosis of left main bronchus on to the trachea. Post discharge she was readmitted with dyspnoea three weeks later. Her post pneumonectomy space was abnormally enlarged which was managed successfully with intercostal tube drainage.

Six weeks later she represented with dyspnoea and sepsis which did not respond to antibiotics. She had a right thoracotomy and bronchoscopy which showed two bronchopleural fistulas (BPF) at the anastomotic site. Unfortunately the BPF persisted. Surgery was not considered appropriate. She then had a rigid bronchoscopy and a 4cm X 16 mm covered stent deployment to cover the defects. A day later she still had an air leak. Chest X-ray four days later showed that the stent had migrated upwards. She had replacement of the stent with a larger 4cm X 18 mm device. Following day, the air leak stopped completely. Her follow up chest x-ray three months later has been stable with no recurrence of BPF.

This case illustrates the management difficulties of BPF complicating high bronchial to tracheal anastomosis with differing airway diameters. Placement of large stent could have jeopardised the integrity of the airway anastomosis. The first stent migrated because it was preferentially sized with respect to the bronchial diameter. When a larger stent was inserted adequate closure ensued without airway anastomotic dehiscence.

Although surgical treatment of BPF is gold standard carefully selected patients may benefit from endobronchial closure.

**P3589**

Models must be able to bleed – The real interventional bleeding simulator a new training model for interventional bronchoscopy procedures as a sufficient substitute for training on live animals

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Introduction: Until now bleeding could be only trained on live pigs. Background: The current available models are not able to demonstrate acute bronchial bleedings.

Methods: We developed a new Simulation model for interventional bronchoscopy including a real-life-simulation of bleeding in bronchial tree. The model contains 2 transparent covers,a full expanded pig lung, an intubation head and an artificial diaphragm. We inserted “endobronchial tumors” and simulated different realistic bleeding situations with artificial blood.

Results: At an interventional training course organized by the Austrian Society for Pneumology (2010/2011) the simulator different simulated bleedings. The feedback given by all the 32 trainees showed a convincing
386. The different ways to establish a diagnosis: needle and forcep

P3590 Does pseudo-ROSE enhance the diagnostic utility for conventional TBNA? Andrew Modford, Anikumar Pillai. North Bristol Lang Centre, Southmead Hospital, Bristol, United Kingdom

Background: Conventional transbronchial needle aspiration (TBNA) is a useful mediastinal diagnostic and staging technique. It is more accessible and cheaper than endobronchial ultrasound. Some centres use ROSE (rapid on-site evaluation for cytology with a cytotechnologist) to improve results but limited by cost and resources. There are less published studies on pseudo-ROSE (a cytotechnician assesses sample adequacy alone).

Hypothesis: Pseudo-ROSE improves diagnostic utility of TBNA.

Methods: 22 consecutive patients underwent pseudo-ROSE-TBNA for investigation of suspected lung cancer (with N2 or N3 disease on CT) in a UK teaching hospital by previously described methods. Diagnostic utility to detect mediastinal metastases was calculated via contingency table analysis (GraphPad Prism 5).

Results: Pseudo-ROSE-TBNA resulted in 13 true positive cases (59% of cohort) of malignancy (5 small cell, 8 non-small cell) with 7 true negative cases and 2 presumed false negative cases (10mm nodes in stations 10R and 3 on CT but not confirmed). 87% sensitivity, (compared to 78% in a UK non-ROSE study) 78% negative predictive value, 68% cancer prevalence and 91% accuracy. Pseudo-ROSE-TBNA detected granulomatous disease due to sarcoidosis in 3 of the 7 true negative cases.

Conclusion: Pseudo-ROSE improves the diagnostic utility of conventional TBNA for lymph node metastases in high prevalence cohorts with malignancy. In the absence of endobronchial ultrasound or conventional ROSE, pseudo-ROSE should be used as an effective and inexpensive adjunct to conventional TBNA.

References

P3591 Transbronchial node aspiration for intrathoracic lymphadenopathy Hooman Deorgi Yankov1, Arda Kiani1, Mehdi Bakhtian1, Negar Shekhi1, 2Thoracic Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran. 3Chronic Respiratory Diseases Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran. 4Tobacco Prevention and Control Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Background and objectives: Lymph node evaluation has been important for many years both regarding diagnosis and staging. This study was aimed at evaluating the diagnostic yield of transbronchial needle aspiration biopsy (TBNA) in patients with intrathoracic lymphadenopathy.

Methods: Our understudy population included all patients suffering from undiagnosed intrathoracic lymphadenopathy (LAP) with no accompanying pulmonary lesions on chest CT scan who had referred to bronchoscopy unit of Masih Daneshvari Hospital. After determining the anatomical location of LAP patients underwent fiberoptic bronchoscopy (FOB) and TBNA using 19-gauge eXelson aspiration needle. Four samples were taken from each patient from the same LAP location.

Results: In this study 39 patients were evaluated. The most common anatomical location of LAP was the paratracheal area seen in 14 patients (35.2%). Next was subcarinal area and also hilar area with 12 cases (38.5%) for each of them. Five patients (15.6%) had LAP in other anatomical locations. Evaluation of the aspirates obtained by TBNA showed that the sample was adequate and diagnostic in 21 patients (55.26%); adequate but non-diagnostic in 9 patients (23.68%) and inadequate in 8 cases (21.06%). Definite diagnosis was made in 22 patients among which the most common differential diagnosis was atypical and malignant lesions in 11 cases (55%) followed by sarcoidosis in 8 (36.36%), tuberculosis (TB) in 2 (9.09%) and other diagnoses in 1 (4.55%) case.

Conclusion: Based on our study results, TBNA was diagnostic in more than half the cases. Various studies have reported a wide range of results in this respect but all of them including ours emphasize on the acceptable diagnostic yield of this technique.

P3592 Minimally invasive diagnostic techniques for mediastinal lesions Rossen Petkov1, Yordanka Yamakova2, Emilka Petkova1, Danail Petkov1, Deceg Yankov1. 1Thoracic Surgery Department, University Hospital of Pulmonary Diseases, Sofia, Bulgaria. 2Clinic of Anesthesia and Intensive Care, University Hospital of Pulmonary Diseases, Sofia, Bulgaria. 3Endocrinology Clinic, USBL of Endocrinology, Sofia, Bulgaria

Aim: The aim of the study is to evaluate the diagnostic value and the complication rate of various minimally invasive diagnostic techniques by patients with mediastinal lesions (ML).

Materials and methods: In a prospective study (from 2001 to 2009) we observed 421 patients (pts) (227 males and 194 females, age x ± SD: 45.7±16.7 yrs.) with ML (x ± SD: 56 mm ± SD: 20mm). By 275 pts US guided true-cut needle biopsy (US-TCNB) were performed. By 18 pts we did CT guided TBNA. VATS (n=124), mediastinoscopy (n=18), anterior mediastinotomy (n=16) and thoracotomy (n=29) were performed by 187 pts: 17 pts with uninformative TCNB results (14 US-TCNB and 3 CT-TCNB), 37 with benign lesions proved by TCNB and 133 pts with ML inaccessible for image guided TCNB.

Results: US-TCNB gave an adequate material to the morphological diagnosis in 261 (94.9%) of patients with ML, sensitivity (Se) 96% and NPV 80%. The complication rate was 0.8%. CT-TCNB yielded positive diagnosis in 88.9% of cases, Se 88% and NPV 33%. The complication rate was 22%. VATS gave a morphological diagnosis in 121 pts (97.6%), Se 97% and NPV 84%. The complication rate of VATS was 9.7%. The accuracy of the mediastinoscopy was 87.5%, Se 86% and NPV 50%. The accuracy of the anterior mediastinotomy was 88.9%, Se 87.5% and NPV 50%. The complication rate of these procedures was 5%

Conclusion: US – TCNB appears to be effective and a safe method in patients with US accessible ML. According to our results US- or CT-guided TCNB should be the first step in tissue diagnosis of mediastinal masses. Mediastinal lesions that are inaccessible by these methods can be diagnosed by mediastinoscopy, anterior mediastinotomy and VATS.

P3593 Interobserver analysis of assumed optimal positions for transbronchial needle aspiration Kariel Roth1, Tomas Eagan2, Jon Hardie1. 1Department of Internal Medicine, Helse Møre og Romsdal, Ålesund Hospital, Ålesund, Norway. 2Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

Background: Various guidelines have described the optimal positions for transbronchial sampling from lymph node stations. The variability in expert opinion for these positions is unknown.

Objective: To describe the interobserver variability in the assumed optimal position for transbronchial needle aspiration (TBNA) from lymph node station 4, 7, 10 and 11.

Methods: Four physicians with large experience in TBNA were shown six bronchoscopic pictures and asked to describe the optimal positions for TBNA. The physicians marked an area for the assumed best position for different lymph node stations. A mean diameter was calculated for each area. The mean diameter represented the intraobserver spread for each expert in the lymph node station. The distance to the average X and Y-coordinate defined the interobserver variation.

Results: The mean diameter that represented the average spread was 1.14 cm (95% confidence interval: 0.91-1.38 cm). Lymph node station 11 had an average intraobserver diameter below the 95% confidence interval. The average intraobserver diameter in lymph node station 4R and 10L were above the 95% confidence interval.

The median interobserver distance was 0.64 cm (interquartiles range 0.17-1.04 cm). Lymph node station 7L had a mean interobserver distance smaller than the 25% quintile, lymph node station 10R and 10L had an interobserver distance larger than the 75% quintile.

Conclusions: The interobserver spread was large in station 4R and 10L, the interobserver variation was large in 10R and 10L compared to the other lymph node stations that were evaluated.
P3594
The diagnostic yield and safety of fine needle aspiration of intrathoracic hydatid cysts: A three year retrospective study
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Background: Hydatid disease remains a clinically relevant entity in much of the developing world. A presumptive diagnosis may be confirmed by cytological analysis of liquid obtained by percutaneous aspiration of the cyst. There is, however, a paucity of data on the safety and diagnostic yield of this approach.

Objectives: To assess ultrasound (US)-assisted transthoracic fine needle aspiration (TTFA) of suspected thoracic hydatid cysts with regards to safety and diagnostic yield.

Methods: We retrospectively included 11 cases (35±9±9.1 years, 7 females) who underwent US-assisted TTFA over a three-year period and who were eventually confirmed to have histological proof (surgical resection) of hydatid cyst. Cytological review, and the diagnostic yield of US-assisted TTFA was compared with serology (using histology as the gold standard).

Results: Cytology was diagnostic in 5±1±1 of cases (45.5%), compared to serology that was diagnostic in 6±8±1 cases (75%, p = 0.352). Cytology was diagnostic in one case with negative serology. A serious complication (empyema) was observed in one case.

Conclusions: US-assisted FNA of thoracic hydatid cysts has a modest diagnostic yield. US-assisted FNA should be reserved for cases with indistinct imaging and/or a negative serology, given the risk of complications.

P3595
EBUS-TBNA for diagnosis of granulomatous mediastinal lymphadenopathy
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Methods: Retrospective review of all patients who underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy at Singapore General Hospital between 2008 and 2011.

Results: Over 3 years 33/371 patients underwent EBUS-TBNA for suspected granulomatous mediastinal lymphadenopathy – 18 for tuberculosis(TB) and non-tuberculous mycobacterial (NTM) lymphadenitis, 15 for sarcoidosis. Mean age 47±18 years, 54.5% male. Total of 49 lymph node stations were sampled, with stations 7 the most frequent (43%). Median size of lymph node was 17mm (8-30), median number of passes per lymph node 2 (1-5), and core biopsy obtained in 45/92±1. Median follow-up was 9 months (0.5-26).

Conclusions: EBUS-TBNA can be useful in the diagnosis of suspected granulomatous mediastinal lymphadenopathy. A presumptive diagnosis may be confirmed by cytological analysis or microbiology culture. A negative result does not exclude the diagnosis of granulomatous lymphadenitis and further workup is required.

P3596
EBUS-TBNA in a tertiary care center: Real life experience and quality assessment
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Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become the standard minimally invasive modality for sampling mediastinal lymph nodes. In this study, we evaluate our performance with the technique and propose a methodology that can be used in other centers.

Method: We included all EBUS-TBNA procedures performed in 2011 in our service. We proceeded to a thorough analysis of each case from a pragmatic perspective to evaluate the regional node sampling yield and our ability to conlude the investigation by achieving diagnosis and staging, avoiding unnecessary surgery and allowing direction for management.

Results: EBUS-TBNA was performed in 53 consecutive patients. The indication was suspicion of malignant disease in 46 patients (87%) and benign in 7 patients (13%). In total, 117 nodes were sampled. The overall sensitivity ranged from 76 to 91% and the negative predictive value ranged from 78 to 92%. The median size of nodes was discovered, histological precision was obtained in 68%. EBUS-TBNA was clinically sufficient in 43 of the 53 patients (diagnostic yield = 81%) and prevented 18 out of 27 patients (67%) from undergoing surgery. No major complications were reported.

Conclusion: The attained sensitivity and negative predictive value are similar to what has been published. Thorough analysis of patient cases is key in improving performance with this technique, and we encourage all centers to analyze their practice periodically in order to maintain quality standards. Finally, in our establishment, EBUS-TBNA offers clinicians an additional step to simplify healthcare and probably reduce the economic burden of such investigations.

P3597
Transesophageal ultrasound-guided fine needle aspiration (EUS-guided FNA) as first diagnostic step of intrapulmonary lesions
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Background: Bronchoscopy fails to establish a diagnosis in up to 30% of patients with centrally located lung cancer. EUS-guided FNA has been used for the diagnosis of suspected lung cancer near or adjacent to the esophagus in patients who had undergone a non-diagnostic bronchoscopy. Aim: To prospectively assess the feasibility and yield of EUS-FNA as first diagnostic step in the diagnosis of intrapulmonary tumours located near or adjacent to the esophagus.

Study design: Patients with a CT-scan of the chest revealing an intrapulmonary nodule located near or adjacent to the esophagus were enrolled. They underwent EUS-FNA (Olympus, GF UCT 160) under deep sedation.

Results: Forty-three patients were included, and EUS-FNA diagnosed lung cancer in 33 cases (12 NSCLC, 2 SCLC) (yield=100%). No complications occurred. The typing of NSCLC was allowed by cytological specimens in 9 cases (65%), by cell blocks in 3 cases (21%), whereas NSCLC could not be subtyped in 2 cases (14%).

Conclusions: EUS-guided FNA might represent the first diagnostic step in patients with intrapulmonary tumours located near or adjacent to the esophagus.

P3598
Virtual bronchoscopic navigation combined with endobronchial ultrasound for diagnosing small peripheral pulmonary lesions
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Background: Flexible fiberoptic bronchoscope may be a valuable procedure to evaluate pulmonary nodules. However, a diagnostic yield has been reported as low as 34% for peripheral lesions less than 5 cm in size.

Objectives: This case series study evaluated the value of the virtual bronchoscopic navigation (VBN) combined with endobronchial ultrasound (EBUS) for diagnosing peripheral pulmonary lesions.

Methods: Enrolled subjects were patients with pulmonary lesions which were deemed too small and peripheral for a conventional bronchoscopy sampling, who were referred to Kameda Medical Center for diagnostic bronchoscopy between September 2010 and February 2012. VBN was utilized to produce a pathway into the target lesion. Once the fiberoptic bronchoscope was advanced as far as possible in this pathway, a guide sheath with EBUS probe was then advanced to the target lesion under fluoroscopic guidance. After fluoroscopy guidance of the lesion by EBUS, the probe was removed leaving the guide sheath in place. Samplings were then performed through the guide sheath under fluoroscopic guidance.

Results: Study subjects included 58 patients with 62 lesions, mean age 68 years.

The mean lesion size was 20 mm in diameter. Bronchi seen on VB image were highly consistent with the actual structure. The sensitivity for diagnosing malignancy was 43% and negative predictive value was 61%. Overall accuracy for diagnosis of all lesions was 69%.

Conclusion: VBN combined with EBUS is useful method for collecting samples from small peripheral pulmonary lesions and may help increase the diagnostic yield of trawbronchial samplings in diagnosing small peripheral pulmonary lesions.

P3599
Efficacy of transbronchial biopsies in diagnostics of smear-negative pulmonary TB
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Background: Around half of all cases of tuberculosis are smear-negative. In order to achieve the final diagnosis and to find a susceptibility profile of mycobacteria, bronchoscopy is used. Aim: To investigate the effectiveness of bronchoscopy in the diagnosis of smear-negative TB

Materials and methods: We analyzed 99 cases of smear-negative, therapy-naive patients with pulmonary TB without cavity according to chest CT. All of them undergo a bronchoscopy with bronchial swabs with/without brush-biopsy of targeted bronchi. We analyzed further dataset: results of cytological examination of brush-biopsy (acid-fast bacilli detection, components of specific granuloma,
P3600 Intratransternal injection of tranexam acid for control of biopsy-induced bleeding: Two years’ experience of a new bronchoscopic technique
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Background: Significant bleeding may occur following forceps biopsy or brushing of necrotic or hypervascular tumors in the airways. In some cases, such methods as endobronchial instillation of iced saline lavage and epinephrine may fail to control the bleeding.

Objective: To describe and assess the efficacy of a new bronchoscopic technique using intratumoral injection of tranexam acid (IIT) for control bleeding during biopsy procedure.

Methods: IIT was performed in those patients who had endoscopically visible tumor lesions with continued active bleeding following the first attempt of bronchoscopic sampling (forceps biopsy or endobronchial needle aspiration). Tranexam acid (TEA) in dose of 250-500 mg was injected through a 22-gauge Wang cytology needle (MW-122) into the lesion. After 2-3 minutes of waiting, multiple forceps biopsy specimens were obtained from the lesion.

Results: Between Oct 2009 and Jan 2012, 14 male patients (mean age, 61 yrs; range, 41-80 yrs) underwent bronchoscopy IIT. Two patients with drug-eluting stents were on continuous dual antiplatelet therapy (aspirin plus clopidogrel). Multiple (3 to10; mean, 5.7) and deep biopsy specimens were obtained from the lesions without producing active bleeding. The following histopathologic diagnoses were made: squamous cell carcinoma (n=9), non-small cell lung cancer (n=3), and small cell carcinoma (n=2). There were no side effects observed with TEA.

Conclusion: Bronchoscopic IIT is a useful and safe technique for controlling significant bleeding due to forceps biopsy procedure, and might be suggested as a prebiopsy injection for endobronchial necrotic or hypervascular tumors.

P3601 Comparison of conventional forceps biopsy and cryobiopsy in endobronchial lesions
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Background and objectives: Forceps biopsy has long been the standard method of extracting samples from endobronchial lesions, however diagnostic yield of the specimen obtained by this method<72% is not very desirable due to small size and artifact. Therefore, in order to increase the diagnostic yield in endobronchial lesions as well as diminish the complications we evaluated a new technique called cryobiopsy using flexible cryoprobes to obtain frozen samples.

Methods: All patients with endobronchial lesion except for vascular lesions referred to Intervention ward of Masih Daneshvari Hospital were included in this study. For each patient, 6 specimens were obtained by conventional forceps, and 2 were extracted through cryobiopsy, one of them 3 seconds after freezing (CB3), and the other one 5 seconds after freezing (CB5) during the bleeding procedure, and diagnostic yield of the samples were evaluated closely.

Results: Of all 30 patients, diagnosis was achieved for 27 patients (90%). Diagnostic rate of forceps biopsies was 67.8%, while this rate was 86% and 78% for CB3 and CB5 respectively. Although there was no significant difference between these three rates, total diagnostic yield of both CB3 and CB5 together was significantly higher than conventional biopsy (P-value=0.016). Severe bleeding requiring APC to be controlled occurred in 2 cases during CB5, while no major hemoptysis happened during forceps biopsy.

Conclusion: According to our results, obtaining at least two samples from endobronchial lesions by cryobiopsy technique can lead to a higher rate of diagnosis compared with 6 samples by forceps biopsy. However, duration of freezing 3 or 5 seconds does not have a significant impact on the quality of specimen.

P3602 Additional benefit of cryotechnique in transbronchial biopsy for histological diagnosis in interstitial lung disease (ILD)
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Background: Due to the small specimen size of transbronchial forceps biopsy, the histodiagnostic quality of the specimen is often difficult. In comparison transbronchial cryobiopsies were shown to be bigger and to contain more often and larger amount of alveolar tissue.

Methods: Since 2009, all histological results of patients suspicious of ILD (clinical signs, pulmonary function, CT-scan-criteria) who underwent bronchoscopy with transbronchial forceps- and cryobiopsy were analysed concerning the impact of the additional use of cryotechnique.

Results: We evaluated 34 cases of patients (age 60.0±13.2 years) who underwent forceps- and cryobiopsy. For 10 patients (29.4%) neither forceps- nor cryobiopsy assured a histological diagnosis. In 11 cases (32.4%) both methods assured a diagnosis. In 12 cases (35.3%) a histological classification was found only in the cryobiopsy, in 1 case (2.9%) only in the forceps biopsy.

Conclusion: By additional use of the cryprobe in transbronchial biopsy, in this prospective case series up to today we were able to increase the amount of ensured histodiagnostic diagnoses in ILD from 12/34 = 35.3% without cryobiopsy to 23/34 = 67.6% with cryobiopsy. This shows the high potential of cryotechnique as a tool in transbronchial biopsy in the diagnostic of ILD.

P3603 In vivo probe-based confocal laser endomicroscopy in chronic diffuse parenchymal lung disease
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Diagnosis of diffuse parenchymal lung diseases (DPLD) is challenging and requires a multidisciplinary approach. Probe-based confocal laser endomicroscopy (pCLE) enables microimaging of the distal lung in vivo.

Objective: To describe pCLE features in DPLD patients.

Methods: pCLE was performed in 52 patients (mean age 67.6 years) who underwent forceps biopsy and/ or cryobiopsy. Furthermore, 21 healthy volunteers (HV) were investigated by pCLE. Results were compared between HV and each of the pathologic groups, blinded to the diagnosis (Fisher’s exact test and Bonferroni correction). The association between the pCLE and CT-scan features was assessed using multivariate analysis.

Results: 9 of the 17 pCLE descriptors were significantly more frequent in DPLD patients than in HV (131 areas) by the 20-Chromosome of bronchial cells, convoluted alveolar elastic fibers, alveolar nodules; in idiopathic pulmonary fibrosis (n=8, 36 areas) by interalveolar septal fibers and a rigid acinar elastic network; hypersensitivity pneunonitis (n=6, 34 areas) by bronchial and alveolar cells; non-specific interstitial pneumonia (n=6, 38 areas) by fluorescent bronchial cells, septal fibers and a rigid network; asbestosis (n=10, 72 areas) by alveolar mouths <200 μm, alveolar fibers >20 μm, septal fibers, and a rigid and dense acinar elastic network; systemic sclerosis (n=8, 38 areas) by fluorescent alveolar cells, septal fibers and a rigid network. HRCT honeycombing was associated to pCLE large alveolar mouths and a disorganized elastic network; both interlobar septa thickening and cysts were associated to the presence of septal fibers using pCLE.

Conclusion: pCLE could be added to the multidisciplinary discussion for the etiological diagnosis of DPLD.

P3604 Retrospective study of transbronchial cryobiopsy (TCB) data in a case series of 20 patients with interstitial lung disease
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Introduction: So far surgical lung biopsies are the state-of-the-art technique to ensure histological data in patients with interstitial lung disease. We analyzed whether histological specimens obtained by TCB could contribute to establishing the definite diagnosis and whether the procedure is a safe one.

Methods: A series of 20 patients showing interstitial patterns in high-resolution computer tomography underwent the procedure of TCB. In all patients, 2-3 biopsies were performed and 13.2 years) who underwent forceps- and cryobiopsy.

Results: In 16/20 (80%) the pathological findings correlated well with the other suspected diagnosis according to clinical, serological, radiological and bronchoalveolar lavage fluid evaluation findings. In 4/20 (20%) patients the diagnosis
remained doubtful after TCB so that these patients were subsequently forwarded to video-assisted thoracoscopic biopsy. In 3/4 (75%) of these cases the surgical approach and the TCB specimen showed the same histological pattern, therefore leading to a definite diagnosis. Regarding the study of the studied procedures in 4/20 (20%) patients an iatrogenic pneumothorax occurred after TCB, endobronchial bleeding was severe in 1/20 (5%) cases and moderate in 11/20 (55%) cases. Bleeding in all patients could be stopped by endoluminal application of adrenaline.

Conclusions: TCB seems to be a suitable minimal-invasive tool in the diagnostic work-up of IFL-patients with a moderate peri-procedural risk.

P3607
Diagnostic approach of lung malignancies through CT-guided percutaneous needle cytology and biopsy
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Background: The use of CT-guided percutaneous needle procedures is well established in the diagnostic approach of suspected lung malignancy.

Aim: To evaluate the efficacy and the complication rate of these procedures.

Methods: A retrospective study of patients submitted to thoracoscopic needle cytology/core biopsy for suspected lung malignancy in a 2 year period.

Results: We assessed 129 episodes concerning 117 patients (213 punctures), 76% male, mean age 65.4 years. Most common localizations were RUL 35.7% and RIL 22.5%. 55% had other lesions.

Cytology was performed in all patients; core needle biopsy was needed in 23.3%. 107 patients have a definite diagnosis (malignancy in 83.2%) of which 63.6% were done as an extemporaneous exam. The most frequent diagnosis was lung adenocarcinoma (36.4%) and NSCLC (12.1%).

We assessed 15 episodes of pneumothorax (7% of punctures), 3 needle aspiration and 1 tube drainage, 3 small hemorrhagic episodes and 1 hemoptysis. The distance to the chest wall significantly affected the presence of pneumothorax (3.8 vs 17.6mm; p<0.01).

Nodules that were diagnosed as cancer were statistically bigger than non malignant lesions (51.7 vs 33.8 mm) (p=0.01). Big nodules had a higher need of core needle biopsy in order to obtain a diagnosis (p=0.01).

The presence of caviation or ground glass opacification did not interfere with diagnostic accuracy.

Conclusions: CT-guided percutaneous lung punctures are important tools in the diagnostic approach of lung malignancies with a low rate of complications. The possibility of having a pathologist to provide an extemporaneous exam speeds the diagnosis and reduces the need for further invasive diagnosis and iatrogenic damage.

P3608
Role of bronchial artery embolisation in chronic recurrent haemoptysis
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Introduction: Bronchial artery embolisation (BAE) involves selective bronchial artery angiography, followed by embolisation of identified abnormal vessels. It is well used in massive haemoptysis. But there are only a few literatures on its use in chronic recurrent haemoptysis.

Aims and objectives: To assess the efficacy and safety of BAE in the management of chronic recurrent haemoptysis.

Methods: This is a retrospective study of all patients with chronic recurrent haemoptysis who underwent BAE between January 2007 and January 2012 in a tertiary care hospital. The decision to offer BAE and its timing was jointly made after assessment by respiratory physician and interventional radiologist.

Results: 63 patients, (39 males and 24 females), underwent BAE for chronic recurrent haemoptysis during the period of study. Mean age of patients was 32.5 years (range: 18-81 years). Maximum number of patients recruited in this study had active pulmonary tuberculosis (29 cases – 46.0%). Amongst them, five patients had MDR, and one case had XDR-TB. 18 (28.5%) patients had bronchiectasis. Malignancy was the cause of haemoptysis in 7 (11.1%) cases. Mycetoma was present in 5 (7.9%) cases. One patient (1.5%) had lung abscess. BAE was successful in 58 (92.1%) cases. Bleeding stopped in 3 more patients following repeat procedure within a period of 48 hours. There was no major complication. Three patients had a short period of self limiting febrile illness. Three other patients developed local haematoma which improved following compression of the local part.

Conclusions: BAE is an effective means of controlling chronic recurrent haemoptysis. It is also a safe procedure.

P3609
Bronchial artery embolization in chronic recurrent haemoptysis: A multicenter study in 218 cases
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Aim: To evaluate the sort and long term results in control of massive and chronic recurrent hemoptysis in 218 patients with special microspheres (embospheres).

Material and methods: Fifty six patients with massive and 162 with chronic recurrent hemoptysis were included. Microspheres were used to achieve distal embolization with precisely calibrated microspheres of hydrogel core and polyezene
cover, sized 300-400μm in more than 500μm if antenguted shunting were seen. The mechanical properties of these spherical particles prevent aggregation and clogging allowing more optimal embolization and accurate choice of the diameters of vessels to be occluded.

REULTS: The most common cause of hemoptysis was bronchectasis in 126 (58%) of patients, of whom 27 (12.4%) had cystic fibrosis, followed by lung cancer in 27 (12.4%), tuberculosis cavities in 14 (6.4%), mycetomas in 3 (1.6%), fibrotic tumor in 2 (1.6%), bullae cyst in 5 (2.3%), Takayasu arteritis in 1 (0.5%), arteriovenous malformation in 1 (0.5%) and cryptocogenic in 19 (8.7%) cases. Non bronchial collaterals were embolized in 36 (16.6%). Successful control of the hemoptysis was seen in 89% after the 1st session and in 94% after the 2nd. Mean follow up period was 3.7 years. In cystic fibrosis bronchecsis the overall recurrence was 36%, with a mean time to recur 26.2 months, whereas without cystic fibrosis recurrence was 11%, in amean time of 3.3 years.Major hemoptysis free rate was 92.2%, 83.3% and 69.6% at 1, 3 and 5 years respectively. Fever was seen in 3.6% and transient chest pain in 12.4% of cases.

Conclusion: The management of massive and chronic recurrent hemoptysis is safe and successful using precisely calibrated embospheres.

### 387. Diffuse parenchymal lung disease I

**P3610** From basic lesions to a pathological staging of pulmonary fibrosis

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**Introduction:** Pulmonary fibrosis is characterized by some morphological basic lesions which are associate to different degrees at the time of diagnosis. Based on this issue, a pathological staging of pulmonary fibrosis could be helpful to predict the evolution and the response to therapy.

**Material and methods:** We have quantified the severity of lesions on 20 patients with lung fibrosis namely: the aspect of the pulmonary parenchyma, the presence and density of the inflammatory infiltration, the density and distribution of the collagen fibres and variable evolution and four cases (20%) of degree II (4-6) were more likely to remain stable. Collagen fibres were not organized in fascicles.

**Results:** Four cases (20%) of degree IV (10-12) had a poor survival. There were found major changes of the parenchyma, extended nodular fibrosis and inflammatory infiltration as a marker for progressive evolution. Twelve cases (60%) of degree III (7-9) showed collagen fibres in homogenous fascicles and variable evolution and four cases (20%) of degree II (4-6) were more likely to remain stable. Collagen fibres were not organized in fascicles.

**Conclusion:** Histological score could represent a useful tool in the evaluation of pulmonary fibrosis and reflects its heterogeneity. Our results suggest that the actual scoring system of pulmonary fibrosis can be improved, to give more precise information about clinical outcome.

**P3611** Th1/Th2/Th17-related cytokines in the bronchoalveolar lavage fluid of patients with sarcoidosis in relation to smoking

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**Introduction:** Sarcoidosis (SA) is a multiorgan granulomatous disease. The inflammatory process in involved organs is characterized by Th1/Th2 imbalance and participation of Th17 cells, what was recently documented. SA is more prevalent among non-smokers than in smokers, however the impact of cigarette smoking on inflammation in SA remains unclear.

**Methods:** The aim of the study was to evaluate the Th1/Th2/Th17-related cytokine concentrations in bronchoalveolar lavage fluid (BALF) of patients with pulmonary SA in relation to smoking status. 61 SA patients were investigated (26 ever (S) and 35 never-smokers (NS)). The concentrations of IL-17A, INFγ, TNFα, IL-10, IL-6, IL-4 and IL-2 were measured by flow cytometry using Cytometric Bead Array method. The concentrations of TNFα, IL-10, IL-4 and IL-2 were below minimum of detection in most cases. There was significant correlation of INFγ concentration with number of macrophages and between IL-6 concentration with number of neutrophils (R=0.6, P<0.05, r=0.3, P<0.05, respectively).

**Results:** We found higher concentration of INFγ and lower of IL-6 in S than in NS (1.28 ± 1.6 vs 2.38, respectively, different very significant). The mean concentration of IL-17A was 6.1 pg/mL and did not differ between S and NS. There was significant correlation of IL-17A with IL-6 concentration (R=0.9, P<0.05) in the whole group and in S group. The concentration of IL-6 correlated negatively with the results of pulmonary function tests.

**Conclusion:** Our observation shows a slightly different profile of cytokine concentration in the BAL of smoking patients with SA. The lack of significance may be related to the short smoking history of patients.

**P3612** Validation of a novel prognostic tool for idiopathic pulmonary fibrosis

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**Introduction:** Idiopathic pulmonary fibrosis is a progressive disease with a median survival of 2-3 years. There is no universally accepted tool for identifying individuals with a poorer prognosis. du Bois et al proposed a 4 point scoring system to predict 1 year mortality. This tool requires external validation.

**Methods:** Data was collected on 94 consecutive patients with IPF. The du Bois score was calculated based on age, respiratory hospitalisation, baseline forced vital capacity (FVC) and 6 month change in FVC. The predictive value of the score was assessed using the area under the receiver operator characteristic curve (AUC). Patients were followed up for at least 3 years or until death.

**Results:** Median age was 69 years (interquartile range 64-76). 74.7% were male. 1 year mortality was 10.6%. The 1 year mortality was 0% for those scoring 0-14 points, 11.5% for those with 15-21 points, 23% for those scoring 22-29 and 21% for those scoring >30 points.

Prediction for 1 year mortality, the AUC was 0.76 (95% CI 0.67-0.85,p=0.004) indicating moderate predictive value. For prediction of 3 year mortality, AUC was 0.72 (0.64-0.78,p=0.0005).

**Conclusions:** This study validates a novel risk score for prediction of outcome in patients with idiopathic pulmonary fibrosis.

**References:**


**P3613** Expression of interleukin-27 (IL-27) in human lower airways.

Pathophysiological implications in pulmonary sarcoidosis (PS)

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**Background:** Interleukin-27 was recently discovered as a cytokine secreted by antigen presenting cells, participating in T cell priming and supporting Th1 type immune polarization. IL27 expression has not been examined yet in lower airways. **Aims:** Identification of IL27 sources in human lower airways. Preliminary assessment of IL27 expression in bronchoalveolar lavage (BAL) in interstitial lung diseases (ILD) patients.

**Materials and methods:** Two IL27 expression in BALF of patients with systemic sarcoidosis (SA) and controls were detected by indirect phenotyping and flow cytometry in BALF cells from patients with PS (incl. steroid treated subjects), idiopathic pulmonary fibrosis (IPF) and controls, as well as in Human Lung Fibroblasts (HLF) and pneumocyte type II (A549) cell lines. IL27 extracellular secretion was tested by ELISA (cat. no E90385Ha, Diaclone) in supernatants of BALF and cell cultures.

**Results:** BAL detectable IL27 levels were shown by ELISA in 6 (median 9ng/ml) of 13 PS untreated patients. IL27 was not found in BAL supernatants of steroid-treated PS, IPF and controls. HLF and A549 and alveolar macrophages were positive for intracellular IL27. Surprisingly, IL27+ BAL lymphocytes were found in all tested groups (PS: 8.1±6.2%; IPF: 37±13.4%; controls: 46±15.8%, median±SEM, insignificant).
Conclusions: In physiological conditions, IL27 is produced in lower airways by lung fibroblasts, epithelial and BAL immune cells, including lymphocytes. Its increased expression in PS suggests IL27 to play a role in I LD pathophysiology, probably as Th1 activity marker.

P3614
Pulmonary graft-versus-host disease (GVHD) post- stem cell transplant (SCT) for haematological malignancies: Good response to treatment if diagnosed early
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Introduction: Grafl-Versus-Host Disease (GVHD) of the skin and gut are relatively common following allogeneic transplant for haematological malignancies but GVHD affecting the lung can be subtle. In this study, we evaluated patients who developed lung GVHD post stem cell transplant (SCT) to determine early warning signs and response to treatment.

Method: Patients undergoing SCT for haematological malignancies were monitored with serial pulmonary function (PFT). Symptoms of increased breathlessness (SOB) or fall in PFT prompted investigation with high resolution CT scan (HRCT).

Results: 11 patients developed lung GVHD following allogeneic SCT for lymphoma (n=7) or leukemia (n=4). 6 had adjuvant chemotherapy, and 7 total body irradiation. 10 had exertional SOB. 3 developed pulmonary GVHD within 1 year of SCT.

PFT changes are shown.

All patients had mosaicism with gas trapping on HRCT at diagnosis, and were commenced on steroids, with 6 having other immunosuppressants.

Conclusion: Exertional SOB and changes in PFT are important early indicators of developing GVHD which can be confirmed on HRCT. Treatment with immunosuppressants results in successful resolution in the majority, particularly in those who were diagnosed early in the course of this complication.

P3615
Response to physical exercise in sarcoidosis
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The aim of this study was to analyze the response to exercise in untreated patients with pulmonary sarcoidosis. We recruited 39 patients (15 females) at mean age 39±4.9 years to undergo lung function testing (spirometry, bodyplethysmography, CO diffusing capacity) and symptom limited cardiopulmonary exercise test on a treadmill. Histological confirmation of sarcoidosis was obtained in 64% of patients; on the basis of radiologic findings 37% of patients were diagnosed with stage I, 51% with stage II and 11% with stages III and IV. Muscle fatigue was the main reason for exercise termination (82% of patients), followed by ECG abnormalities, blood pressure increase or vertigo and dyspnea reported by 10% and 5% of patients, respectively. Decreased exercise tolerance (defined as V′O2peak < 82% of predicted) was diagnosed in 15 (38%). V′O2peak in patients with decreased exercise tolerance was significantly lower than in patients with normal response to exercise (32.6±7.8 vs 27.2±6.6 ml O2/kg/min; p<0.05). Patients with impaired response also had a lower PaO2 at peak exercise (87±18.5 vs 100±18.6 mmHg; p=0.05) and widened alveolar-capillary oxygen gradient (17.5±10.1 vs 7.9±8.1 mmHg; p=0.05). Some significant correlations between V′O2max and FEV1% pred. (r=0.40; p<0.05), FVC % pred. (r=0.43; p=0.008), RV/TLC (r=0.41; p<0.01) were also noted.

Conclusions: Impaired exercise tolerance can affect up to 40% of patients with sarcoidosis. Lower PaO2 and widened alveolar-capillary oxygen gradient suggest an important role of gas exchange abnormalities in the pathogenesis of impaired response to exercise.

P3616
Isolated lymphocytic bronchiolitis with B cell clonality: Diagnosis in 3 cases using immunoglobulin gene rearrangement analysis
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Background: Lymphocytic bronchiolitis is characterised by diffuse infiltration of the bronchiolar walls by lymphocytes, which may organise into germinal centres (follicular bronchiolitis). B cell clonality demonstration may result in a diagnosis of low- grade B-cell lymphoma.

Patients and methods: Patient #1: 59-yr old female, non-smoker, presented with chronic cough, dyspnea, sicca syndrome, negative anti-SSA/SSB antibodies, severe airflow obstruction, ground glass opacities at HRCT, and 51% of lymphocytes at BAL. Patient #2: 54-yr old female, non-smoker, presented with chronic cough, restrictive lung disease, diffuse micronodules at HRCT, 90% lymphocytes at BAL, monoclonal IgG lambda of 4.2 g/l. Patient #3: 66-yr old female, non-smoker, with history of rheumatoid arthritis and Sjögren syndrome, anti-SSA and -SSB antibodies, presented with hemoptysis, Bence-Jones protein, airflow obstruction, 2 lung amyloid nodules and multiple cystic lung disease.

Results: Lung biopsy with immunohistochemistry demonstrated lymphocytic bronchiolitis in all three cases with a majority of CD 20 positive B –cell. PCR-based DNA testing for immunoglobulin gene rearrangement analysis of lung biopsy demonstrated B-cell clonality in all three cases (VK-JK, FR1-JH), and low-grade MALT lymphoma was eventually diagnosed.

Conclusions: Lymphocytic bronchiolitis may correspond to low-grade MALT lymphoma which may be demonstrated by gene rearrangements rearrangement analysis.

P3617
The relationship between leptin and proinflammatory cytokines with bone mineral density in patients with sarcoidosis (pts)
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Aim: The aim of the study was to investigate whether there is a relationship between leptin or cytokines and BMD in pts.

Methods: 85 pts, none was treated with steroids, 46M and 39F, age 41+9 years to undergo lung function testing (spirometry, bodyplethysmography, CO diffusing capacity) and symptom limited cardiopulmonary exercise test on a treadmill. Histological confirmation of sarcoidosis was obtained in 64% of patients; on the basis of radiologic findings 37% of patients were diagnosed with stage I, 51% with stage II and 11% with stages III and IV. Muscle fatigue was the main reason for exercise termination (82% of patients), followed by ECG abnormalities, blood pressure increase or vertigo and dyspnea reported by 10% and 5% of patients, respectively. Decreased exercise tolerance (defined as V′O2peak < 82% of predicted) was diagnosed in 15 (38%). V′O2peak in patients with decreased exercise tolerance was significantly lower than in patients with normal response to exercise (32.6±7.8 vs 27.2±6.6 ml O2/kg/min; p<0.05). Patients with impaired response also had a lower PaO2 at peak exercise (87±18.5 vs 100±18.6 mmHg; p=0.05) and widened alveolar-capillary oxygen gradient (17.5±10.1 vs 7.9±8.1 mmHg; p=0.05). Some significant correlations between V′O2max and FEV1% pred. (r=0.40; p<0.05), FVC % pred. (r=0.43; p=0.008), RV/TLC (r=0.41; p<0.01) were also noted.

Conclusions: Impaired exercise tolerance can affect up to 40% of patients with sarcoidosis. Lower PaO2 and widened alveolar-capillary oxygen gradient suggest an important role of gas exchange abnormalities in the pathogenesis of impaired response to exercise.

P3618
Multi nodular parenchymal pulmonary amyloidosis in primary Sjogren’s syndrome: A case report
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Lymphocytic bronchiolitis may correspond to low-grade MALT lymphoma which may be demonstrated by gene rearrangements rearrangement analysis.

Results: Pts with low BMI had decreased lumbar spine BMD(T–score<-1). The differences were statistically significant for group with normal BMI(18.5-BMI<25), compared to overweight(25-BMI<30), p=0.045 and to obese (BMI>30), p=0.0005. There were no such results for femoral neck BMD. The highest values of leptin were found in pts with obesity. The differences between pts with normal BMI compared to those with obesity was statistically significant (p=0.026). There was a weak correlation between leptin and BMI, R=0.2, leptin and IL-1, R=0.27, leptin and phosphate in urine, collected over 24h, R=0.31. No correlation was found between leptin and TNF-a or IL6.

Conclusions: In our group BMD was related to BMI but not to leptin levels nor other cytokines. Obesity, through its mechanical loading effect have a protective influence on bone tissue metabolism. Leptin, cytokines have a role in bone growth, development and loss. Further research is required to ascertain the importance of adipokines or cytokines for BMD.

Amiolyodosis is a rare cause of pulmonary infiltrates in primary Sjögren’s syn-
be moderate restriction, and BAL fluid was negative for acid-fast bacilli (AFB), fungi. Bronchoscopic with transbronchial lung biopsy revealed hyaline eosinophilic material associated with a giant cell granulomatous reaction, a patchy lymphocytic infiltrate. The Congo red stain was positive in this hyaline material and showed apple green birefringence on polarising microscopy. Electrophoresis of serum proteins revealed a monoclonal IgG. In the bone marrow (BM) plasma cells were increased to 10-15%. PSA (AL) associated with SS was diagnosed. Amyloid deposits were found not only in the lung but also in skin and BM biopsy specimens. Staining for amyloidosis should be performed in patient with SS and pulmonary infiltration.

P3619
Sarcoidosis is a frequent benign cause of lymphadenopathy in neoplastic patients
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Background: Clinical and radiographic aspects of sarcoidosis and malignancy might mimic one another, making the distinction between the two difficult in some cases. Cancer and sarcoidosis have been associated in some case series from the literature but this association remains controversial. Objectives: A descriptive retrospective study to evaluate the incidence of sarcoidosis in patients followed-up for previous cancer and referred for hilar/mediastinal lymphadenopathies, with no pulmonary lesions.

Methods: We conducted a retrospective chart review of all patients who were referred to our pulmonology department in the period between January 2007 and December 2011 with a new onset hilar/mediastinal lymphadenopathies during follow-up for previous neoplasms.

Results: Forty-eight patients (31 males, 17 females) of mean age 63 years (range 20-81) underwent EBUS/EUS trans-bronchial needle aspiration (TBNA). Patients were referred to our pulmonology department between January 2007 and December 2011 with a new onset hilar/mediastinal lymphadenopathies during follow-up for previous neoplasms.

Results: Forty-eight patients (31 males, 17 females) of mean age 63 years (range 20-81) underwent EBUS/EUS trans-bronchial needle aspiration (TBNA). Patients were referred to our pulmonology department between January 2007 and December 2011 with a new onset hilar/mediastinal lymphadenopathies during follow-up for previous neoplasms.

Conclusions: Our study suggests that sarcoidosis should be considered in the differential diagnosis of patients with a history of malignancy who develop hilar/mediastinal lymphadenopathies; a tissue diagnosis should be obtained before instituting therapy for presumed cancer recurrence.

P3620
Clinical study of pulmonary hypertension complicating pulmonary Langerhans cell histiocytosis
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Objective: To study the clinical features of pulmonary hypertension (PH) complicating pulmonary Langerhans’ cell histiocytosis (PLCH).

Methods: Medical records of 11 PLCH patients were reviewed from June 2006 to June 2011.

Results: 4 of the 11 PLCH patients presented PH with more severe clinical presentations. The major symptoms were laboring dyspnea and diminished exercise capacity (NYHA functional class III/IV), which were complicated with the sigh of right heart failure. The cystic change and pulmonary artery/main artery >1 were predominated on chest high-resolution computed tomography. Right heart enlargement was also found. As to pulmonary function presentation, the patients displayed severe carbon monoxide diffusing capacity impairment and significant hypoxemia. The pulmonary artery systolic pressure were highly increased. Besides the clinical symptoms, the laboratory features presented, involvement of both arteries and veins was also observed. Oxygen and symptomatic therapy were essential in the part of clinical treatment. 3 of the 4 PLCH-PH received corticosteroids or immunosuppressive agents, but the effect was not ideal. Only one case of PLCH-PH have a stable condition.

Conclusion: Pulmonary hypertension is a common complication of PLCH and seems to predict a poor prognosis. It is necessary to derive an early diagnosis and prevention.

P3621
BAL findings in idiopathic NSIP and IPF
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The role of bronchoalveolar lavage (BAL) in differentiating idiopathic NSIP (i-NSIP) and idiopathic pulmonary fibrosis (i-IPF) is still controversial. Some authors described that BAL lymphocytosis is more likely suggestive of NSIP rather than IPF. Others stated that BAL neutrophilia is more suggestive of IPF, whereas other authors reported that BAL findings are not discriminating between NSIP and IPF.

BAL findings were retrospectively assessed in 57 patients, 26 with a histologically proven diagnosis of iNSIP (surgical lung biopsy n=19, criobiopsies n=7), and 31 with a diagnosis of IPF. BAL was obtained before lung biopsy, or at the first patient evaluation for some of the IPF patients. All patients underwent bronchoscopy during stable clinical conditions, and BAL excluded malignancy and/or infections before BAL. Total and differential cell counts did not differ between iNSIP and IPF.

Seventeen of the 26 iNSIP patients (65.3%) and 20 of the 31 patients with IPF (64.5%) displayed severe carbon monoxide diffusing capacity impairment and significant hypoxemia. The pulmonary artery systolic pressure were highly increased. Besides these classical symptoms, the laboratory features presented, involvement of both arteries and veins was also observed. Oxygen and symptomatic therapy were essential in the part of clinical treatment. 3 of the 4 PLCH-PH received corticosteroids or immunosuppressive agents, but the effect was not ideal. Only one case of PLCH-PH have a stable condition.

Conclusion: Pulmonary hypertension is a common complication of PLCH and seems to predict a poor prognosis. It is necessary to derive an early diagnosis and prevention.

P3622
BAL markers of alveolar/capillary abnormality in IPF
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Several lines of evidence suggest that alveolar-capillary abnormalities, including increased alveolar sepal capacity and pulmonary vento-occlusive disease, are characterizing feature of IPF and may play a role in its progression. This study assess altered capillary permeability, abnormal intra-alveolar coagulation and alveolar hemorrhage as markers of alveolar/capillary abnormality.

Methods: Bronchoalveolar lavage (BAL) samples from 62 subjects (53 IPF patients and 14 healthy volunteers) were evaluated for s-alveolar macrophagin (s-AM) and f-alveolar macrophagin. All patients were studied by EBUS/EUS by linear approach.

Results: 26-12.6 BAL total and differential cell counts did not differ between iNSIP and IPF. The median (range) lymphocytes% was 11.5 (2-75) in iNSIP, and 7 (1-48) in IPF; the median (range) neutrophils% was 10.5 (0-59) in iNSIP and 20 (1-83) in IPF. In the iNSIP group (age 56±12 years) patients were significantly younger than in IPF (age 70±6; p<0.001), with a predominance of females (iNSIP n=17, IPF n=22) and 15 patients in the IPF group (48%) died during follow up. BAL findings were based of survival of changes in lung function.

Conclusion: BAL findings are not helpful to discriminate the diagnosis between iNSIP and IPF patients. However, these data suggest that there might be different clinical-biological phenotypes in both iNSIP and IPF patients.

P3623
Survival after surgical lung biopsy in patients with a histological pattern of non specific and usual interstitial pneumonia
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Background: Surgical lung biopsy involves a mortality risk, but is warranted to differentiate between fibrosing interstitial pneumonias with varying prognosis and response to therapy.

Objective: We evaluated 1 and 3-month mortality rate and post-operative course in patients with histopathological confirmed Usual Interstitial Pneumonia (UIP) and Non-Specific Interstitial Pneumonia (NSIP) after surgical biopsy.

Methods: Data and lung function were retrospectively collected from 1993 until 2008 from 57 patients that underwent surgical biopsy in our center that resulted in a histological pattern of UIP or NSIP. We analyzed 1 and 3-month mortality rate, post-operative hospital stay, drain removal, prolonged air leak and infectious complications.

Results: 1-month mortality rate was 5.1% (2/39) for UIP versus 0% (0/18) for NSIP. 3-month mortality rate was 10.2% (4/39) for UIP versus 0% for NSIP. No significant differences were observed in outcome measures. Notably, the NSIP...
group had a worse pre-operative lung function than the UIP group. Mean forced expiratory volume in 1 second (FEV1) was 71% percent of predicted in NSIP versus 82% in UIP (p < 0.005) and NSIP had a lower mean diffusing capacity of the lung for carbon monoxide (DLCO) of 41% versus 51% in UIP patients (p < 0.002).

**Conclusion:** After lung biopsy 3-month mortality in fibrosing interstitial pneumonias is relatively high (7%) and the majority (68%) of biopsies resulted in a UIP pattern. Four patients died within 3 months after biopsy all with a UIP pattern corresponding with a diagnosis of Idiopathic Pulmonary Fibrosis. This is remarkable because they had a significantly better pre-operative lung function.

### P3624

A newly developed sling incorporating a shock absorber to minimize the motion effect on SpO2 during the 6-minutes-walk test

**Katsi Miyamoto, Yuya Tanaka, Toshiaki Kurimoto. Department of Rehabilitation, Faculty of Health Sciences, Hokkaido University, Sapporo, Japan**

Recently, the degree of desaturation during 6-minute walk test (6MWT) is considered to have prognostic value in patients with idiopathic pulmonary fibrosis. In this study, we demonstrate a negative effect of motion on SpO2 during the walking and present a newly developed device that minimizes the negative effect during the test.

**Subjects and methods:** Ten healthy volunteers (26±11 yrs) performed 6MWT in 4 different manners: 1) usual walking, 2) usual walking while trying to minimize the effect of motion on the finger on which the oximeter-probe was placed, 3) usual walking using a newly developed sling with a shock absorber (75%) wrapped around the finger and the probe, and 4) walking on a treadmill at the same speed as the usual 6MWT while the finger and the probe were in a resting position without movement. SpO2 was measured continuously using a Pulsox 300i (Konica-Minolta)

**Results:** During the usual walking with/without the moving finger, there was severe desaturation of more than 4% from the baseline. However, when walking with the new device or on the treadmill there was only a small change in the SpO2 which was within the accuracy of the oximeter.

**Motion effects on SpO2**

<table>
<thead>
<tr>
<th>Degree of desaturation</th>
<th>Usual walking</th>
<th>Walking while trying not to move the finger and the probe</th>
<th>Walking using the new device</th>
<th>Walking on the treadmill</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% &lt; dSpO2 &lt; 4%</td>
<td>32.9±51.3</td>
<td>67.2±78.9</td>
<td>39.6±73.2</td>
<td>16.5±33.2</td>
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<td>4% &lt; dSpO2 &lt; 6%</td>
<td>13.3±39.6</td>
<td>14.5±38.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6% &lt; dSpO2</td>
<td>3.4±10.5</td>
<td>9.2±27.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Conclusions:** SpO2 monitoring during 6MWT does not provide reliable data on desaturation. However, using the new device, more reliable data on desaturation are available.

### P3625

Effects of lymphadenopathy on pulmonary function tests in sarcoidosis

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**Background and objectives:** The pulmonary function test (PFT) is an important examination in the follow-up of sarcoidosis. We aimed to investigate the effect of the presence of lymphadenopathy (LAP) alone or after controlling parenchymal involvement in PFT.

**Materials and methods:** A total of 63 sarcoidosis patients were enrolled retrospectively in the study. Respiratory functions were evaluated via PFT. Radiological evaluations of the patients were done with chest x-ray and high-resolution computed tomography (HRCT). Bronchoscopy investigations were performed on all patients. Possible factors that affect PFT were evaluated.

**Results:** There is statistically significant correlation between the bronchoscopic findings and PFT parameters (p < 0.01). Forced vital capacity (FVC) was affected more in the presence of LAP in bronchi neophants, it was more or less the same for forced expiratory volume in the first second (FEV1). Considering grade of HRCT findings, there is a statistically significant relation between FVC, FEV1, and the presence of hilar LAP, intrahilar LAP and lobar LAP (p=0.001). There is a statistically significant correlation with the presence of micronodules in HRCT and all parameters of PFT. There is a statistically significant negative correlation between the radiological stage of sarcoidosis and FVC, FEV1.

**Conclusion:** We revealed that besides parenchymal involvement of the disease, special localization of lymph node involvement also has an important effect on the PFT parameters of sarcoidosis patients.

### P3626

Airway-centered interstitial fibrosis – Two case reports

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Airway-centered interstitial fibrosis (ACIF) is a rare interstitial lung disease (ILD) of unknown cause characterized by chronic cough and progressive dyspnea and history of inhaled exposure. There is progressive peribronchial infiltration of interstitial inflammation and fibrosis with bronchiolar metaplasia. The majority of patients are non-responsive to corticotherapy and prognosis is poor. We describe two female patients, 65 and 66 years, presenting with chronic dry cough and progressive dyspnea. They were non-smokers, farmers and with a history of inhaled exposure to birds. Pulmonary function tests showed a moderate obstructive pattern in one case and moderately decreased CO diffusion in both patients. Chest radiographs revealed diffuse reticulonodular infiltrates. Chest computed tomography (CT) showed reticular fibrosis and ground glass infiltrates in one case and a UIP pattern in the other. Bronchoalveolar lavage showed an increase in lymphocytes and neutrophils in one case. The diagnosis was made by surgical biopsy revealing peribronchovascular lesions and lymphoplasmocytary infiltrate compatible with ACIF. Treatment with oral steroids for 12 months in both patients. In one case the disease progressed with worsening symptoms, pulmonary function tests and CT imaging even after combined immunosuppression with Azathioprine. In the other case the patient’s symptoms and CT imaging improved. These cases had similar clinical, radiological and pathological features as most of the few cases reported in literature. Both were non-smokers but had been exposed to birds. However, disease progression varied considerably as one patient improved but the other worsened even after combined immunosuppression.
P3629
The markers of inflammatory process activity and fibrinogenesis activity in patients with idiopathic pulmonary fibrosis
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Purpose: To define the inflammatory markers and severity of idiopathic pulmonary fibrosis (IPF).

Methods: There were examined 29 patients with IPF (men - 21, women - 8) in the age of 35 - 57 years. Duration of disease was from 2-3 months till 2-3 years. Control group included 10 practically healthy persons (donors).

Methods: Common clinical methods, X-ray examination, definition of hemostasis parameters. The hardphase method of immune analysis was used for measuring level of plasma fibronectin (PFN) and lavage fibronectin (LFN). Patients had been examined during the period of disease aggravation.

Results: Patients with IPF had increased level of PFN and decreased activated blood recalcification time (ABRT) (p < 0.05). The level of PFN was 319,211 ± 0,5482 and r=0,4969; p =0,05). Severity of patients condition correlated with increased level of PFN.

Conclusions: Revealed inflammatory markers and changes in hemostasis system testify about activation of fibrinogenesis and forming of chronic disseminated intravascular coagulation.

P3630
Hypersensitivity pneumonitis by feather duvet: A series of Vall d’Hebron Hospital
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Introduction: Exposure to avian proteins is a frequent cause of Hypersensitivity Pneumonitis (HP). We describe a series of HP secondary to exposure to feather duvet.

Material and methods: In the outpatient clinic of interstitial lung disease during the years 2004-2011, 28 patients were diagnosed with HP with definite causality from exposure to feathers contained in the feather duvet. Diagnosis criteria: diagnosis of HP, contact with feather duvet coincident with the onset of symptoms; IgG + and/or positive bronchal challenge test (BCT). In neither case had history of exposure to any agent known as a producer of HP.

Results: 15 male; mean age 59 years. Presentation was acute in 5, subacute in 4 and chronic in 19 cases. Anosultation was normal in 10 patients, revealed crackles in 17 and wheezing in 1. PEC mean was 67.57%. DLCO 52.60%. IgG + in front of avian antigens in 11/24, and in front of fungi in 16/24. A culture of feather duvet was positive for fungi in 6 cases. The BCT was positive in 8/11 in front of avian antigens and 47% against fungi. Pathological study was performed in 16/28 patients, showing a characteristic pattern of subacute HP in 6/16, consistent with HP in 8/16 and UIP pattern in 2/16. Surgical lung biopsy (BPQ) was performed during the study in 7 cases and revised from the samples of another center in 7. During the follow up lung transplantation, was performed in 4 patients (2 of them already had previous BPQ).

Conclusions: Our study confirms that exposure to a minimum but persistent agent may be sufficient for disease development. Diagnosis at an advanced stage of chronic HP is common. Project funded by FIS PI101577 (ISCIII) and SEPAP 2010.

P3632
Macrolides inhibit cytokine production by alveolar macrophages in bronchiolitis obliterans organizing pneumonia
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Background and objective: Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct clinicopathological entity histologically characterized by intra-alveolar granulation tissue and absence of extensive fibrosic lesions. Effective macrolide treatment of BOOP has been reported anecdotally. This study aimed to investigate whether alveolar macrophages (AMs) produce aberrant proinflammatory cytokines and chemokines which may be pivotal in the disease pathogenesis. Macrolides inhibit this cytokine production, CAM more efficiently than AZM.

Methods: AMs collected from bronchialalveolar lavage (BAL) from 6 BOOP patients and 8 non-ILD controls were cultured for 24 hours in the presence or absence of CAM, AZM, lipopolysaccharide (LPS), or dexamethasone (DEX). Tumor necrosis factor alpha (TNF-α), soluble TNF receptor 1 (sTNFR1), sTNFR2, interleukin 1beta (IL-1β), IL-6, IL-8, IL-10, interferon gamma inducible protein 10 (IP-10) and CC chemokine ligand 18 (CCL18) were measured in the culture supernatant by ELISA.

Results: The spontaneous and LPS-stimulated production of all investigated cytokines by AMs was significantly increased in BOOP compared to controls. CAM and AZM induced a dose-dependent suppression of spontaneous TNF-α, sTNFR2, IL-6, IL-8 and CCL18 production (p < 0.05). CAM also inhibited the IL-1β, IL-6 production. CAM and AZM significantly and dose-dependently attenuated the LPS-stimulated production of sTNFR1, sTNFR2, IL-8 and CCL18 (p < 0.05). CAM also inhibited the LPS-stimulated TNF-α, IL-1β, IL-6 and IL-10 production.

Conclusions: AMs from BOOP patients produce abundant proinflammatory cytokines which may be pivotal in the disease pathogenesis. Macrolides inhibit this cytokine production, CAM more efficiently than AZM.
Table 2. Laboratory findings and pulmonary function tests

<table>
<thead>
<tr>
<th>Patients with lung cancer and CPFE</th>
<th>Patients with lung cancer and IP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 40)</td>
<td>(n = 30)</td>
<td></td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>85 ± 5.03</td>
<td>85 ± 5.02</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>43 ± 4.97</td>
<td>43 ± 5.02</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>265 ± 14.8</td>
<td>265 ± 14.6</td>
</tr>
</tbody>
</table>

Laboratory

<table>
<thead>
<tr>
<th>KL-6 (U/ml)</th>
<th>Median (IQR)</th>
<th>n</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 (200-1000)</td>
<td>1500 (500-2000)</td>
<td>100</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Radiographic findings

<table>
<thead>
<tr>
<th>Function tests</th>
<th>Median (IQR)</th>
<th>n</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC% predicted</td>
<td>95 (80-110)</td>
<td>100</td>
<td>0.28</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>65 (60-70)</td>
<td>100</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Conclusions: Although IPF was more frequent in the CPFE group than in the IP group, the occurrence of acute exacerbations after surgery was not different between the two groups.

P3633

A case of lymphoid interstitial pneumonia associated with common variable immunodeficiency

Martin Schreder1,2, Fabrizio Mezzasalma 1, Pasquale Di Martin Schreder

Case report: In October 2009, a 51 year old woman presented with a 12-months history of recurrent pyrexia and was subsequently diagnosed with CVID. CT scans showed bilateral pulmonary consolidations, while bronchoscopy revealed acute inflammation of the bronchial mucus and purulent secretion. The patient received antibiotic treatment and immunoglobulin replacement. She remained asymptomatic until January 2012, when she was readmitted with increasing dyspnea and fatigue for 2 weeks prior to admission. CT scans showed progressive opacities mainly in the lower zones. Despite immediate treatment with broad-spectrum antibiotics, the patient developed acute respiratory failure requiring invasive mandatory ventilation and, ultimately, extracorporeal membrane oxygenation. Open lung biopsy was performed 5 days after admission. Histologic workup showed diffuse interstitial infiltration of T lymphocytes, plasma cells and histiocytes, consistent with a diagnosis of LIP. Treatment with prednisone (1mg/kg) resulted in rapid clinical and radiological improvement. The patient was discharged 4 weeks after admission. At present, she remains clinically stable at a steroid dose of 0.25mg/kg.

Discussion: The finding of bilateral ground-glass infiltrates in a patient with CVID should raise suspicion of LIP. Open lung biopsy is required to establish the diagnosis.

Conclusions: The finding of nontuberculous granulomas alone is not sufficient for the final clinical diagnosis of tuberculosis. Due to high incidence of tuberculosis in our country there is a tendency to overdiagnose tuberculosis.

P3634

Disease progression according to IPF phenotype

David McAllister1, Pauline Macfarlane2, Gareth Stewart6, Andrew Robson2, Donatella Castria1, Rosa Metella Reim1, Fiztrizio Mezzalazza1, Pasquale Di Sipio1, Elena Bargaghi1, Rita Filippi1, Carlo Perle2, Paola Rottoli1, 1Department of Clinical Medicine and Immunological Science, Respiratory Disease and Lung Transplantation Section, Siena, Italy, 2Department of Cardiology, Haemodynamic Unit, Siena, Italy

Introduction: The aim of our study is(1) to evaluate the prevalence of Pulmonary Hypertension (PH) in Idiopathic pulmonary fibrosis (IPF) patients; (2) to determine the accuracy of PAP measurements with Doppler echocardiography (DE) versus Right Heart Catheterization (RHC); (3) to analyze survival in pts with or without PH; (4) to determine any correlation between functional data and haemodynamic parameters. We analyzed 54 IPF pts referred to our Centre who underwent RHC. PH was defined when PAPm ≥25 mmHg. PH was diagnosed in 30/54 pts (55%, PAPm=30±5 mmHg, PAPS=48±10, PW=11±3, RVP=3±1.2). There was a significant correlation between PAPm values at DE and RHC (r=0.0001), but Bland-Altman analysis illustrated mean difference: -5.1±4.4. The large limits of agreement (-17 +27) showed that DE should not be used to replace RHC. No difference in survival was found between PH group(1) and no PH group(2). Pts were divided according PH onset (<12 months) from IPF diagnosis: group A, or >12 m: group B) and we observed a significant difference in survival between group A and B (p=0.0042, 35m versus 56). The correlation between PH group and other pts groups (2B+, 3B, 0.0005, 35 versus 52.11% of group A needed oxygen-therapy after a median time of 8m since IPF diagnosis, while 32.76% of all other pts (group 2B+ after 16m<0.002). We observed a significant correlation between Six Min Walking test distance (WTD) performed in room air and PAPm at RHC(p=0.039).

Our data confirms that PH has an high prevalence in IPF and RHC is the gold standard for PH diagnosis. An early onset of PH is related to a worst prognosis and to a precarious oxygen-therapy request. A decrease of WTD could help clinicians to suspect PH in IPF pts.

P3637

Obstructive findings in sarcoidosis, diagnosis and therapies modalities

Jelica Videnovic-Ivanov, Snezana Filipovic, Violeta Vacunic, Vlada Zugic, Pulmonology, Clinic for Lung Diseases and Tuberculosis, Belgrade, Yugoslavia

Introduction: Symptoms of respiratory disturbances are common during the interstitial lung disease after surgery. Although IPF was more frequent in the CPFE group than in the IP group, the occurrence of acute exacerbations after surgery was not different between the two groups.

Introduction: Lymphoid interstitial pneumonia (LIP) represents a rare disease that typically occurs in association with autoimmune diseases and dysproteinemia. We report a case of LIP in a patient with common variable immunodeficiency (CVID).

Case report: In October 2009, a 51 year old woman presented with a 12-months history of recurrent pyrexia and was subsequently diagnosed with CVID. CT scans showed bilateral pulmonary consolidations, while bronchoscopy revealed acute inflammation of the bronchial mucus and purulent secretion. The patient received antibiotic treatment and immunoglobulin replacement. She remained asymptomatic until January 2012, when she was readmitted with increasing dyspnea and fatigue for 2 weeks prior to admission. CT scans showed progressive opacities mainly in the lower zones. Despite immediate treatment with broad-spectrum antibiotics, the patient developed acute respiratory failure requiring invasive mandatory ventilation and, ultimately, extracorporeal membrane oxygenation. Open lung biopsy was performed 5 days after admission. Histologic workup showed diffuse interstitial infiltration of T lymphocytes, plasma cells and histiocytes, consistent with a diagnosis of LIP. Treatment with prednisone (1mg/kg) resulted in rapid clinical and radiological improvement. The patient was discharged 4 weeks after admission. At present, she remains clinically stable at a steroid dose of 0.25mg/kg.

Discussion: The finding of bilateral ground-glass infiltrates in a patient with CVID should raise suspicion of LIP. Open lung biopsy is required to establish the diagnosis.

Conclusions: The finding of nontuberculous granulomas alone is not sufficient for the final clinical diagnosis of tuberculosis. Due to high incidence of tuberculosis in our country there is a tendency to overdiagnose tuberculosis.

P3635

Sarcoidosis and tuberculosis: A rare combination?

Diana Calara1, Oxana Manteu1, Victor Bontan1, Internal Medicine, State Medical and Pharmaceutical University "Nicolae Testemitanu", Chisinau, Republic of Moldova

Tuberculosis and sarcoidosis are chronic granulomatous diseases that are similar in many aspects, although different. They occur concomitantly very rarely. TB is an infectious disease caused by M. tuberculosis morphologically defined by granulomas with caceous necrosis. Sarcoidosis is a systemic disease of unknown etiology, and is characterized by noncaseous granulomas.

Conclusions: Patients with both definite and probable IPF have poor prognoses, but survival was worse in definite IPF. The IPF index may be of clinical value in definite and probable IPF.

P3636

Precocious detection of pulmonary hypertension in idiopathic pulmonary fibrosis

Donataella Castria1, Rosa Metella Reim1, Fiztrizio Mezzalazza1, Pasquale Di Sipio1, Elena Bargaghi1, Rita Filippi1, Carlo Perle2, Paola Rottoli1. 1Department of Clinical Medicine and Immunological Science, Respiratory Disease and Lung Transplantation Section, Siena, Italy; 2Dept. of Cardiology, Haemodynamic Unit, Siena, Italy

The aim of our study is(1) to evaluate the prevalence of Pulmonary Hypertension (PH) in Idiopathic pulmonary fibrosis (IPF) patients (pts);(2)to determine the accuracy of PAP measurements with Doppler echocardiography (DE) versus Right Heart Catheterization (RHC);(3) to analyze survival in pts with or without PH;(4)to determine any correlation between functional data and haemodynamic parameters.

We analyzed 54 IPF pts referred to our Centre who underwent RHC. PH was defined when PAPm ≥25 mmHg. PH was diagnosed in 30/54 pts (55%, PAPm=30±5 mmHg, PAPS=48±10, PW=11±3, RVP=3±1.2). There was a significant correlation between PAPm values at DE and RHC (r=0.0001), but Bland-Altman analysis illustrated mean difference: -5.1±4.4. The large limits of agreement (-17 +27) showed that DE should not be used to replace RHC. No difference in survival was found between PH group(1) and no PH group(2). Pts were divided according PH onset (<12 months) from IPF diagnosis: group A, or >12 m: group B) and we observed a significant difference in survival between group A and B (p=0.0042, 35m versus 56). The correlation between PH group and other pts groups (2B+, 3B, 0.0005, 35 versus 52.11% of group A needed oxygen-therapy after a median time of 8m since IPF diagnosis, while 32.76% of all other pts (group 2B+ after 16m<0.002). We observed a significant correlation between Six Min Walking test distance (WTD) performed in room air and PAPm at RHC(p=0.039).

Our data confirms that PH has an high prevalence in IPF and RHC is the gold standard for PH diagnosis. An early onset of PH is related to a worst prognosis and to a precarious oxygen-therapy request. A decrease of WTD could help clinicians to suspect PH in IPF pts.
course of sarcoidosis. The aim of analysis is to notice obstructive findings in sarcoidosis.

Method: The analyses is retrospective in all incoming patients to the Clinic for lung diseases and tuberculosis CC of Serbia in Belgrade.

Results: 127 (8.7%) patients with dry cough and occasionally dyspnea was the imparient of lung function. The main findings were: FEV1/FVC 63.1% in 57.44.8% patients; in 27.21.1% patients – FEV1/FVC were 55.7%, in 3.2.3% patients FEV1/FVC were 68.7%. Gender distribution were as followed: 264 (66.2%) Female-Male 135 (33.8%); average ages were 43.32 years. Extrathoracis sarcoidosis involvement were find out in 3 (2.3%) patients (skin, lymph nodes). Lung and nonpulmonary sarcoidosis is notify in 27 pts and in 97 pts lung were the only sarcoi
dosis manifestation. Radiographic stage of lung involvement: I:87 (68.5%), II:31 (24.4%), III:7 (5.5%), IV:1 (0.78%). Acute onset of sarcoidosis is predom
inantly with average level of ACE: 75.3 U/L. After obtaining the diagnosis of sarcoidosis, inhaled corticosteroids were administered, 160 mcg-daily through 3 months with controls which means: ACE and UCA/24h levels, lung function, chest X ray. Regression of symptoms such as dry cough were obtained in 55% for patients after the period of 2 months; 45% patients were excluded due to persistent of symptoms seeking prednisone.

Conclusion: Inhaled corticosteroid have the role in sarcoidosis treatment resolving symptoms such as cough, improvement of FEV1, but the main therapy in most of the patients is still orally administered prednisone.

P3638 Natural history of idiopathic pulmonary fibrosis: Are slowly progressive and rapidly progressive really steady conditions?

Elisabetta Balestero, Emanuela Rossi, Ariel Fiorianini, Claudia Rinaldo, Francesca Lunardi, Monica Loy, Federico Rea, Manuel Cosio, Marina Saetta, Fiorella Calabrese. Department of Cardiologie, Thoracic and Vascular Sciences, University of Padova Medical School, Padova, Italy

Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease with heterogeneous

clinical course. Some patients experience an accelerated disease progression (rapid progressors) while other remain relatively stable over time (slow progressors).

The aim was to investigate the different course of the disease in relation to survival. The study population included 55 IPF patients (age at diagnosis 53±1) categorized in rapid progressors and slow progressors by two distinct criteria: pre-diagnosis criteria (symptoms onset and IPF diagnosis) or post-diagnosis criteria (decline in FVC% over 12 months). When stratified by pre-diagnosis criteria 18% were rapid progressors while 66% were slow ones. When stratified according to post-diagnosis criteria 67% were rapid progressors and 33% were slow ones. The patients were divided as 70% and 25% for rapid and rapid progressors respectively indicating that up to 30% of patients did not maintain the same label. Stratification by pre-diagnosis criteria was not related to survival. Conversely, stratification by post-diagnosis criteria had a prognostic significance; indeed, rapid progressors had decreased survival as compared to slow ones (28.1±49.8mo, p=0.02). Of interest, rapid progressors according to post-diagnosis criteria, often display an unstable decline alternating periods of functional stability to a rapid deterioration.

In conclusion our data suggest the need to be cautious in labelling IPF patients to a fixed phenotype from the beginning of symptoms till death. It is possible that IPF patients show a variable and unpredictable clinical course rather than a steady condition.

P3639 The clinical relevance of autoimmunity in idiopathic pulmonary fibrosis

Sara Tomassetti, Christian Giurioli, Claudia Ravaglia, Sara Piccisci, Gian Luca Casoni, Micaela Romagnoli, Carlo Giurioli, Venerino Poletti. Pulmonary, GB Morgagni Hospital, Forli, Italy

The aim of this study was to evaluate the clinical significance of autoimmunity in IPF:

This is a retrospective controlled study comparing clinical characteristics and outcome of IPF patients with (n=73) and without (n=87) positive autoimmunity. Seventy-three cases with positive autoimmunity included: 46 (63%) ANA (anti nuclear antibody), 20 (27%) RF (rheumatoid factor), 2 (3%) anti CCP (anti cyclic- citrullinated), 3 (4%) ENA (antibodies to extractable nuclear antigens), 2 (3%) ANCA (anti-neutrophil cytoplasmatic antibody). No differences were found between patients with positive and negative autoimmunity in terms of age, gender, smoking history, prevalence of familial IPF, high resolution computed tomography features.

Abstract P3641 – Table 1. Correlations between radiographic stage, HRCT scores and subscores and functional parameters

<table>
<thead>
<tr>
<th>Thickness of the bronchovascular bundle</th>
<th>Parenchymal consolidation</th>
<th>Intraparenchymal nodules</th>
<th>Septal/non-septal lines</th>
<th>Focal pleural thickening</th>
<th>Total HRCTscore</th>
<th>Radiographic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>-0.34**</td>
<td>-0.16</td>
<td>-0.12</td>
<td>-0.38**</td>
<td>-0.31**</td>
<td>-0.38**</td>
</tr>
<tr>
<td>FVC</td>
<td>-0.23</td>
<td>-0.19</td>
<td>-0.13</td>
<td>-0.29**</td>
<td>-0.32**</td>
<td>-0.51**</td>
</tr>
<tr>
<td>DLCO</td>
<td>-0.26*</td>
<td>-0.41**</td>
<td>-0.36**</td>
<td>-0.55**</td>
<td>-0.52**</td>
<td>-0.38**</td>
</tr>
<tr>
<td>MMEF25-75</td>
<td>-0.31**</td>
<td>-0.17</td>
<td>-0.27**</td>
<td>-0.51**</td>
<td>-0.52**</td>
<td>-0.38**</td>
</tr>
<tr>
<td>TPC</td>
<td>-0.31**</td>
<td>-0.17</td>
<td>-0.27**</td>
<td>-0.51**</td>
<td>-0.52**</td>
<td>-0.38**</td>
</tr>
<tr>
<td>TEP</td>
<td>-0.31**</td>
<td>-0.17</td>
<td>-0.27**</td>
<td>-0.51**</td>
<td>-0.52**</td>
<td>-0.38**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001.

During follow up two patients developed an autoimmune disease (one rheumatoid arthritis and one scleroderma).

Survival between IPF patients with and without positive autoimmunity did not differ 77.4 months (95% CI 56.1-97.8).

Conclusion: A small minority (2.7%) of IPF patients with positive autoimmunity test at diagnosis developed an autoimmune disease during follow-up. The presence of positive autoimmunity testing do not influence neither IPF clinical presentation nor survival.

P3640 Sarcoidosis and autoimmune thyroid disease

Claudia Ravaglia, Carlo Giurioli, GianLuca Casoni, Micaela Romagnoli, Sara Tomassetti, Christian Giurioli, Venerino Poletti. Pulmonology, Department of Thoracic Diseases, Morgagni Hospital, Forli, FC, Italy

Background: Association between Sarcoidosis and other autoimmune diseases has been previously described and a common pathogenesis has been hypothesized.

Objectives: A descriptive retrospective study has been conducted to evaluate the incidence of thyroid diseases in patients with pulmonary sarcoidosis.

Methods: We conducted a retrospective chart review of all patients diagnosed with sarcoidosis between 2004 and 2011 at the Morgagni Hospital, Forli; those who were also diagnosed as having an autoimmune thyroid disease were selected. Results: 39 out of 246 (15.9%) patients with sarcoidosis were identified as having autoimmune thyroid disease, 9 male and 30 female. Sarcoidosis presented as Löffgren’s syndrome in 6 patients patients (15.4%). 3 patients developed Graves’ disease (7.7%), 12 patients developed Hashimoto’s thyroiditis with hypothyroidism (30.8%) and 24 patients had thyroid nodules with normal thyroid function (61.5%).

Conclusions: Our study suggests that sarcoidosis may be associated with autoimmune thyroid diseases at some time of its evolution, either as hyperthyroidism or hypothyroidism. We are now following up sarcoidosis patients with no thyroid disease to see if any thyroid disease can develop after the diagnosis or during the period of activity of sarcoidosis.

P3641 Assessment of disease severity using imaging scores in pulmonary sarcoidosis

Vicent Botnamu, Diana Calarga, Oxana Munteanu. Internal Medicine, State Medical and Pharmaceutical University “Nicolae Testemitanu”, Chisinau, Republic of Moldova

The value of imagistic methods in diagnosing and assessing the inflammatory activity in sarcoidosis is well known. The aim was to assess the association between imagistic findings (radiographic score, and HRCT score by Oberstein et al.[SarcoidosisVasc Diffuse Lung Dis 1997,14:65–72]) and disease severity defined by functional disturbances in sarcoidosis.

We have evaluated the clinical records of 70 patients with biopsy proven or highly suggestive of sarcoidosis, cases registered in a 3rd level medical institution, during year 2011, who underwent chest X-ray, HRCT, and pulmonary function tests. The HRCT images were scored by two readers. Spearman’s rank correlation coefficients were calculated to estimate the association between imagistic scores and respiratory function disturbances.

We found a relationship between both radiological staging and HRCT abnormalities with functional parameters. All HRCT subscores, except lymph node enlargement, correlated with FEV1, FVC, MMEF25-75, and DLCO (p<0.001).

Compared with radiological stages, HRCT findings appeared to be more sensitive in tracing abnormal gas exchange, with no significant difference in other functional parameters.
Aline Domingos Pinto Ruppert, Vera Capelozzi, Edwin Roger Parra

Background: Speckle tracking has emerged as valuable tool for comprehensive assessment of regional myocardial function, providing angle-independent measurements of ventricular strain. Aim of this study was to evaluate left ventricular (LV) function in patients with newly diagnosed sarcoidosis, utilizing the novel method of 2D speckle tracking.

Methods: Forty one patients with sarcoidosis and unremarkable medical history were included. Image acquisition was performed in a conventional 2D Doppler and TDI measurements, speckle tracking echocardiography was applied and LV global longitudinal strain was derived from the obtained images. LV base and apex rotation angles were assessed from which LV twist was derived.

Results: The mean age of patients (17 men) was 41.65 years old. Compared with controls, patients had similar conventional 2D and Doppler measurements. TDI revealed increased E/E' in the patient group vs control group (8.72±1.65 vs 4.6±1.32, p<0.05). Strain analysis demonstrated reduced global longitudinal strain values in the patient vs control group (18.86±1.79% vs 21.88±2.18% p<0.05). Furthermore, LV twist was increased in the patient group as compared to the boiundaries (12.52±2.6% vs 10.21±1.80, p<0.05).

Conclusions: Speckle tracking echocardiography revealed impaired strain and rotational indices, implying elevated filling pressures of the left ventricle. This may represent a sign of myocardial involvement in patients with sarcoidosis. Therefore deformation imaging could be valuable adjunct for screening.

P3643

Overexpression of angiotensin II type 1 receptor (AGTR1) and lymphatic vasculature rarefaction is present in scleroderma with pulmonary involvement

Aline Domingos Pinto Ruppert, Vera Capelozzi, Edwin Roger Parra, Faculdade de Medicina da Universidade de São Paulo, Brazil

Background: The aim of this study was to evaluate the activity of angiotensin II type 1 and 2 receptors and lymphatic vessels in lungs of patients with systemic sclerosis comparing to normal lung tissue (NLT).

Methods: Lung specimens were obtained from 23 female patients with scleroderma. NLT were obtained from 10 individuals who died suddenly of non-pulmonary causes. Immunohistochemistry and histomorphometry were used to evaluate the expression of AGTR-1 and AGTR-2 pulmonary expression. We also studied the lymphatic (D2-40) expression and the percent of area occupied by lymphatic vessels in lungs specimens. Pulmonary fibrosis was obtained from high-resolution computed tomography (HRCT) score.

Results: We observed higher amount of AGTR-1 and AGTR-2 expression in the pulmonary parenchyma of patients with scleroderma when compared with NLT (p<0.01). The density of lymphatic vessels was markedly reduced in pulmonary parenchyma of patients with scleroderma compared with NLT (p<0.001). Similar situation was observed when we compared the area occupied by these lymphatics in lungs specimens. Pulmonary fibrosis was obtained from high-resolution computed tomography (HRCT) score.

Conclusions: Our data showed that the AGTR-1 and AGTR-2 expression in the pulmonary parenchyma of patients with scleroderma was higher when compared with NLT (p<0.01). The density of lymphatic vessels was markedly reduced in pulmonary parenchyma of patients with scleroderma compared with NLT (p<0.001). Similar situation was observed when we compared the area occupied by these lymphatics in lungs specimens. Pulmonary fibrosis was obtained from high-resolution computed tomography (HRCT) score.

P3644

The relationship between the shuttle walk test, lung function and BMI in patients with sarcoidosis

Rebecca Freeth, Colin Leonard, Jayne Holme, Annette Duck. North West Lung Centre, University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom

Introduction: Monitoring patients with sarcoidosis is important and challenging.

The incremental shuttle walk test is used in outpatient settings and we assessed its correlation with lung function, BMI and age.

Methods: A retrospective study of data from 63 patients with sarcoidosis who had a shuttle walk test with their lung function tests. Spearman’s correlation coefficient (rs) was used to assess the relationship between the shuttle walk test (distance walked, oxygen saturations) and Borg score (before and after exercise), with lung function (FEV1, FVC% predicted), age and BMI. A stepwise multiple linear regression model of distance walked was developed.

Results: Correlation is seen between the shuttle walk and lung function (table 1). The distance walked also correlated with age (rs=-.372, p=0.003) and BMI (rs=-.303, p=0.016). There was correlation between the Borg score post exercise and the BMI (r=-.253, p=0.046). The multiple regression model of distance walked identified BMI (rs=3.195, p=0.002) and FEV1 (rs=0.061, p=0.003) as significant independent variables.

P3645

Interstitial lung disease associated with autoimmune thyroiditis (ILD-AT)

Osama Stefanian, Marina Koval, Evgeniy Shmelev, George Kaltsakas, Anastasios Kallianos, Ouranis Anagnostopoulou, George Tzelepis, Konstantina Aggeli, Universidade de São Paulo, Brazil

Background: Interstitial lung disease (ILD) associated with autoimmune thyroiditis (AIT) is considered an orphan syndrome mainly seen in women. The level of thyroid peroxidase in serum initially elevated in all of patients returned to normal after treatment. The results of treatment were as much better as shorter was the disease duration.

Objective: To show some peculiarities of an orphan syndrome which is often misdiagnosed.

Methods: Patients and 8 methods, which were related to ILD-AT were revealed among about 5000 patients with various interstitial lung diseases during 25 years.

Results: ILD-AT was diagnosed in 7 female patients (age 49-60 years) and 1 male (age 23 yrs). In 5 cases the onset of pulmonary and thyroid disease was simultaneous in 3 autoimmune thyroiditis (AT) appeared several years earlier than ILD. The average duration of disease was 8.6 yrs to the moment of ILD-AT was diagnosed (range 1-27 yrs). In all patients ILD-AT presented with constant dry cough, dyspnea and crackles in lungs. NSIP pattern was seen on HRCT scans of all patients. Spirometry found out restriction in 6 of 8 cases (FVC 52-20%) while FEV1/FVC ratio was not decreased and bronchodilator test was negative. DLCO was lowered to 52.6-25.2% as well as PaO2 arterial blood level (69-49 mm Hg) in all patients. Long term treatment with low dose corticosteroids (during 2-27 yrs) prevented disease progression. The level of thyroid peroxidase in serum initially elevated in all of patients returned to normal after treatment. The results of treatment were as much better as shorter was the disease duration.

Conclusions: Appearance of constant dry cough and dyspnea should be the reason for chest HRCT, spirometry and DLCO measurement in patients with AT. Patients with interstitial lung disease of unknown origin should be tested for AT. In spite of rather favorable course ILD-AT should be diagnosed in time and treated long to avoid diffuse pulmonary fibrosis formation.

P3646

6-minute walk test predicts pulmonary artery pressure in patients with collagen vascular disease associated interstitial pneumonia

Kota Takahashi, Hiroaki Asakura, Hiroyuki Taniguchi, Yasuhiro Kondoh, Tomoki Kimura, University of California, Los Angeles, CA, USA

Objective: It has been reported clinical importance of pulmonary hypertension (PH) in collagen vascular disease (CVD), however the role of PH in interstitial pneumonia related CVD (CVD-IP) has been scarcely evaluated. We sought to determine the prediction factor of mean pulmonary artery pressure (MPAP) in patients with CVD-IP.

Methods: Patients with CVD-IP underwent right heart catheterization (RHC) within 3 months of initial evaluation at our institution. Patients with left ventricular dys-function, incomplete follow-up, and patients with respiratory failure were excluded.

Results: We studied 44 patients (19, male mean age 59.8±11.0 years). They were 13 with RA, 13 with SSC, 9 with PM/DM, and 9 with others. PaO2 at rest was 83.1±6.9 mmHg, MPAP was 17.2±5.5 5mmHg (12.2±3.8mmHg, 13.2±9.5%), cardiac index (CI) was 3.6±0.8 L/min/m², pulmonary vascular resistance index (PVR) was 223±102 Wood units/m², 5 Minute ventilation (VC) was 78.4±21.0%, percentage of carbon oxide of minuscule capacity (9DLCO) was 50.9±16.7%, and 6-min walk distance (MDW) was 502±142 m, and minimum SpO2 at 6-min walk test (SpO2md) was 85.6±5.9%, respectively. The median observation period was 3.8 months (range 4-11 months) for patients with CVD-IP.

Conclusions: In the univariate model, MPAP was significantly correlated with 9DLCO (r=0.377, P=0.013), and SpO2md (r=0.552, P<0.001). In the multivariate model, MPAP was significantly correlated with 9DLCO (r=0.360, P=0.014) and SpO2md (r=0.595, P<0.001).
P3647
Sarcoidosis – Diagnostics, prognosis and therapy in everyday pneumological practice. A retrospective analysis
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Background: Currently, prognostic factors, or therapy in sarcoidosis are frequently discussed, however, up-to-date data concerning the incidence and the management of sarcoidosis in everyday pneumological practice are still missing. Therefore, we decided to analyze the characteristic of comprehensive cohort of sarcoidosis patients.

Methods: We retrospectively analyzed all 169 patients, whom the diagnosis of sarcoidosis was set at our pulmonary department in years 2005-2010. After excluding 19 patients that had other diseases and 9 because of non-Caucasian origin, 141 patients were added for further analysis. Male sex outnumbered females 55%-45%. Median age was 44 years, however 20% of patients were younger than 20 years. The median age of sarcoidosis patients was 48 years (20-79). Females:males ratio was 1:5.1. Non smoker:smoker ratio was 2:2.1. Familial occurrence was observed in 4 patients. At diagnosis, stage 0 was present in 3.5% patients, stage I in 34% patients, stage II in 49.5% patients, stage III in 11% patients, and stage IV in 2% patients. In 76 patients there was extrapulmonary sarcoidosis. The coincidence of sarcoidosis with other autoimmune diseases was observed in 10 patients (6 patients had systemic lupus erythematosus). Spontaneous remission was seen in 36% patients, 57% of stage I, 29% of stage II, and 11% of stage III. 64% received corticosteroids. 16% of patients developed chronic sarcoidosis. In sarcoidosis patients with spontaneous resolution, no relapse of disease was observed. On the other hand, 10% of treated patients relapsed. Median time to sarcoidosis relapse was 6 months. There was no difference in age between good and poor risk groups of patients. Observed lethality was 1.2% (2 patients).

Conclusion: Male gender, X-ray stage I or II, lymphocytic alveolitis in bronchoalveolar fluid, spontaneous regression, and active disease duration up to 2 years appear to be good prognostic factors.

P3648
BALF cells expression phenotypes and cytokine levels in BALF supernatant in fibrosing interstitial lung diseases
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Aims: Fibrosing interstitial lung diseases (fILDs), namely idiopathic pulmonary fibrosis (IPF) and fibrotic nonspecific interstitial pneumonia (NSIP), are processes with unknown etiology and grim prognosis. We hypothesize that expression profile of BALF cells and cytokine concentrations in fILDs depend on Th2 cytokine milieu and enhance fibroproliferative healing.

Methods: 10 patients with fILDs and 9 controls (C) were included into the study. BALF samples were used for FACs to detect spontaneous and stimulated proliferation of TNF alpha, percentage of lymphocytes expressing IL-2, IFN-gamma and TNF-alpha, and percentage of epithelial cells expressing proteinase-activated receptors (PAR 1,2,3). IFN-gamma, IL-1 beta, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12p70 and TNF beta values were evaluated by means of bead-based analysis. Concentrations of CD124, PAR-2, TGF-beta 1 and TNF-alpha in BALF were detected by ELISA as well.

Results: We observed significantly higher concentrations of IL4R and TGF-beta 1 in BALF in fILDs versus C. The expression of PAR-2 on EP was higher in fILDs compared to C as well.

Conclusion: Our results supported a hypothesis about the role of Th2 type immune response in pathogenesis of fibrotic ILDs. The higher concentrations of IL-4R might be a sign of IL-4 influence, and the increased expression of TGF-beta and PAR-2 gives evidence for ongoing epithelial- mesenchymal transition and fibrogenesis in fILDs.

P3649
Pulmonary eosinophilic syndromes characterization. The role of peripheral eosinophilia
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Introduction: Pulmonary eosinophilic syndromes (ES) are a heterogeneous, rare and not fully characterized group of diseases. The eosinophils accumulate in the airways and the alveoli. The main causes are asthma, parasitic diseases, inflammatory bowel disease, and infections. The most common esophageal cause is eosinophilic esophagitis. These disorders can be associated with idiopathic pulmonary fibrosis, bronchiectasis, and sarcoidosis.

Objectives: Evaluation of ES patient's clinical features and its evolution.

Methods: 47 patients with >20% BAL eosinophils or compatible histological features were included and its clinical files retrospectively analyzed.

Results: 10 patients that had sarcoidosis and 9 because of lacking information, 19 patients were enrolled: 8 presented Chronic Eosinophilic Pneumonia (CEP), 6 Churg-Strauss Syndrome (CSS), 3 Acute Eosinophilic Pneumonia and 2 Allergic Bronchopulmonary Aspergillosis (ABPA). Mean age at symptoms onset 37±14.6 and at diagnosis 43±14.3 years. The majority was female (68.4%) and nonsmokers (76.5%). Peripheral eosinophilia was observed in 78.9% patients (1.7±3.1 32x10^9/L), mean eosinophils in BAL was 51±29.16%. airflow obstruction was observed in 55.6% patients, 22.2% had restrictive pattern, 16.7% mixed pattern and 5.6% normal values, without significant differences among entities. Concerning CEP, CSS and ABPA cases after treatment, 83.3% presented obstructive pattern, 16.7% normal values and a significant increase of FEV1 (p=0.038) and RV (p=0.019) were observed. The RV was associated with mild peripheral eosinophilia or persistent eosinophilia (p=0.045). Mild peripheral eosinophilia at diagnosis was associated to its persistence after treatment (p=0.023).

Conclusion: In this series, mild peripheral eosinophilia was associated with its persistency and respiratory hyperinflation after treatment, suggesting that the degree of peripheral eosinophilia is associated to a distinct clinical evolution.

389. Diffuse parenchymal lung disease III

P3650
The decrease of surfactant protein D in bronchoalveolar lavage fluid in patients with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia
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Background: Surfactant protein (SP)-A and SP-D are useful biomarkers for the diagnosis and evaluation of activity of interstitial lung diseases. SP-A and SP-D, which are lung specific proteins, belong to a subgroup of the C-type lectin su-

Results: In IFP and NSIP patients, SP-D levels in BALF were significantly lower than those from healthy controls (p=0.006 and p=0.003) and sarcoidosis patients (p=0.02 and p=0.01). SP-A levels in BALF were no significant difference among these patients and controls. The significant positive correlation of SP-D levels between serum and BALF was found in IFP patients (p=0.529, p=0.008). In NSIP patients, the correlation of SP-D levels between them was not significant. No correlation of SP-A levels between serum and BALF was observed in any patients groups.

Conclusion: In IFP patients, SP-D levels in BALF were lower than those in healthy controls and had significant positive correlation with those in serum.

P3651
Characteristics of inspiratory and expiratory reactance in interstitial lung disease
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Forced oscillometry is a noninvasive method to measure respiratory impedance and widely used in obstructive lung diseases, but has not been well studied in restrictive lung diseases. This study was conducted to investigate the characteristics of measurements obtained by impulse oscillation system (IOS) in patients with interstitial lung disease (ILD).

IOS and spirometry were performed in 64 ILD patients, 54 asthma patients, 49 chronic obstructive pulmonary disease (COPD) patients, and 29 controls. Respiratory resistance and reactance were assessed as measurements averaged over several tidal breaths (whole-breath analysis) and as measurements separately averaged during inspiration and expiration (inspiratory-expiratory analysis). Whole-breath analysis failed to distinguish between ILD and obstructive lung diseases. Inspiratory-expiratory analysis demonstrated no difference between inspiratory and expiratory reactance at 5 Hz (X5) in controls and asthmatic patients. Expiratory X5 was more negative than inspiratory X5 in COPD patients. In contrast, expiratory X5 was found to be less negative than inspiratory X5 in ILD patients. Furthermore, within-breath change in X5 was inversely correlated with vital capacity and diffusing capacity of carbon monoxide in ILD patients. These results suggest that increased magnitude of X5 during inspiration compared with that during expiration is a characteristic feature of IOS measurements in ILD patients.
The efficacy of pirfenidone in scleroderma related interstitial lung disease
Yukiko Miura1, Yoshia Tsuonuda, Toru Tanaka, Hiroyuki Takoi1, Yohi Yatagai, Shiuh Lyon Lin, Yoshia Yatagai, Akimasa Sekine1, Kenji Hayashi2, Taketumi Saito1, Chiharu Iinuma1, 1Department of Respiratory Medicine, National Hospital Organization Ishikawa Memorial Hospital, 2Department of Pulmonary Medicine, National Hospital Organization Ishikawa Memorial Hospital, Tokyo, Japan

Introduction: Major cause of death in Systemic Sclerosis (SSc) is interstitial lung disease, and cyclophosphamide is an only agent which significantly demonstrated a beneficial effect on lung function in patients with scleroderma-related interstitial lung disease (SSc-ILD), however the effect was quite modest, and it is necessary to identify a reasonable alternative.

Objectives: TGF-beta1 plays a critical role in the pathophysiology of pulmonary fibrosis. Pirfenidone exerts its antifibrotic effect through regulation of TGF-beta1 which is one of the important inducers of fibrogenesis in SSc. We suggest pirfenidone may be a possible option for SSc-ILD.

Methods: We administered pirfenidone to 3 patients with SSc-ILD and evaluated pulmonary function.

Results: Case 1 is a 62-year-old female. Vital capacity (VC) improved by pirfenidone. The change rate was +27.3% (+0.51L) for 5 months. Case 2 is a 75-year-old female. VC improved remarkably, at the change rate of +44.4% (+0.21L) for 25 months. Case 3 is a 66-year-old female. VC improved at the rate of +8.0% (+0.17L) for 26 months.

Conclusion: All of 3 patients with SSc-ILD demonstrated the favorable efficacy of VC by pirfenidone without severe adverse events. The previous studies documented that deteriorating lung function was associated with increased mortality in SSc-ILD. Therefore, it is necessary to identify and treat early stages of patients with SSc-ILD for the prevention of pulmonary function impairment. Pirfenidone exerts its antifibrotic effect through regulation of TGF-beta1, which is one of the important inducers of fibrogenesis in SSc. We suggest pirfenidone may be a possible option for SSc-ILD.

Effect of pirfenidone on chronic interstitial pneumonia
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Introduction: Several reports reveal the favorable effect of pirfenidone on early stage of idiopathic pulmonary fibrosis (IPF), but impacts on non-specific interstitial pneumonia (NSIP) and interstitial pneumonia (IP) associated with collagen-vascular diseases (IP-CVD) are not clear.

Objectives: To examine the effect of pirfenidone on chronic IP including IPF, NSIP and NSIP-CVD.

Methods: Thirty-two patients were enrolled in the study evaluating the safety and efficacy of pirfenidone in IPF. NSIP, and IP-CVD. Clinical diagnosis are IPF14, NSIP14, IP associated with scleroderma3, and rheumatoid arthritis1. Based on IPF/CVD at rest and SPO2 after 6 minutes walk test (6MWT), disease severity of those patients were classified into four groups [Table 1]. We retrospectively analyzed subjective symptom in British Medical Research Council scale, pulmonary function, KL-6, SP-D and CT findings before and during pirfenidone administration.

Table 1. Disease severity of patients

<table>
<thead>
<tr>
<th>PaO2 at rest (mmHg)</th>
<th>SPO2 after 6MWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: 81-94</td>
<td>60-69</td>
</tr>
<tr>
<td>II: 70-79</td>
<td>When &lt;90%, to III</td>
</tr>
<tr>
<td>III: 60-69</td>
<td>When &lt;90%, to IV</td>
</tr>
<tr>
<td>IV: 60-69</td>
<td>unmeasurable to perform 6MWT</td>
</tr>
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<td></td>
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</tbody>
</table>

Results: Correlations was observed between subjective symptom and VC, but was not between subjective symptom and KL-6, SP-D, CT findings. After administration of pirfenidone, VC improved above 5% in 22%, 50%, 25%, 45% of patients (severity grade I, II, III, IV, respectively). Subjective symptoms highly improved in patients with scleroderma (improvement rate: 63% in scleroderma vs. 14%, 14%, 0% in IPF, NSIP, RA, respectively).

Conclusions: Pirfenidone might have the favorable efficacy independent of disease severity, without severe adverse events, in chronic IP, especially in associated with scleroderma.

P3654 Telephone consultations for follow-up of interstitial lung disease: Patient satisfaction survey
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Introduction: The long-term follow-up required by Interstitial Lung Disease (ILD) patients imposes a significant burden on healthcare resources. Telephone consultations have been piloted as an alternative to some face-to-face consultations in a teaching hospital based ILD service. Patients whose next consult is anticipated to be uncomplicated (eg stable patients having interval lung function tests) are offered a phone consult with the ILD consultant.

Aims and objectives: To assess whether ILD patients are as satisfied with a telephone consultation as with a face-to-face consult.

Methods: A postal survey was sent to 95 consecutive ILD patients who had a phone consult over a 12-month period. Patients used a 5-point score to report if, in comparison to a face-to-face consult, the phone consult was as punctual, convenient, reassuring, and afforded the same opportunity to ask questions, and facilitated the same understanding of information.

Results: 52 patients (55%) posted responses (see Table 1). 67% agreed phone consultations were as punctual. 78% agreed they were as convenient. 77% felt as reassured and as able to ask questions. 88% understood the information given just as easily. 80% were willing to have another phone consult.

Table 1

<table>
<thead>
<tr>
<th>%</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>As punctual</td>
<td>2</td>
<td>17</td>
<td>12</td>
<td>40</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Convenient</td>
<td>0</td>
<td>10</td>
<td>11</td>
<td>48</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Felt as reassured</td>
<td>2</td>
<td>10</td>
<td>11</td>
<td>48</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Able to ask questions</td>
<td>0</td>
<td>11</td>
<td>12</td>
<td>44</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Understood the information</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>52</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

Discussion: The majority of ILD patients selected for a telephone consultation were at least as satisfied as with a face-to-face telephone. Telephone consultations are acceptable to the majority of ILD patients for at least some of their follow-up.

P3655 NSIP: A diagnosis? Thomas Nivière1, Pierre-Alain Gevenois1, Benjamin Bondue1, Paul De Vuyst2,1 Hematology, Institut Jules Bordet, Brussels, Belgium, 2Radiology, Erasme, Brussels, Belgium

Introduction: Nonspecific interstitial pneumonia (NSIP) is the most discussed entity in the group of idiopathic interstitial pneumonias. Recognized in 2002 by the American Thoracic Society and the European Respiratory Society as a provisional diagnosis, NSIP may be idiopathic or associated with a number of clinical settings.

Objective: The objective of this study was to determine the proportion of strictly idiopathic NSIP among a cohort of patients whose initial lung CT scan considered NSIP as a possible diagnosis.

Method: 73 adult patients with an initial CT pattern of NSIP were selected in our database of adult patients with ILD (1998-2011) and were enrolled in a monocentric retrospective study. Anamnestic, clinical, functional, biological and pathological data were reviewed for each patient as well as the evolution of disease.

Results: In only 21 patients (71.2%) an alternative diagnosis could be made, most frequently an underlying connective tissue disease (n= 22, 30.1%) and idiopathic pulmonary fibrosis (n=12, 16.4%).

The other diagnoses include hypersensitivity pneumonitis (n=7, 9.6%), drug-induced lung disease (n= 5, 6.8%), sarcoidosis (n=1, 1.4%), a sequel of ARDS (n=1, 1.4%), LIP (n=1, 1.4%) and a RBILD (n=1, 1.4%).

Conclusion: This study demonstrates that idiopathic NSIP is a rare condition among patients presenting a radiological NSIP pattern. Therefore an integrated multidisciplinary approach is recommended in order to diagnose alternative/associated diseases needing for most of them a specific treatment.

P3656 6-minute walk test (6MWT) in patients with idiopathic pulmonary fibrosis (IPF): Confirmation of the minimal clinically important difference (MCID) Steven Nathan1, Carlo Albera2, Roland du Bous1, 1Williamson Bradford4, Ulrich Costabel1, Talmadge King1,2, Paul Noble1, Steven Sahn1, Dominique Valeyre1, 1Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA, United States; 2Clinical and Biological Sciences, University of Turin, Italy; 3Department of Medicine, Imperial College, London, United Kingdom; 4Clinical Research, InterMune, Inc., Brisbane, CA, United States; 5Pneumology/Allergy, Ruhrahlandklinik, Essen, Germany; 6Department of Medicine, University of California San Francisco, CA, United States; 7Department of Medicine, Duke University School of Medicine, Durham, NC, United States; 8Department of Medicine, Medical University of South Carolina, Charleston, SC, United States; 9Department of Medicine, Assistance Publique-Hôpitaux, Paris, France

Introduction: The 6MWT is a practical measure of exercise tolerance in patients with IPF. MCID estimates for 6MWT distance (6MWED) in patients with IPF have ranged between 10–58 in [1-3]; we sought to confirm these estimates in an independent cohort of patients with IPF.

Methods: All patients randomized to placebo in the CAPACITY studies were
The efficacy of transbronchial biopsies without fluoroscopy control in patients with IPF.

Conclusions: Analysis of 6MDW data from a large cohort of IPF patients yielded an MCID estimate of 22–37 m. This finding is consistent with previous estimates which, taken together, provide a meaningful benchmark for assessing 6MDW in patients with IPF.

P3657
The efficacy of transbronchial biopsies without fluoroscopy control in diagnostics of extrinsic allergic alveolitis
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Background: Extrinsic allergic alveolitis (EAA) is usually established based on results of CT exam, immunology, and transbronchial lung biopsy (TBLB) during flexible bronchoscopy (FSB). As a rule, TBLB should be performed under fluoroscopy control, but it is not always possible, and in such situation efficacy of TBLB is controversial.

Aims: To investigate the effectiveness of TBLB and bronchoalveolar lavage (BAL) during FBS in patients with newly diagnosed EAA.

Materials: 66 patients with EAA were enrolled into the study, all of them underwent CT of the chest with subsequent FBS with TBLB and BAL. We analysed the diagnostic efficacy of TBLB upon histology and cytology, and diagnostic changes in BAL. Additionally, mean and median number of tissue samples, samples quality, frequency of pneumothorax and severe bleeding were analyzed.

Results: There were 37 females in the group, mean age for both sexes - 48.3 years, varied from 19 to 73 years. Mean disease duration from first symptoms/chest abnormalities was 87.1 weeks. Mean tissue samples number was 2.23, varied from 1 to 5, median 2. There were no complications. Lung tissue was observed in 42/66 cases (64.5%). Upon histology, granulomas and tissue infiltration were seen in 30 out of 66 patients (45.4%), additionally due to cytology granulomas were found in 4 cases, thus total efficacy of TBLB was 34/66 (51.5%). Among the rest 32 patients, diagnostically significant changes in BAL were found in 16 patients, so the total efficacy of TBLB plus BAL reached 50/66 (75.7%).

Conclusion: Bronchoscopy with TBLB and BAL even without fluoroscopy control is effective and safe way to establish the diagnosis of allergic alveolitis.

P3658
KL-6 compared to LDH as a prognostic factor in Caucasian patients with idiopathic pulmonary fibrosis
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Background: Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease with a poor prognosis. Little is known about sensitive prognostic markers for IPF. Aims: The aim of our study was to investigate the significance of KL-6 compared to LDH as a prognostic marker in Caucasian patients with IPF.

Methods: We prospectively collected 79 Caucasian patients with IPF. Serum samples were obtained at enrollment. Serum levels of KL-6 and lactate dehydrogenase (LDH) were measured by ELISA and the correlation between baseline serum levels of the markers and the survival was evaluated.

Results: Median follow-up period was 372 (1-7088) days. Sixteen (20%) patients died during follow-up. There was no significant difference in the baseline serum KL-6 levels between patients who survived and not survived. Receiver operating characteristic (ROC) curve analysis for predicting non-survival showed larger area under the curve for KL-6 than LDH (0.617 and 0.553, respectively). When the cut-off levels of 1300 U/mL for KL-6 and 280 IU/L for LDH were set, sensitivity, specificity and accuracy for predicting non-survival were 81%, 60% and 66% for KL-6 and 56%, 51% and 52% for LDH. In Kaplan-Meier analysis, patients with baseline serum KL-6 level ≥1300 U/mL showed shorter survival compared with patients with baseline serum KL-6 level <1300 U/mL (p=0.02). LDH showed no statistical impact on the prognosis (p=0.20). In multivariate analysis, baseline serum KL-6 level ≥1300 U/mL was an independent predictive factor for poor prognosis (hazard ratio=4.46, p=0.030).

Conclusions: Baseline serum KL-6 level ≥1300 U/mL is an independent predictive factor for poor prognosis in Caucasian patients with IPF.
herpes I and II viruses (HVI and HVII). We also correlated sex, age, AIDS and immunosuppression therapy.

Results: We detected by immunohistochemistry the epithelial alveolar infection of MV and CMV in 30.8% and 15.4% in DAD pattern, respectively. Endothelial CMV infection was observed in 25% of CLF pattern. When we divided the age in two groups 1 patients with ≤ of 43 years old and ≥ of 72 years old, the first group had more infection of MV, CMV than the second group. The Spearman’s correlation showed a positive correlation between epithelial and endothelial CMV infection and AIDS (r=0.472, p=0.003).

Conclusion: The epithelial and endothelial viral infections observed in these diseases reinforce the possible viral participation in the pulmonary fibrosis disease. These findings are particularly relevant given the increased interest in the epithelial injury and repair as it relates to the pathogenesis of many diffuse lung diseases.

Financial support: FAPESP, CNPq.

P3661
Pirfenidone, proton pump inhibitor, N acetyl cysteine (PINPOINT) therapy for IPF: Tolerance and safety profile among Indian patients

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Rationale: To our knowledge there are no data of PirfenDine, P3Oon pump Inhibitor. N-acetyl cysteine (PINPOINT) therapy in IPF. We retrospectively examined the safety & tolerability of PINPOINT in IPF-UIP.

Methods: 40 consecutive patients with IPF-UIP administered PINPOINT, Pirfenidone 200 mg three times day & titrated to 400 mg three times day over 2 to 4 weeks, a proton pump inhibitor & N-acetyl cysteine 1800 mg/day. Baseline liver function tests were performed. Lung function & 6MWT were possible in 25 patients. Patients were followed at 2 weeks, then monthly/quarterly. Predisuasion was adhered to follow up based on clinical assessment. Four newly diagnosed patients were given only PINPOINT.

Results: Baseline mean spO2 at rest was 95% & mean FVC 1.30 litres (55% predicted). Baseline liver function were normal in all patients. Mean lowest spO2 on 6 minute walk test was 90%. There was no significant increase in liver enzymes at follow up. 17 patients had pulmonary hypertension on 2D Echo. Mean duration of follow up was 241 days. In 25 patients, Pirfenidone could be increased to 1200 mg/day. Dose could not be increased to 1200 mg/day in 11 patients due to gastrointestinal side effects (nausea/vomiting 10 patients, loose motions - one patient). Pirfenidone was stopped in five patients because of skin itching & rash (4 patients 600mg/day, 1 patient 1200 mg/day). 5 patients continued to take Pirfenidone despite skin itching (no skin discoloration) after counseling about side effects & took symptomatic treatment. 5 patients expired during this period. Conclusion: PINPOINT therapy appears to be well tolerated in patients in IPF-UIP.

P3662
Frequency and impact of interstitial lung disease on clinical state and mortality in systemic sclerosis

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Background: Interstitial lung disease (ILD) is a frequent complication and a leading cause of morbidity and mortality in Systemic Sclerosis (SSc).

The aim of our study was to determine the frequency of ILD in a cohort of Tunisian SSc and to assess the influence of this association on clinical, biological features and outcome of SSc.

Methods: A retrospective study included 30 consecutive patients with SSc who fulfilled the American Rheumatism Association’s criteria. Patients were divided into four descriptive disease subsets: lcSSc, dcSSc, SSc sine scleroderma and other organ involvement.

A retrospective study based on the follow up (FU) of ILD patients who developed CTD during at least 3 years follow up period. Patients: A cohort of 120 ILO patients attending a specialist clinic with an increased ILD pattern. Patients were divided into four descriptive disease subsets: lcSSc, dcSSc, SSc sine scleroderma and overlap syndrome.

Results: The ILD cases without clinical history of CTD and with UIP-like or NSIP pattern on the background of histology specimens, must be followed for long time period.

It is of important value such patients to be checked initially and in follow up by HRCT, clinical and laboratory tests.

In these subgroups of patients the prognosis is better than UIP/IPF patients.

P3663
Pirfenidone in idiopathic pulmonary fibrosis (IPF): Early single centre Irish experience

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Introduction: Pirfenidone is an orally bio-available synthetic molecule, which has recently been approved for the treatment of mild to moderate IPF in Europe. It regulates the activity of TGF-β and TNF-α in vitro. Open label pirfenidone prescription commenced in June 2011 in the Republic of Ireland. We report the early experience of a single centre with pirfenidone.

Methods: We conducted a retrospective review of medical records of those patients who were prescribed pirfenidone. We analysed baseline demographics, symptoms and pulmonary function. Comparisons between groups were conducted using paired t-testing.

Results: 26 patients (20 male) received the medication. 22 patients remain on the medication. 1 patient died due to IPF exacerbation and 3 others discontinuing the medication secondary to side effects. 15 (58%) of patients have reached target dose of medication. 7 subjects continue to take pirfenidone at a reduced dose. 14 participants reported side effects potentially related to pirfenidone. The most commonly reported side effect was fatigue followed by gastro-intestinal disturbance and photo-sensitivity. An increase (< 2 fold) in transaminases was noted in 1 patient. Patients who experienced side effects or required dose reduction were on average older but this did not reach statistical significance. Amongst subjects who had repeated pulmonary function testing (n=14), there was no significant decline in TLC or FVC between baseline and follow up.

Conclusions: Pirfenidone is a novel agent for the treatment of limited IPF. The side effect profile in an Irish population appears consistent with recent published data. Further follow up is required to establish efficacy in an Irish population.

P3664
Lung fibrosis and ILD in patients with systemic sclerosis: an Irish experience

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Aim: A retrospective study based on the follow up (FU) of IPD patients who developed CTD during at least 3 years follow up period.

Methods: A cohort of 120 ILO patients attending a specialist clinic with an increased ILD pattern and HRCT findings. A number of 12 cases who were undertaken surgery biopsy (OLB/VAAT) were selected for the study.

Results: The above 12 patients developed during the follow up period CTD, six cases have f-NSIP on the background and 6 have UIP-like pattern.

Conclusions: The ILD cases without clinical history of CTD and with UIP-like or NSIP pattern on the background of histology specimens, must be followed for long time period.

It is of important value such patients to be checked initially and in follow up by HRCT, clinical and laboratory tests.

In these subgroups of patients the prognosis is better than UIP/IPF patients.

P3665
Pulmonary functions in systemic sclerosis

Abdalla Khoury1, Piras Abou-Trebeh1, Saeid Hammoud2.

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Background: Pulmonary involvement is the leading cause of systemic sclerosis (SSc)-related deaths.

Objective: To determine the prevalence of pulmonary involvement in systemic sclerosis and its distributions on the disease subsets, and to study its relation with other organ involvement.

Methods: We analyzed 43 SSc patients, a careful history and clinical examination was performed to each patient. All the patients were submitted to chest radiographs and high-resolution CT (HRCT) and underwent pulmonary function testing and echocardiography and electrocardiography and six minutes walk test. Patients were grouped into four descriptive disease subsets: lcSSc, dcSSc, SSc sine scleroderma and overlap syndrome.

Results: Of the 43 patients, (53.5%) of patients had lcSSc and (27.9%) dcSSc. Overlap syndrome was diagnosed in (11.6%) of patients, SSc sine scleroderma was present in (7%) of patients, (93%) were female and the mean age of 41.6±11.51, (55.8%) of the patients had pulmonary symptoms or signs, dyspnea was the most prevalent symptom (37.2%). Pulmonary fibrosis was most prevalent involvement (41.9%), and it was more common in dcSSc (41.6%) compared with lcSSc (30.4%). Pulmonary hypertension was second in prevalence (PASP> 35 mmHg) 20.9% and it was more common in lcSSc (21.7%) compared with dcSSc (8.3%). (62.8%) of the patients had restrictive pulmonary function test. (65.1%) of the patients had normal six minutes walk test.

Discussion: Our results will be discussed with well known international studies.

Tuesday, September 4th 2012
Introduction: University Hospitals Coventry and Warwickshire is a large acute teaching NHS trust which serves a population of over 1 million. There has been an ILD MDT since 2006. In July 2010 a consultant with an interest in ILD was appointed. The MDT constitutes a thoracic surgeon, pathologist and radiologist with expressed interest in ILD.

Aim: To describe the spectrum of ILD presenting in secondary care.

Method: It is departmental policy to discuss all incident cases of ILD in the MDT. Diagnoses were made according to BTS guidelines, and by consensus. Numbers were compared by χ², and ages by Mann-Whitney U-test.

Results: From September 2010 to July 2011, 89 suspected cases were discussed in the ILD MDT, 10 of whom proved not to have significant ILD. The diagnoses of the remaining 79 are given in table below.

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<tr>
<td>Idiopathic Pulmonary fibrosis (IPF)</td>
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Definite IPF made up 15% of the cohort, with a median age of 77. Smoking related ILD – Respiratory Bronchiolitis associated ILD and Desquamative Interstitial Pneumonia – account for (11%) of cases. The median age of diagnosis is 27 years younger than those with IPF (p<0.001).

Conclusion: Smoking related ILD makes a significant proportion of cases discussed at the ILD MDT. Patients are significantly younger than those with IPF. This may reflect an increasing awareness of the radiological and pathological features consistent with IPF.

TUESDAY, SEPTEMBER 4TH 2012

P3666
Analysis of cases from an interstitial lung disease (ILD) MDT in a teaching hospital in the West Midlands: Patients with smoking-related disease comprise 11% of cases and have a median age of 50 years

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Conclusion: Smoking related ILD makes a significant proportion of cases discussed at the ILD MDT. Patients are significantly younger than those with IPF. This may reflect an increasing awareness of the radiological and pathological appearance of these diseases.

P3667
A retrospective cohort study of interstitial lung diseases in Denmark

Charlotte Hyldegaard, Elisabeth Bendstrup, Ole Hilberg. Department of Respiratory Diseases, Aarhus University Hospital, Aarhus C, Denmark

Introduction: Interstitial lung diseases are a heterogeneous group of diseases with varying degrees of inflammation and fibrosis. Epidemiological data based on the current diagnostic criteria are sparcible.

Objectives: The aim of this study was to characterize the distribution of ILD subtypes in a cohort of Danish patients referred to a tertiary referral hospital.

Methods: We included 431 patients diagnosed with interstitial lung disease (sarcoidosis excluded) and first visit at our department between April 1, 2003 and April 1, 2009. All diagnoses were re-evaluated according to current diagnostic criteria including the 2011 ATS/ERS IPF-guidelines. Details on diagnostics, lung function, comorbidity and treatment were recorded at baseline and throughout the follow-up period.

Results: A total of 186 patients were diagnosed with idiopathic interstitial lung diseases. In this group IPF (n=121) was the most common diagnosis (108 definite and 13 probable IPF) followed by NSIP (n=30), and DIP (n=20). Other large groups comprised 11% of cases and have a median age of 50 years (Quitters) while 8 either continued to smoke or were inconsistent in their cessation attempts (Smokers). Baseline lung function at diagnosis was compared to current values of FEV1, FVC, TLCO and KCO between Quitters and Smokers.

<table>
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<th>Parameter</th>
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<th>Quitters (n=4)</th>
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<tr>
<td>FEV1</td>
<td>–63%</td>
<td>–84%</td>
</tr>
<tr>
<td>FVC</td>
<td>–89%</td>
<td>–89%</td>
</tr>
<tr>
<td>TLCO</td>
<td>–58%</td>
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</tr>
<tr>
<td>KCO</td>
<td>–31%</td>
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There was a significant difference in median rate of decline of TLCO (p=0.036) and KCO (p=0.014) between Quitters and Smokers, with a trend towards a difference for FEV1 (p=0.141) and FVC (p=0.285).

This case series confirms previous findings supporting the importance of smoking cessation which can have a positive impact on lung function. Continued smoking however can result in continued decline at a rate faster than that reported in healthy normals and patients with COPD.

Spontaneous pneumomediastinum & subcutaneous emphysema in idiopathic pulmonary fibrosis (IPF) with bronchial wall leak

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Spontaneous pneumomediastinum & subcutaneous emphysema in IPF is due to alveolar rupture but air leak due to bronchial rupture is rare. We present unique case of bronchial leak seen on bronchoscopy in a patient of IPF. Non traumatic subcutaneous & mediastinal emphysema due to bronchial rupture in IPF is rare & is being reported for the first time. Case report-55 years male admitted with severe progressive dyspnoea & dry cough of 1 month. Massive subcutaneous emphysema was seen on chest, neck & arms. CT thorax showed pneumomediastinum & IPF in lower lobes.

Put on steroids & 100% O2 but no relief. Bronchoscopy showed air bubbles oozing from irregular opening near superior segment of left lower lobe.

Glue was applied to seal bronchial wall leak & to our amaze subcutaneous emphysema started regressing with clinical improvement. Repeat CT scan showed decrease in mediastinal air. Discussion-Bloomberg considered the cause of non traumatic subcutaneous & mediastinal emphysema to be due to weakness of the air or bronchial wall. Air escapes via bronchovascular channels to mediastinum & subcutaneous tissues, described as Maclin effect.

668s
390. Diffuse parenchymal lung disease IV

P3670 Coagulation factor IX deficiency does not afford protection from pulmonary fibrosis in the experimental murine bleomycin model
Kerem Erkmen1, Lin Cong2, Bruno Crestani3, Olivier Christophe4, Arnold Spek5, 6INSERM U700, Faculté de Médecine Xavier Bichat, Paris, France; 2Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, Netherlands; 3Pulmonology, Hospital Bichat, Paris, France; 6INSERM U770, Hopital le Kremlin Bicêtre, Le Kremlin-Bicêtre, France

Introduction: Animal and human studies strongly suggest the importance of the coagulation cascade in acute and chronic lung injury. Indeed, beyond their role in hemostasis, coagulation factors can signal via their cellular receptors, the protease-activated receptors. We hypothesized that the absence of coagulation FactorFIX, which is essential for the activation of the coagulation cascade would reduce fibrosis development and progression.

Methods: We used the murine model of bleomycin-induced pulmonary fibrosis in wild-type (WT, n=14) and FIX deficient mice (n=13). After 14 days, we assessed markers of tissue fibrosis, inflammatory cell influx in the bronchoalveolar lavage fluid (BALF), and cytokines levels in the BALF, blood and lung homogenate of the animals.

Results: Mortality during the experiment was higher in the FIX deficient mice compared to wildtypes (23% versus 7%). The remaining FIX deficient mice (n=10) developed pulmonary fibrosis to a degree similar to WT (n=13). There was no significant difference in the Ashcroft score between WT and FIX deficient mice (4.0±1.4 versus 4.2±0.4), in the alpha-actin alpha (0.94±0.09 versus 0.70±0.07) and in the inflammatory cell number. In contrast, we observed in the placebo of the FIX deficient mice significant elevations in levels of cytokines IL-12, TNFs, IFNγ, MCP-1 and IL-6.

Conclusion: Mice with a congenital deficiency of FIX are not protected against bleomycin-induced pulmonary fibrosis. These data strongly argue against an important role of the blood coagulation cascade in the progression of pulmonary fibrosis, and raise important concerns about the use of anticoagulant therapy in patients.

P3671 Aggravation of bleomycin-induced pulmonary fibrosis in senescence-accelerated mouse
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Objective: Idiopathic pulmonary fibrosis (IPF) is predominantly a lung fibrotic disease of older adults, and the process underlying aging might significantly influence the development of pulmonary fibrosis. Bleomycin-induced lung injury was investigated in murine models of accelerated senescence (SAMP8) and of normal aging (SAMR1). The levels of TH1/TH2 related cytokine were also measured.

Methods: Bleomycin or PBS was injected into the tracheal lumen of 12-month-old SAMP8, 4 and 12-month-old SAMR1 mice. Seven, 14 and 28 days after the injection, the mice were killed and the lungs were harvested for pathological examination, hydroxyproline assay and protein detect. Lung TGF-β1 expression was determined by western blot, and the levels of IL-4 and IFN-γ were detected by ELISA.

Results: The aggravated bleomycin induced lung injury was observed in 12-month-old SAMP8 compared with 4 and 12-month-old SAMR1. Twenty eight days after injection of bleomycin, Aschoff score was significant higher in 12-month-old SAMP8 than in 4 and 12-month-old SAMR1 (P<0.05, respectively). Seven days, 14 days and 28 days after bleomycin injection, lung TGF-β1 expression was increased in 12-month-old SAMP8 and SAMR1 compared with 4-month-old SAMR1. Similarly, the level of IL-4 and the IL-4/IFN-γ ratio of the lungs tended to be higher in 12-month-old SAMP8 and SAMR1 than in 4-month-old SAMR1, but the differences were not statistically significant.

Conclusion: Bleomycin-induced pulmonary fibrosis in SAM was aggravated by aging. The old SAM with bleomycin-induced pulmonary fibrosis might be inclined to Th2-biased immune responses. (This work was funded by Natural National Science Foundation of China Grants 81070046).

P3672 Lung function progression in Langerhans cell histiocytosis
Sophie Krivinskas1, Philip Ind1, Anthony Chu2, 3Respiratory Medicine, Imperial College Healthcare Trust, Hammersmith Hospital, London, United Kingdom; 4Dermatology, Imperial College Healthcare Trust, Hammersmith Hospital, London, United Kingdom

It is a rare, multisystem dendritic cell disorder commonly involving the lungs. The natural history is variable with little lung function outcome data. Our database of 92 patients referred to AC for treatment, 51 patients were male; mean age at diagnosis was 31 (range 1-77) years (y). 1702 patients, 10 male, mean age 31 y, had primary lung disease (PLCH). 14/75 had systemic LCH with lung involvement (SLCH). All PLCH had smoked with mean 13 pack-yr; 9/17 continued smoking after diagnosis. Initial lung function (n=115) showed mean %predicted FEV1, 76 (34-113)%; VC 81 (53-114)%; TLC 67 (19-108)%. 2 patients had obstructive, 3 restrictive, and 3 mixed lung disease. 9/14 SLCH patients were male, mean age 25y, 10 had smoked; mean 12 pack-y, 7 continued smoking after diagnosis. Initial lung function (n=9) showed mean %predicted FEV1, 83 (72-105)%; VC 89 (72-104)%; TLC 76 (49-106)%. Method: 14 (range 8 to 14 months) patients were followed after injection of bleomycin, 70 (30-103)%predicted, VC was 84 (51-109)%; TLC was 63 (17-105)%. Mean change in FEV1; -7.1±3 to 12%+, in VC was 1 (1.9 to +14%+), in TLC was -10 (-49 to +29)%, in 11/17 patients received treatment. To date 3 have died, 10 are in remission and 4 have active disease.

In SLLCH (n=6) at mean follow up of 6 (2-22) y mean FEV1 was 83 (66-101)%predicted, VC was 92 (79-103)%; TLC was 93 (82-94)%. Mean change in FEV1, was -3 to -9 to +55%, in VC was -1 (14 to +92%) and in TLC was 14 (+2 to +45%). 12/14 patients received treatment. To date 1 has died, 8 are in remission and 5 have active disease.

LCH is rare but is in this relatively small, selected series lung function is worse and declines more in patients who present with primary lung involvement than those with lung involvement in systemic LCH.

P3673 Correlation between spirometry, six minute walk test and HRCT characteristics of patients with interstitial lung diseases in a tertiary care center in Sri Lanka
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Objectives: To find out the correlation between spirometry, six minute walk test and HRCT characteristics of patients with ILDs.

Methods: Study was done in chest unit, general Hospital, Kandy (GHK) from January 1, 2011 to December 31, 2011. Ethical clearance was granted by Ethical Committee of GHK. Patients with suspected ILDs on chest radiography and showed restrictive lung defect on spirometry underwent HRCT scan of the chest. Pathological findings of HRCT (parenchymal nodules, fibrosis, ground glass and mosaic perfusion) were graded a score using the scoring system described by Zara et al. (Ann. Med. 2005, 12, 31-34). Six minute walking test was performed. Correlations were analyzed using Pearsons and Spearmans correlation coefficient.

Results: Twenty one patients [5 (23.8%) males, 16 (76.2%) females] with ILD were studied. There was a significant positive correlation between resting satura-tion and forced vital capacity (FVC) (r = 0.52, p = 0.02), resting saturation and forced expiratory volume in 1 second (FEV1) (r = 0.549, p = 0.012), six minute walk distance and FVC (r = 0.505, p = 0.023). There were no correlations between HRCT scores with spirometry, and six minute walk test parameters.

Conclusion: Although there was a correlation between spirometry and six minute walk test, pathological distribution described by HRCT showed no correlation with spirometry or six minute walk test in patients with ILD.

P3674 Uncommonly common? Common variable immunoglobulin deficiency 'masquerading' as sarcoidosis
Rana Alkur1, David Miller1, Anne-Marie Shanks1, Richard Herriot2, 1Chest Clinic C. Aberdeen Royal Infirmary, Aberdeen, Scotland, United Kingdom; 2Immunology Department, Aberdeen Royal Infirmary, Aberdeen, Scotland, United Kingdom

Introduction: Multisystem granulomatous inflammation can be a presenting fea-ture or a complication of common variable immune deficiency (CVID). A propor-tion of patients diagnosed with 'sarcoidosis' may actually have underlying CVID, recognition of which may be associated with considerable diagnostic delay.

Method: 2 cases are presented to illustrate this along the results of an audit.

Case 1: LC presented aged 28 with chronic cough and deranged LFTs. HRCT showed multiple pulmonary nodules and generalised lymphadenopa-thy. Granulomas were seen on liver biopsy. A diagnosis of sarcoidosis was made 4 years later after several chest infections, severe panhypogammaglobulinemia was demonstrated and a revised diagnosis of CVID made.

Case 2: DG presented aged 29 with cough, breathlessness and generalised lymphadenopathy. Granulomas were seen on liver biopsy. A diagnosis of sarcoidosis was made after lymph node aspirate demonstrated granulomata.13 years later, investigations after a protracted pneumonia revealed panhypogammaglobulinemia.

Standard immunoglobulin replacement therapy at a dose of 40mg/kg/month was started in both cases after the diagnosis of CVID. An audit of our cohort of 148 patients with diagnosed sarcoidosis found that 47% had not had serum immunoglobulins checked during diagnostic work-up.

Conclusion: Chest physicians often omit to check immunoglobulins when assess-ing patients with suspected sarcoidosis. This may not be surprising given the lack
of advice on measurement of immunoglobulins in current Intersitial Lung Disease guidelines. While CVID is uncommon, awareness, early diagnosis and effective treatment can reduce morbidity, mortality and complications and improve quality of life.

P3675 Electrocardiographic characteristics in patients with sarcoidosis
Elias Gialafos, Vasileios Kouranos, Alfonso Jurado Roman, Maria Gallego, Juan Jiménez, Anastasios Kallimanis, Ourania Anagnostopoulou, John Aragis, Aggeliki Rapti, George Tzelpis. 1: 1st Cardiology Unit, University of Athens, Greece; 2: 5th Pulmonary Clinic, General Hospital of Chest Diseases “Sotiria”, Athens, Greece; 3: Cardiology Clinic, Heart Hospital UCL, London, United Kingdom; 4: 2nd Pulmonary Clinic, General Hospital of Chest Diseases “Sotiria”, Athens, Greece; 5: Department of Therapeutics, University of Athens, Greece

Background: Several studies have emphasized the importance of early identification of cardiac sarcoidosis. Aim of our study is the evaluation of electrocardiographic (ECG) characteristics in a cohort of sarcoidosis patients indicating myocardial involvement.

Methods: Consecutive patients with biopsy proven sarcoidosis (n=315) were examined from October 2002 through October 2011. Exclusion criteria were presence of pacemaker and/or implantable cardioverter defibrillator. Heart rate (HR), PQ, QRS, QT and QT corrected intervals, PQRS and T wave axis were collected. Also, complete and incomplete right (RBBB) and left (LBBB) bundle branch block, right (RVH) and left (LVH) ventricular hypertrophy, repolarization and intraventricular abnormalities were noted.

Results: Only 59 out of 315 patients had a normal ECG. Mean HR was 75±13.5 beats/min, QT=417.5±21.2 ms while axis of P, QRS and T wave were: 42.6±19.8°, 20.79±34.0° and 34.7±25.9°, respectively. Six patients were found at atrial fibrillation while the rest were at sinus rhythm. PQ interval ±17.56 msec. RBBB was detected in 55 (11 complete and 44 incomplete) and LBBB in 9 patients (8 complete and 1 incomplete). Sixty patients were found with ventricular hypertrophy (56 LVH/4 RVH). At least one lead repolarisation abnormality was found in 177 patients including inferior lead abnormalities at 28, anterior lead abnormalities at 23 and lateral leads abnormalities at 23 patients.

Conclusion: Although ECG is a widely available tool used in the diagnosis of cardiac sarcoidosis various abnormalities were described implying necessity of extensive investigation in order to detect cardiac involvement.

P3676 Survival predictors in a cohort of patients with idiopathic pulmonary fibrosis
Mauricio Salinas, Matias Florenzano, Gabriel Cavada, Alvaro Underaga.
1: Facultad de Medicina, Universidad de Chile, Santiago, Region Metropolitana, Chile

Idiopathic Pulmonary Fibrosis (IPF) is a bad prognosis disease with heterogeneous progression. Only few studies, including relative small sample size, have searched for bad prognosis factors. The aim of this study was to analyze survival predictors in a retrospective cohort.

The study was conducted at the National Thorax Institute in Santiago, Chile. Registrers of patients in the period between 1991 and 2008 with clinical, radiological and surgical biopsy concordant with IPF were analyzed. We performed survival analysis with mixed models and proportional Weibull hazard models. A total of 142 patients were analyzed. The average age was 58 years and 41.5% were males.

The mean survival was 80 months. In univariate analysis were predictors of mortality: diffusing capacity of the lung for carbon monoxide (DLCO) less of forty percent and desaturation during six minute walk test (6MW) at baseline. The rate of decline of forced vital capacity (FVC) was mortality predictor. The rate of decline of FVC is a strong mortality predictor in this study and allows distinguishing bad prognosis groups.

P3677 Pathological findings in histiocytosis X with pulmonary hypertension
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Objective: To evaluate the hemodynamic characteristics, pulmonary function and pathological findings in patients with Langerhans cell histiocytosis (LCH) and Pulmonary Hypertension (PH) not explained otherwise.

Methods: A retrospective study was conducted in patients with Langerhans cell histiocytosis. Echocardiogram, lung biopsies, lung function tests and hemodynamic recordings were reviewed.

Results: Twenty patients were studied, with a mean age of 41±10 years. 8 patients (40%) had severe PH. The mean delay between the diagnosis of LCH and PH was 2.1 years. Six minute walk distance was 409±101 m. Systolic PAP: 62±15 mmHg. FVC was 62±15% of predicted, FEV1 45±21% and DLCO 41±9. All patients were on long-term oxygen therapy. After a median follow-up of 9.1 years, 1 patient is clinically stable, 1 patient had died of cardiac arrest while waiting for lung transplant, and 6 patients had undergone lung transplantation with 83% survival at 1 and 3 years. Histopathological lesions studied in explanted lungs suggested a veno-occlusive origin for this kind of complication, with capillary congestion, interstitial granulomatosis-like changes and fibrosis of septa, something that has been rarely described in LCH.

Otherwise, it is interesting to remark the presence of three cases of malignant neoplasias in the global serie. This association has been described as isolated cases in literature review. Two patients suffered from malignant lymphoma and one female patient had an uterine cervix carcinoma.

Conclusions: Pulmonary Hypertension could have a veno-occlusive origin in LCH. A relationship between malignant neoplasias and LCH may be possible.

P3678 A combinational approach to optimize biomarkers efficacy in identifying patients with sarcoidosis and monitoring respiratory functional worsening
Gregorino Paone, Gian Luca Di Tanna, Sandro Batella, Francesco Belli, Salvatore D’Antonio, Mario Giuseppe Alma, Giovanni Schmidt, Giovanni Puglisi, Annarita Vestri. 1: Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, University “La Sapienza”, Rome, Italy; 2: Department of Public Health and Infectious Diseases, University “La Sapienza”, Rome, Italy; 3: Department of Respiratory Diseases, S. Camillo-Forlanini Hospital, Rome, Italy;

Background: Sarcoidosis is a multisystemic granulomatous disease of unknown aetiology which affects lungs and lymphatic system its diagnosis is established by histologic evidence of non-caseating granuloma and the clinical course is unpredictable.

Aims: We aimed to investigate whether a panel of biomarkers combined together may help identify sarcoidosis and predict its functional worsening.

Methods: We analyzed 30 subjects with sarcoidosis and 34 with IPF. Participants underwent PFTs, radiologic investigations, and fiberoptic bronchoscopy. We examined BALF cellular profiles and BALF and serum concentrations of ECP, MPO, tryptase, procollagenIII, IL-6, and TNFα.

Results: The linear predictor score based on the combination of BALF lymphocytes, CD4, C4D, and ECP, correctly allocated 29 patients with sarcoidosis (97% of correct classification; 95% CI, 84.4%-99.8%) and 28 with IPF (82% correct classification; 95% CI, 68.8%-92.2%). The AUC was 0.93.

We also analyzed PFTs of participants with sarcoidosis during a 2-years follow-up period. At revaluation 76% of participants had stable disease, and 24% experienced a worsening of the respiratory function. The combination of BALF neutrophil percentage, ECP, and tryptase, yielded a 100% correct classification of patients (95% CI, 90.6%-100%); the AUC was 1. None of the markers analyzed as a single variable reached a similar allocation rate and a dissatisfying discrimination was obtained using markers from peripheral blood.

Conclusion: This combinational method could be a valuable approach to optimize biomarkers performance in the effort to identify sarcoidosis and to predict its clinical course.
Peripheral blood and in BAL were performed in 10 subjects. Of bronchial obstruction which made the BAL impossible. T-SPOT.TB tests in suspected for sarcoidosis were included in this study. 1 was withdrew because radiographs were abnormal in 22% patients. Most common radiological finding was obstructive defects in 12% and mixed defect in 6%. FEF25-75% was abnormal on HRCT thorax were interstitial lung disease suggestive findings (31%) and with abnormal Spirometry in 51% and abnormal HRCT in 59.30% patients. Chest diagnosis between sarcoidosis and tuberculosis? – Pilot study

Material and method:

11 subjects (4 female, 7 male; mean aged 45.8 ± 15.1 years) were evaluated in a prospective fashion. All patients underwent clinical interview, chest radiography, high resolution computerized tomography and lung function tests (spirometry, lung volumes by plethysmography and carbon monoxide diffusion DLCO).

Results:

Clinical characterization: 69.4% female, age 54.9 ± 13.6. Smoking status: 64% non-smokers. Disease duration was 9.2 ± 6.1 years. Disease activity was the most prevalent (91.7%), followed by lymph nodes and cutaneous involvement. Number of extra pulmonary organ involvement was 1.6 ± 1.1 organ per patient. Near 62% of patients had interrupted working activity, 15.5% had to change job due to sarcoidosis morbidity. Up to 26% of patients had used immuno-presssure drugs for sarcoidosis, and 81.6% had taken corticosteroids. Three patients (4.1%) used oxygen therapy. Scadding stage: 28.2 ± 25% stage 1; 16.9% stage 2; 23.9% stage 3; 15.5% stage 3 and 15.5% stage 4. Lung function data: FVC 85.9 ± 16.5%, VEF1 82.7 ± 15.1%, VEF25-75% 96.8 ± 15.6%, TLC 89.7 ± 14.9%, RV 103.1 ± 26.1%. DLCO 76.7 ± 17.7%. Tomographic findings: parenchymal involvement in 64.5% of patients. Large (> 1.5 cm) lymph nodes in 13.9%. Conclusion: Our sample of patients prospectively evaluated is quite similar to other series of outpatients described.

Prevalence of pulmonary involvement in rheumatoid arthritis patients in Indian population

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Rheumatoid arthritis (RA) is the most common chronic connective tissue disorder that significantly affects the lungs. The aim was to evaluate the pulmonary involvement in RA patients and its correlation with duration of RA. A total of 100 diagnosed cases of RA, divided into two groups of 50 patients each on the basis of duration of RA i.e. < 5 years and > 5 years were evaluated. All the patients were assessed for clinical characteristics. High resolution computed tomography (HRCT) thorax and Spirometry findings. Disease severity was assessed by DAS28 score. Respiratory symptoms were present in 41% patients. Pulmonary involvement (either abnormal HRCT thorax/Spirometry or both) was found in 67% patients with abnormal Spirometry in 51% and abnormal HRCT in 59.30% patients. Chest radiograms were abnormal in 22% patients. Most common radiological finding on HRCT thorax was interstitial lung disease suggestive findings (31%) and bronchiectasis (29.41%). On Spirometric, restrictive defect was found in 33% obstructive defects in 12% and mixed defect in 6%. FEF25-75% was abnormal in 18.8% patients. Risk factors for the presence of pulmonary involvement were increasing age and presence of rheumatoid factor. No association was found with gender, duration of disease, severity of disease. A high prevalence of pulmonary involvement was found in RA independent of duration of illness. HRCT appeared to be more sensitive tool.

Results: All 10 patients were AFB and MTB DNA negative in BAL. T-SPTOP.TB test was positive in peripheral blood in 2/10 and in BAL in 1/10. The culture of BAL was positive for MTB only in the case who had positive T-SPTOP.TB test both in BAL and in peripheral blood.

Conclusion: Positive T-SPTOP.TB performed in BAL could be helpful in differential diagnosis between sarcoidosis and tuberculosis. Further studies are needed.
Patients with idiopathic pulmonary fibrosis (IPF) have limited exercise capacity due to dyspnea, abnormal lung mechanics, pulmonary hypertension and other mechanisms. We tested the hypothesis that 24 sessions of exercise in the form of a rehabilitation program would improve six-minute walk test (6-MWT) distance, peak exercise oxygen uptake (VO2 peak) and dyspnea (Borg dyspnea index) after exercise in patients with typical IPF. We investigated possible underlying mechanisms including hypoxemia, oxidant stress and pulmonary hypertension. Subjects with IPF defined by clinical criteria were randomly assigned to a 3-month pulmonary rehabilitation program or to a control group that did not participate in rehabilitation. Before and after the 3-month rehabilitation or observation, subjects underwent 6-MWT and exercise gas exchange studies (cycle ergometry). Blood samples were obtained for 15-F2t-isoprostanes, lactate and NT-proBNP measurements immediately before and after cycle ergometry. Rehabilitation did not cause a significant increase in 6-MWT distance or a decrease in dyspnea. Subjects who completed pulmonary rehabilitation maintained VO2 peak at baseline over three months. The control group had a significant decrease in VO2 peak over the same 3 months. Plasma lactate increased significantly after ~50-watt cycle ergometry exercise testing at 0- and 3-month evaluations in both groups; this was associated with significant decreases in arterial oxygen saturation. Pulmonary rehabilitation maintained peak oxygen uptake, but did not improve exercise capacity of patients with moderately severe IPF. Low-level exercise was associated with significant hypoxemia and systemic oxidant stress.

391. Distinguishing phenotypes and dealing with comorbidities in primary care

P3687
Diagnostic delay of pulmonary embolism in primary and secondary care: A retrospective study

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1Pulmonary Diseases, Isala Klinieken, Zwolle, Netherlands; 2General Practice, Isala Klinieken, Zwolle, the Netherlands. 261 patients were included for analysis.

391 patients diagnosed with pulmonary embolism between 2008 and 2009 in the community and is associated with worse clinical outcomes. It is also a stronger predictor of mortality. Multivariate logistic regression analyses showing number and length of hospital admissions depending on Charlson index and degree of dyspnoea. Presence of diabetes as comorbidity independent predictor of longer hospital admission.

P3688
Effects of aerobic and strength training on symptoms and exercise capacity of IPF patients

Robert Jackson1, Carol Ramos1, Diana Cardenas1,2, Constanza Sol3

1Pulmonary Diseases, Isala Klinieken, Zwolle, Netherlands; 2General Practice, Isala Klinieken, Zwolle, the Netherlands. 261 patients were included for analysis.

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P3689
The impact of anemia on patients with chronic obstructive pulmonary disease in the community

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Background: Anemia of chronic disease (ACD) has been shown to be linked with multi-faceted clinical consequences in patients with chronic obstructive pulmonary disease (COPD) enrolled in clinical trials. The predictive value of ACD has not been evaluated in stable COPD patients in the community.

Methods and results: We evaluated 488 patients (9.4%) with stable COPD under the care of a regional nurse-led community respiratory team between June 2008 - November 2010. 86% of patients were on inhaled beta agonists; 43% on long acting anti-muscarinics, 54% on inhaled steroids and 8% on oral steroids. Mean age of the patients was 73.9±6.1 years, 43% were females and mean MRC grade was 2.2±0.7. ACD was defined as hemoglobin (Hb) between 9.1-9.2 g/dL. Mean Hb levels were 14.1±0.7; 13.9±0.3; 14.0±0.6 and 13.7±0.2 g/dL at 0, 6, 12 and 24 months. To rule out iron deficiency we sample ferritin. Mean serum ferritin levels in the entire study population were 242±159 g/L at the start and 227±19.8 g/L at the end. The prevalence of ACD was 13.9±1.2 (95% CI) and 14.5±1.3% respectively at the start and end of the study period. 2-year survival was 93% in the entire population; 81% in the anemic group (p<0.001). Risk-adjusted hazard ratio for 24 month mortality was 1.43 (1.19-1.90) for the anemic patients.

Conclusions: High prevalence of comorbidity, particularly cardiovascular disease being the main cause of death. Level of frailty depending on comorbidities of COPD geriatric hospitalized patients related to their prognosis. Implementation of aggressive strategies to prevent or treat comorbidities necessary for a better care of patients, together with the correct management of the respiratory disease.

P3690
Sleep does not affect health status in a primary care COPD population

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Introduction: Knowledge on the relation between sleep quality and health status in mild COPD patients is very limited.

Aims and objectives: The aim of the current study was to evaluate the effect of sleep on health status as measured by the Clinical COPD Questionnaire (CCQ) in a primary care COPD population.

Method: 38 COPD patients were enrolled in the study, which was part of a larger study evaluating health status based treatment versus standard GOLD guideline based treatment. The participants completed the CCQ (symptoms, mental, functional and total scale) and the Pittsburgh Sleep Quality Index (PSQI; duration, disturbances, latency, daytime dysfunction, efficiency, quality, medication need and total score).

Results: Mean participant age was 66 years; mean number of packyears 41; 72% male; GOLD I 36%, GOLD II 56%, GOLD III 8%. In the univariate analyses relations were found between the CCQ total scale and FEVI ( spearman -0.416, p<0.009), CCQ total and daytime dysfunction ( spearman 0.404, p<0.012) and CCQ total and GOLD stage ( spearman 0.369, p=0.023). No relations were found with group allocation, age, social economic status, medication, BMI or packyears. Multivariate analyses confirmed health status to be related to FEVI and daytime dysfunction. The relation with GOLD stage was not confirmed.
Conclusion: Health status by means of CCQ is related to FEV1 and daytime dysfunction. None of the other sleep quality scales showed to have an influence on health status. The current study gives an insight into the possible relation between health status and sleep in a primary care COPD population and shows that the PSQI is a relevant instrument, however the n of 38 is too low for definitive conclusions.

Methods: During 2006-2011 years we studied 128 children with chronic cough and persistent wheezing. Median age was 8.5 months. Clinical history showed that 52 had concomitant symptoms of suspected FA: atopic dermatitis 31 (24.5%), diarrhea 8 (6.2%), rhinitis 6 (4.6%), urticaria 9 (7%), combination of two or more symptoms 15 (11.7%). 47 had concomitant symptoms of suspected GER (persistent regurgitation and vomiting). 29 had only respiratory problems. Regurgitation was found in 63.9% of patients. 58% had at least one laboratory parameter outside laboratory limits: positive skin prick 31, eosinophilia in nasal or sputum secrets 12, increased circulating EGF 16, specific EGF 10.

Conclusion: Patients younger than 24 months with GER and respiratory symptoms should be evaluated for food allergy. There is connection between GER and FA (specially cow milk allergy). Atopy and positive tests can help to separate GER patients for need of elimination diets.

P3602 Daily activities and quality of life in COPD patients: Psychological determinants

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Background: Psychological variables play an important role in COPD patients’ management of their illness and daily life. To develop self-management interventions to improve Quality of Life (QoL) in COPD patients, more detailed studies are needed.

Objective: To study the influence of illness perceptions, proactive coping competencies and depressive symptoms on daily activities and QoL in COPD patients.

Methods: In a 24% sectional study in primary care, 90 COPD patients (GOLDI-3) completed the following questionnaires: Brief Illness Perception Questionnaire, Utrecht Proactive Coping Competence scale, Center for Epidemiologic Studies Depression Questionnaire (CES-D), General Health Questionnaire (GHQ-12). The influence of illness perceptions, proactive coping competencies and depressive symptoms on daily activities and QoL were assessed with multiple linear regression analysis.

Results: COPD patients had worse QoL on most of the daily activities and QoL domains. Higher scores on illness perception questionnaire were related to worse QoL (β = -0.24, p < 0.01). Proactive coping competencies had a significant positive influence on QoL (β = 0.27, p < 0.01). However, higher depressive symptoms were related to worse daily activities and QoL (β = -0.23, p < 0.01).

Conclusion: COPD patients have worse QoL with worse illness perceptions, lower proactive coping competencies and higher depressive symptoms. In this study, illness perceptions were a stronger predictor for worse QoL than depressive symptoms. Further research is needed to evaluate the impact of psychological determinants on daily activities and QoL in COPD patients.

P3604 Diagnosing asthma and COPD in primary care patients in Serbia: A multicenter study

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Background: Asthma and chronic obstructive pulmonary disease (COPD) are often unrecognized and undertreated.

Aim: The aim of this study was to describe the frequency of COPD and asthma in patients with respiratory symptoms and/or smoking history in primary care settings in Serbia, and to examine the agreement between general practitioners (GPs) and pulmonologists on the diagnosis of COPD and asthma.

Methods: In this multicentric, prospective, observational study GPs from practices in 3 different centers in Serbia identified eligible patients from October 2009-Jan 2010. The study included all adult patients with respiratory symptoms and/or smoking history based on structured interview. The patients were referred to a pulmonologist and underwent a diagnostic work-up, including spirometry.

Results: There were 2074 patients, 38.4% men, mean age 54±15.5 years. Patients were mostly current (40.3%) or ex-smokers (27.4%). The common symptoms included shortness of breath (84.9%), cough (79.1%) and wheezing (63.8%). The COPD diagnosis was confirmed by pulmonologists in 455 (21.9%) and asthma in 435 (21.9%) patients. COPD was newly diagnosed in 226 (10.9%) and asthma in 269 (13.0%) of the cases. There was a moderate agreement between general practitioners (GPs) and pulmonologists on the diagnosis of COPD and asthma.

Conclusion: A significant number of patients seen in GPs office were diagnosed with COPD or asthma and half of them represent new cases. A substantial proportion of patients referred to pulmonologist by primary care physicians have been misdiagnosed.
CL, 3.20-8.35), the presence of emphyma in the X-ray - OR, 3.11 (95% CI, 2.37-4.06). Age 57 years and over - increases 5.25 times (95% CI, 3.90-7.70). The likelihood of lower BMD in the 2nd stages is 2.28 (95% CI, 1.36-3.50) and in the 3rd stage is greatly increased - OR, 10.91 (95% CI, 6.98-17.05). The hypoxia (SO2%) significantly increases the risk of secondary reduction of BMD - OR 15, (95% CI 10.05-22.38).

Conclusion: Factors that increase the likelihood of reducing the BMD are the frequency and type of exacerbations, age, duration and severity of disease, the presence of occupational factors, emphyma and hypoxia.

P3696

Distribution of dyspnea etiologies among patients with either acute or chronic breathlessness and normal cardiorespiratory function

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We aimed at investigating the distribution of dyspnea etiology in patients with normal cardiorespiratory function (NCF). We studied 57 pts. (33 male & 24 female) aged 58.4±4.7 yrs. who presented at the Outpatients’ Department during the past 12 months, complaining of breathlessness with no other respiratory symptoms. Patients complainable of either acute breathlessness (AB group- starting within the past 48 hrs.) or chronic (CB-group-more than 48 hrs. duration). All had a chest X-ray along with spirometry, arterial blood gases and heart ultrasound, having been rated as normal. Those in whose diagnosis was not mainly established, underwent further testing including hormonal profile, lung perfusion scan, computerized chest tomography & angioigraphy and respiratory muscle testing. In AB group (31 pts. 15 male & 19 female) aged 46.4±4.7 yrs. the final diagnosis was: 18 pts. (58%) acute psychogenic hyperventilation syndrome (HS), 11 (36%) anemia due to silent gastrointestinal bleeding (GB) and 2 (6%) hypothyroidism (HT). In CB group (26 pts:18 male & 8 female) aged 61 ±36.8 yrs. the final diagnosis was: 6 pts. (23%) HS, 7 (27%) GB, 3 (12%) obesity-deconditioning (OD, 3 (12%) anemia of the abdomen in males was similar to that in females, the ratio of visceral adipose tissue to total adipose tissue was statistically different. In males, total abdominal adipose tissue and visceral adipose tissue were inversely associated with the value of FEV1% predicted (FVC) and FEV1/FVC ratio. In females, total abdominal adipose tissue and visceral adipose tissue, but not subcutaneous adipose tissue, were inversely associated with absolute FVC and FEV1 values. In conclusion, abdominal visceral obesity is inversely associated with lung function.

P3697

Health state and the quality of life in patients with chronic obstructive pulmonary disease (COPD) in Poland: A study using the EuroQol-5D SD questionnaire

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Introduction: Chronic obstructive pulmonary disease (COPD) is a severe disease that leads to respiratory disability and a considerably reduced comfort of living that affects all the aspects of patient activity.

Objectives: The aim of our study was to assess the quality of life (QoL) in patients with diagnosed COPD using, as the research tool, EuroQol-5D, a health-related QoL questionnaire.

Patients and methods: The data were obtained using designed questionnaire by conducting a cross-sectional survey in a large (N=9310) group of patients with COPD.

Results: Mild and moderate COPD patients (GOLD stage 1 and 2) constituted the majority of the study population (16% and 54%, respectively). A perceptible COPD-related low health state was shown for each stage of the disease, including patients with mild to moderate COPD. Significant differences were observed between the groups of patients stratified by spirometry results in perceived health state assessed with the questionnaire and on a visual analogue scale (VAS). Using linear regression models the association between the health status measured using VAS scale and comorbidities (especially heart failure), and severe (or very severe) COPD status was found (p<0.001). Patients with the history of exacerbations had significantly lowered health status assessed by VAS scale (p<0.001).

Conclusions: EQ-SD along with VAS seems to be a useful tool to characterise health state of patients with COPD. It is noteworthy that also in the milder stages of the disease there are limitations in various life aspects that are important to the patients.

P3698

Association of CAT scores with exacerbations and comorbidity in COPD patients in a randomized primary care setting

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Introduction: Health status measurement with CAT has been proposed for COPD management in the updated GOLD guidelines. We aimed to investigate CAT score correlation with AECOPD and comorbidity in a Greek cohort of COPD patients

Methods: Data were selected from 544 COPD patients from Greece through a prospective cross-sectional study, attending primary health care units. Demographic data, previous treatment, lung function testing, exacerbations and co-morbidity were recorded. Chi-square test, bivariate Pearson r correlation and binary logistic regressors were applied on data regarding the CAT score, FEV1 (95 pred.), FVC, FVC% and certain clinical parameters of the disease.

Results: CAT scores classification percentages showed: 38% mild CAT score, moderate impact level 46%, severe score 15% and very severe score 1.9%. 56% of the patients with exacerbated disease had medium CAT score while the 19.6% of them had a high impact score (p<0.001). A positive correlation was found between CAT scores and risk for exacerbation Odds (95%CI): 1.2 (1.0-3.0), p<0.001 for the group with moderate impact CAT score, 1.9 (1.4-3.1), p<0.001 for high impact and 2.1, (1.3-2.9), p<0.001 for very high impact. Patients with comorbidity presented a higher risk of developing high and very high impact of CAT score: Odds(95%CI): Stroke 2.4 (1.7-4.2), p<0.001, heart failure 1.5, (1.19-1.7), p<0.001, peripheral vascular disease 1.3 (1.0-1.8), p<0.001, ischemic heart disease 1.8, (1.3-3.0), p<0.001, osteoporosis 1.5(1.2-1.8), p<0.03 and depressive symptoms 1.3 (1.1-1.8), p<0.04.

Conclusions: The co-existence of other diseases with COPD increases the probability of presenting a worse health status.

P3699

Effects of abdominal visceral obesity measured by bioelectric impedance analysis on lung function

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While many studies suggest the impact of obesity on lung function, studies of abdominal visceral obesity on lung function provide inconclusive informations. The aim of this study was to investigate the association of abdominal visceral fat measured by bioelectrical impedance analysis and changes in lung function. We included never-smokers between the ages of 18 and 80yr, who had undergone spirometry and abdominal adipose tissue analysis with bioelectrical impedance analysis during March 1, 2009 to December 31, 2010 as part of the health examination. Among a total of 67,368 participants, 54.3% were male. The mean body mass index and waist circumference among males and females were 24.8 kg/m² and 23.1 kg/m² and 83.7 cm, respectively. Although total adipose tissue of the abdomen in males was similar to that in females, the ratio of visceral adipose tissue to total adipose tissue was statistically different. In males, total abdominal adipose tissue and visceral adipose tissue were inversely associated with the value of FVC and FEV1. In females, total abdominal adipose tissue and visceral adipose tissue, but not subcutaneous adipose tissue, were inversely associated with absolute FVC and FEV1 values. In conclusion, abdominal visceral obesity is inversely associated with lung function.

P3700

Pilot study of reliability of PQH-9 questionnaire for evaluation of depression in hospitalized asthmatic patients

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In chronic pulmonary disease patients, consideration of physical signs of illness such as difficulty breathing, etc. as well as psychiatric conditions which occur due to lack of adaptability with disease are important. In this study it was tried to evaluate a short and comprehensive questionnaire for screening for psychiatric disease and the PQH-9 for depression and GAD-7 for anxiety were evaluated. This was a cross-sectional study with completion of questionnaire by one inter-viewer. All asthma patients hospitalized at Mash Daneshvari Hospital during the summer of 2011 who were able to respond to questionnaire and agreed to participate were included in the study. Demographic information was also collected. Data was entered into the computer and analyzed via SPSS 12 software. In total 20 patients participated for the pilot study with mean age of 58±18 years and 70% were female. Fifty six percent were illiterate and average years of illness were 9±5 years. Depression and anxiety was found more in women compared to men which a larger study for significance evaluation is needed. The Cronbach alpha values for PQH-9 were 0.645 and for GAD-7 0.837. The shortness of the questionnaires makes them practical. A larger study is in progress by researchers for determining validity and reliability of the two questionnaires and comparison with the GHQ-12.

P3701

The role of inflammatory markers in obstructive pulmonary disease

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Background: Asthma and chronic obstructive pulmonary disease (COPD) are characterised by airway and systemic inflammation, but little is known about
P3702
Neutrophils and the increased risk of cardiovascular events in severe COPD
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Methods: Five male outpatients with COPD (83±4 age, forced expiratory volume in 1 second (FEV1) 39±17%, predicted), all ex-smokers and undergoing long-term oxygen therapy, were included. Measurements were obtained monthly for the ratio of circulating neutrophil cell count to peripheral white blood cell count (neutrophil %), FEV1, forced vital capacity (FVC), hANP, and baPWV from July 1, 2011, to December 15, 2011.

Results: Neutrophil% (67.4±11.1%) was significantly correlated with BaPWV (2465.8±652.7cm/s) (r=0.48, p<0.05) and hANP (27.6±8.7 pg/ml) (r=0.47, p<0.05). However, BaPWV was not correlated with FEV1 or FVC.

Conclusions: This report suggests that neutrophils might be involved in the increased risk of cardiovascular events in sever COPD.

P3703
Status of upper airways in exacerbation of COPD
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Introduction: Inflammatory cells and mediators that may lead to destructive changes in airways, pulmonary vasculature, and lung parenchyma may be associated with an increased risk of cardiovascular events in patients with chronic obstructive pulmonary disease (COPD).

Methods: We tested the hypothesis that neutrophils in venous blood have a relationship with serum human atrial natriuretic peptide (hANP) and brachial-ankle pulse wave velocity (baPWV) in COPD.

Results: Mean neutrophil% was 67.4±11.1% and hANP was 27.6±8.7 pg/ml.

Conclusion: Neutrophil% and hANP were correlated with baPWV in exacerbation of COPD.

P3704
RIB FRACTURE CAUSED BY COUGHING IN A YOUNG PATIENT
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Introduction: A cough is a voluntary or involuntary explosive expiration that protects the lungs against aspiration and promotes the movement of secretions and other airway constituents upward toward the mouth. Rib fracture which is usually caused by coughing usually occurred due to underlying pathologic factors such as osteoporosis, renal failure, metastatic tumors. We presented a young patient with rib fracture caused by coughing.

Case report: A 53-year-old man had visited the hospital with the complaint of immediate onset and localized left-sided chest pain which was occurred due to coughing induced by upper airway infection. The history of patient was not significant and he had no injury to his chest. The crepitation and tenderness were determined on his physical examination. The thorax computed tomography was revealed a rib fracture on the left tenth rib. When we evaluate him for an endocrinopathy, we did not find any abnormality. We decided that his rib fracture was occurred due to coughing.

Conclusion: A rib fracture should be considered in mind in a patient who admitted with immediate onset and localized chest pain.

P3705
Artiology and outcome of dyspnoea in emergency department patients
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Introduction: Dyspnoea is a common and complex diagnostic problem in ED patients.

Aim: To record initial diagnoses and outcome in ED cases of dyspnoea in a general hospital.

Material: Adults whose presenting complaint was dyspnoea during 3 consecutive summer on calls. Methods: On site recording of relevant data. SPSS 18 was used for statistical analysis.

Results: 54/2.9% patients presented to A&E complaining of dyspnoea out of a total attendance of 1861 persons. 33 were male (61.1%) and the mean age was 66.1 years. At triage severity was characterized as: 1(11.1%), 2(28.9%), 3(33.3%), 4(16.7%), 5(50%). BORG scale of dyspnoea was: 1(5.6%), 2(5.6%), 3(4.8%), 4(31.5%), 5(11.1%), 6(5.6%), 7(11.1%), 8(7.7%), 9(9.1%), 10(9.3%). Onset of dyspnoea was acute in 7 patients (13%), subacute in 38 patients (70.4%) and in 9 (16.7%) patients there was acute deterioration of chronic dyspnoea.

Initial diagnoses were: COPD(20.4%), asthma(5.6%), cancer(9.3%), pleuritis(7.4%), haemoptysis(7.4%), pulmonary embolism(1.9%), febrile infection(22.2%), SAOS(1.9%), heart failure(14.9%), coronary artery disease(3.7%), hypertension(1.9%), neuropsychiatric disease(1.9%) and miscellaneous(1.9%).

Patients were treated at short stay units (3.7%), special departments (48.1%), ITU(1.9%), specialist centres(1.9%) and at home(44.4%). The mean duration of hospitalization was 7±2 days.

 Concordance between admission and discharge diagnoses was 70.7%. Additional medical problems were identified in 25.9% of the patients that presented with dyspnoea.

Conclusion: Dyspnoea in ED patients is a complex medical problem that requires meticulous clinical attention.

P3706
The bronchial asthma course change during pregnancy
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It is well known, that the course of bronchial asthma (BA) changes at some of
392. Molecular biology of pro- and anti-inflammatory responses in the lung

P3707
Induction of inflammation, oxidative stress and autophagy in human alveolar type I epithelial cells following exposure to silver nanoparticles
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The use of silver nanoparticles (AgNP) in health products is increasing due to their antimicrobial activity. However, their impact on health is poorly understood. It is known that the particle reactivity increases as size decreases, thus AgNPs may induce inflammatory responses that their bulk sized counterparts do not. It is known that 50% of inhaled nano-sized (<100nm) particles preferentially deposit in the peripheral lung. Thus, inhalation of AgNPs might have adverse effects on the alveolar epithelium. We hypothesise that AgNPs induce an oxidative stress-dependent proinflammatory response in the human alveolar epithelium and activate autophagy.

Human alveolar type I epithelial cells (TT1) were exposed to 80nm AgNPs for up to 24h. IL-6 and IL-8 release was measured by ELISA and reactive oxygen species (ROS) production measured by dihydroethidium staining. n-acetylcysteine (NAC) was used to evaluate the role of ROS in mediator release. The plasmid assay was used to assess free radical-induced DNA damage and the autophagy markers LC3II/LC3I measured by immunoblotting.

AgNPs induced significant oxidative stress within 4h and IL-6 and IL-8 by 24h. NAC pre-treatment inhibited Ag50 (g/ml=0.31; Ag50 g/ml=0.073) and induced a significant increase in the LC3II/LC3I ratio (P<0.01; Ag 50% vs. n), suggesting that AgNPs activate autophagy.

Our study shows that AgNPs induce oxidative stress-dependent inflammation, DNA damage and a unique finding of autophagy responses in TT1 cells suggesting that AgNPs may have adverse effects on the lung.

P3708
Defective macrophage phagocytosis in COPD is associated with reduced STAT1 phosphorylation
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Macrophages are professional phagocytes that maintain sterility and remove in- vading pathogens. Chronic obstructive pulmonary disease (COPD) is associated with increased lung macrophages but the lower airways are colonised with bacteria such as Haemophilus influenzae and Streptococcus pneumoniae. This is associated with a decreased phagocytic response of COPD macrophages to these bacteria. IFNγ stimulation is increased in COPD airways and is associated with decreased phagocytosis. IFNγ stimulation activates the JAK/STAT pathway via phosphorylation of STAT1 to initiate signal transduction. We hypothesise that reduced phagocytosis in COPD is linked to STAT1 phosphorylation and JAK/STAT activation. Monocyte derived macrophages (MDM) from non-smoker, smoker and COPD donors and COPD lung tissue macrophages (n=4-3) were challenged with fluorescently labelled inert beads or heat killed bacteria (H. influenzae or S. pneumoniae). IFNγ stimulation (10ng/ml, 10min) was used as a positive control. STAT1 phosphorylation was assessed by Western blotting.

STAT1 was phosphorylated in response to inert beads in both non-smoker and smoker MDM but not in those from COPD donors. In addition, none of the phagocytic prey initiated STAT1 phosphorylation in COPD lung tissue macrophages. However, IFNγ stimulation caused phosphorylation of STAT1 in all three donor groups.

To conclude, COPD MDM and lung tissue macrophages are capable of STAT1 phosphorylation although not in response to phagophagic prey. This is in contrast to non-smoker and smoker cells that show JAK/STAT activation in response to inert beads. Further investigation of this signalling pathway in phagocytosis may lead to increased knowledge of COPD pathogenesis.
of severe asthma and COPD. We have examined TNFα-induced resistance to GC-dependent transcription by steroidal and non-steroidal GR agonists in the absence and presence of a LABA, formoterol.

Methods: GC-dependent transcription was modeled by a simple 2 x GR-luciferase reporter in human bronchial epithelial BEAS-2B cells treated with TNFs (10 ng/ml) for 1 h prior to addition of GR ligands, and harvested after 6 h for luciferase assay. Results: TNFα reduced by 43-54% the ability to drive 2x-GR-dependent transcription by dexamethasone, budesonide, fluticasone propionate or fluticasone furoate. The GC’s des-ciclesonide, GW70808X, RU24858 and the non-steroidal GR agonist, GS5027, all showed reduced maximal responses (Emax) with intrinsic activities 0.5-0.77 relative to dexamethasone. In each case, TNFα reduced Emax by a further 39-55%. Conversely, formoterol enhanced GR-dependent transcription by each ligand and rescued the resistance induced by TNFα; these effects were proportional to the Emax of each drug. Statistically significant reversal of TNFα-induced resistance was observed with the c-jun N-terminal kinase inhibitor, JNKs, and PS-1415, an IkB kinase 2 (IKK2) inhibitor.

Conclusions: TNFα induces GC resistance to steroidal GR ligands that are both full and partial agonists, as well as to a non-steroidal GR agonist. This effect is rescued by the addition of formoterol. It is possible that inhibition of inflammatory signalling may also reduce GC resistance.

P3712
The effects of human lung mast cell products on the synthetic functions of lung fibroblasts
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Activated mast cell numbers are generally increased in the bronchial wall and alveolar parenchyma of people with asthma. Mast cells release a wide variety of cytokines and mediators that may modulate the activities of structural cells such as fibroblasts and contribute to airway remodelling in asthma.

Objective: To examine the effects of human lung mast cell (HLMC) products on the synthetic functions of airway and parenchymal fibroblasts.

Methods: HLMCs were co-cultured with lung fibroblasts and their supernatants (SN) collected after 2 and 24h. The SN were added to serum-deprived airway and parenchymal fibroblasts for up to 48h. Fibroblast and mast cell cytokine release and extracellular matrix (ECM) deposition were measured using ELISAs.

Results: Both 2 and 24h HLMC SN significantly increased the synthetic functions of parenchymal and airway fibroblasts in a concentration-related manner. Release of CXCL8 was increased up to 3.9 and 3.1-fold from parenchymal fibroblasts by 2 and 24h SN respectively and 2.4-fold from airway fibroblasts in a concentration-dependent manner. Interestingly, although fibroblast deposition was unchanged, both the 2 and 24h SN significantly increased collagen IV deposition by airway, but not parenchymal fibroblasts up to 1.5-fold, whereas only the 24h SN increased tenasin-C deposition [1.8-fold] by the airway cells.

Conclusions: HLMC products increase lung fibroblast cytokine release and differentially regulate airway and parenchymal fibroblast ECM deposition. Thus HLMC may promote further inflammation and airway remodelling in asthma.

P3713
TNFα stimulates the expression different chemokines including CXCL10, CCL5 and ICAM-1 in developing air smooth muscle (ASM) cells:
Modulation by fluticasone and TNFα receptors
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Corticosteroids are only partially effective in treating children with Chronic Lung Disease (CLD) or chronic asthma. Low to moderate doses of steroids are generally effective in limiting symptoms, but higher doses are lead to serious side effects with little extra effect on symptom control. In this study, we used fetal ASM cells from human airways to determine their responsiveness to inflammatory chemokines associated with CLD. Fetal ASM cells exposed to TNFα secrete different chemokines including CXCL10, CCL5 and CXCL8. Pre-treating cells with fluticasone (0.001–100nM) led to a dose-dependent suppression of all chemokines although the magnitude of inhibition was greater on CCL5 (over 95%) when compared to CXCL10 or CXCL8 (less than 60%) at 100 nM fluticasone. Using rFcR α, we also found that expression of cytokine genes was only partially repressed by fluticasone (100nM). Neutralizing antibodies against TNFα receptors revealed that engagement of both TNFR1 and TNFR2 mediates TNFα-induced chemokines expression. Our data suggest that generation of pro-inflammatory chemokines by fetal lung cells is only partially responsive to corticosteroid therapy. The mechanisms underlying this resistance are unclear.

p38 inhibitors suppress release of inflammatory cytokines and may have a therapeutically role in COPD.

P3715
Effect of beclomethasone dipropionate, formoterol and their combination on TNF-α-induced ICAM-1 and IL-8 expression in human bronchial epithelial cells
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Background: The adhesion molecule and chemokine expression in the airways has been implicated in inflammatory lung diseases.

Aim: To investigate the effect of beclomethasone dipropionate (BDP) and formoterol (F) alone and in combination (BDP/F) on TNF-α-induced ICAM-1 expression and IL-8 release in human bronchial epithelial cell line Calu-1.

Methods: Calu-1 cells were treated (30') with BDP (10^-11–10^-5M) or F (6/100nM) to investigate the effect of beclomethasone dipropionate (BDP) and formoterol (F) alone and in combination (BDP/F) on TNF-α-induced ICAM-1 expression and IL-8 release in human bronchial epithelial cell line Calu-1.

Results: Both 2 and 24h SN respectively also increased IL-6 and TNFα release of inflammatory cytokines from macrophage-lineage cells. Peripheral blood mononuclear cells (PBMC) and monocyte-derived macrophages (MDM) were isolated from non-smokers (NS), smokers (S) and COPD patients.

Conclusions: BDP and F in combination provided greater inhibition of ICAM-1 and IL-8 expression as compared to each drug. These observations may imply
that BDPPS exerts anti-inflammatory effects in airways by modulating adhesion molecule and chemokine expression in bronchial epithelial cells.

P3716 Anti-inflammatory and cytoprotective actions of the endogenous docosahexaenoic acid (DHA) electrophilic derivative 17-oxo-DHA
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Inflammation of the airways is a hallmark of chronic obstructive pulmonary disease (COPD), one of the leading mortality cause worldwide. Bronchial epithelial cells and resident macrophages represent the first barrier in the lung against pathogens and external insults such as cigarette smoke, which is a major risk factor for COPD. Although the activation of the innate inflammatory response is required for defense purposes, uncontrolled activation, typical of COPD, leads to chronic inflammation causing tissue damage and enhanced risk of infection. Currently there is no therapy able to revert disease progression in COPD and therefore the search for new drugs is highly active. Omega-3 derived electrophilic fatty acids have been recently discovered as endogenous anti-inflammatory molecules produced by activated macrophages by the action of cylooxygenase-2.

In the present work, the anti-inflammatory and cytoprotective actions of the electrophilic DHA-derivative 17-oxo-DHA were evaluated in lipopolysaccharide-activated macrophages and in bronchial epithelial cells. We report that 17-oxo-DHA suppresses LPS-induced TNFalpha production in macrophages and increases intracellular glutathione and the expression of heme-oxygenase 1 in both cell types, thus providing protection against oxidative stress caused by cigarette smoke and inflammatory actions.

Although the molecular mechanisms are still under investigation, overall the present results support a role for the electrophile, omega-3 derived 17-oxo-DHA in limiting inflammatory reactions and modulating the antioxidant response, thus reducing cellular damage and promoting the resolution of inflammation.

P3717 Comparative anti-oxidative effects of carbocysteine and fumaric acid propionate in cigarette smoke stimulated airway epithelial cells
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Cigarette smoke extracts (CSE) induce oxidative stress, an important feature in chronic obstructive pulmonary disease (COPD). Oxidative stress contributes to the poor clinical efficacy of corticosteroids. Carbocysteine, an anti-oxidant and mucolytic agent, is effective in reducing the severity and the rate of exacerbations in COPD patients. The effects of carbocysteine on CSE induced oxidative stress in nasal and in bronchial epithelial cells as well as the comparison of these anti-oxidant effects of carbocysteine with those of fumaric acid propionate are largely unknown.

The present study was aimed to assess the effect of carbocysteine (10-5 M) in cell survival and intracellular reactive oxygen species (ROS) production in CSE stimulated bronchial (16-HBE) and in CSE stimulated nasal (RPMI 2650) epithelial cells. We compared these effects with those of fumaric acid propionate (10-5 M). Carboceysteine or fumaric acid propionate did not induce cell necrosis (propidium positive cells) or cell apoptosis (Annexin V positive/propidium negative cells) in 16 HBE and in RPMI 2650 at the tested concentrations. CSE increased intracellular ROS production in 16HBE and in RPMI 2650. Fumaric acid propionate was not able to significantly reduce intracellular ROS production in both 16HBE and in RPMI 2650. Carbocysteine was able to significantly reduce intracellular ROS production and was more effective than fumaric acid propionate in reducing these CSE mediated effects in both cell lines. In conclusion, the present study provides compelling evidences that carbocysteine may be considered a promising strategy in diseases associated to corticosteroid resistance.

P3718 Effect of hypoxia and cigarette smoke on hypoxia-inducible factor 1α (HIF-1α) and heat shock protein 72 (HSP72) system of alveolar epithelial cells
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Hypoxia, the main risk factor of alveolar destruction in emphysema/COPD. In COPD airway obstruction causes hypoxemia areas in the lung leading to alveolar hypoxia. HIF-1α plays a key role in the defense against hypoxic cellu-
of the Acrp30 role in the control of local lung inflammatory state may contribute to develop new therapeutic approaches in inflammatory diseases as COPD, a major cause of morbidity and death worldwide.

Acknowledgment: PRIN 2007; Regione Campania, DGRG 1901/2009

Reference:

P3721

Size-dependent particle uptake and trafficking by antigen presenting cells in different anatomical respiratory tract compartments
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Effects of biomedical particles on lung antigen presenting cells (APC) such as dendritic cells (DC) and alveolar macrophages (AM) remain poorly understood to date. BALB/c mice intra-nasally received different sized (20nm, 50nm, 100nm, 200nm, 1000nm) fluorescent polystyrene particles. Two and 24h after instillation, FACS and confocal microscopy were performed to assess uptake of particles+DC 24h after exposure were higher for 20nm particles compared to 1000nm particles (12.0±2.3% vs. 1.22±0.3%; p=0.0283). At 24h, in lungs parenchyma DC, preferential uptake of 20nm (43.2±4.5% ±0.0011) and 50nm particles (36.2±4.8% ±0.0011) occurred compared to 1000nm particles (7.90±0.9%). These changes mirrored LDLN, where DC preferentially trafficked 20nm (17.8±2.1% ±0.0038) and 50nm particles (20.4±1.2% ±0.0011) compared to 1000nm particles (3.47±0.89%). AM ingested all sizes with a preference for smaller particles (20nm: 88.0±1.8%; p=0.0011; 50nm: 8.6±0.5±7.9±1.2%; p=0.0038; 100nm: 69.2±2.1%; p=0.0041; 200nm: 61.5±2.1% ±0.0136; 1000nm: 53.7±2.1% 24h after exposure. Following uptake, DC upregulated expression of CD40 and CD86 independently of particle size. Confocal microscopy confirmed uptake and size distribution in AM and DC in situ. Particle size is a key factor determining uptake and trafficking from the lung to LDLN. This has important consequences on downstream immunological effects of both ambient inhaled particles and novel carriers for pulmonary delivery of drugs or vaccines.

P3723

Airway region-specific effects of carbon black nanoparticles (CBNP)
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CBNP are present in industrially produced soot used for reinforcement of elastomers (e.g. in tyres) but also for paints, toner and batteries. CBNP may have lung cytotoxic and pro-inflammatory effects. In this study, the commercially available CBNP Printex 90 (P90) and the quartz DQ12 were shown to possess cytotoxic and pro-inflammatory properties in mice and human epithelial cell lines. In contrast to previous findings in mice and epithelial cell lines our study could not show pro-inflammatory effects of P90 or DQ12 on microdissected airways. In contrast to previous findings in mice and epithelial cell lines our study could not show pro-inflammatory effects of P90 or DQ12 on microdissected airways. A slight increase in cytotoxicity was indicated with increasing P90 concentrations. Although our results do not show significant cytotoxic or pro-inflammatory effects of P90 and DQ12 on proximal and distal airways, this does not exclude that oxidative stress, apoptosis or proliferation of airway cells are affected by P90 or DQ12. In the future, chemically modified CBNP will be analysed to reveal the impact of functional surface groups on the particle’s toxicological properties. Supported by the BMBF-joint project Carbon Black (03X0893A).

P3722

Targeting miRNA-based medicines to cystic fibrosis airway epithelial cells using nanotechnology
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Cystic Fibrosis (CF) is characterised by chronic pulmonary inflammation. microRNAs (miRs) are regulatory RNAs which inhibit gene expression. miR-126, a regulator of TOM1, is decreased in CF bronchial brushings; TOM1 is reciprocally increased. Polymeric nanoparticles of Polyethyleneimine (PEI) and Chitosan-TPP can be used to deliver nucleic acids into bronchial epithelial cells. Here a proof-of-concept study was performed testing their efficacy at delivery of premiR-126 into non-CF and CF bronchial epithelial cell lines. PremiR-126-nanoparticles were prepared and characterized using a Zetasizer and used to transfect CFBE410- and 6HBE14o- cell lines. RNA extraction and cDNA synthesis, CDNA was prepared and miR-126 and TOM1 expression was assessed using qRT-PCR. Toxicity was measured by high content analysis (HCA). Over-expression of miR-126 resulted in down-regulation of TOM1 in both cell types. The effects of polymeric, cationic nanoparticles was shown to efficiently deliver premiR-126 into cells in order to achieve this knockdown. PremiR-126 encapsulated in PEI at a nanoparticle/premiR (N/P) ratio of 1:1 resulted in knockdown of TOM1 in CFBE410+ cells, with a reduction of ~47% in TOM1 expression in comparison to a scrambled negative control complexed with commercial transfection reagent (p<0.05). HCA showed no significant difference in cell counts between untreated cells and cells treated with PEI- and chitosan-TPEmiR-126 nanoparticles suggesting they are relatively non-toxic. miRs are potential novel targets for respiratory gene therapy and could be targeted to CF bronchial epithelial cells in the future using PEI nanoparticles. Funding: SFI and HRB PD/2007/11.

P3724

Effect of anti-IgE therapy on microRNAs in the lungs of mice with allergen-driven airway remodeling
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Rationale: Current therapies have had limited effect on structural or airway changes in patients with asthma. We recently found that anti-IgE therapy significantly increased asthma airway hyperreactivity and subepithelial fibrosis in a mouse asthma model (Henderson et al., AIRCCM 183: A4066, 2011). MicroRNA (miRn) or miRs, small non-coding RNAs, are key regulators of gene expression that may serve as novel biomarkers and therapeutic targets in disease states.

Study Aim: Determine the effect of anti-IgE therapy on miRNA expression in a mouse asthma model with airway remodeling.

Methods: Mice periodically given OVA (days 14-163) were treated with 100 μg monoclonal rat IgE anti-IgE (R35-92, Pharmingen) (OVA/anti-IgE group), rat IgG1 isotype control antibody (OVA/IgG1 group), or saline (OVA/Saline group) days 73-75, and then once weekly until day 163 when lung miRNA was isolated. miRNA transcriptional profiling was carried out using Affymetrix miR 2.0 arrays with data analysis by Bioconductor limma package. MRnRNas whose expression was changed >1.5-fold (p<0.05) were considered differentially expressed.

Results: 21 miRNAs were significantly changed in the OVA/Saline group vs saline-treated controls including upregulation of proinflammatory miR-21 and miR-155. MRnRNAs 467e, 511, and 744 were downregulated and the antiinflammatory miR-16* upregulated in the OVA/anti-IgE group vs the OVA/IgG1 group. Conclusion: The ameliorating effect of anti-IgE treatment on established airway remodeling in this asthma model is likely mediated by its differential effects on gene expression in the lung. Our data direct attention to key miRNAs that may serve as biomarkers for this remodeling process.

P3725

microRNA profiling of murine alveolar epithelial type II cells
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Rationale: Alveolar epithelial type II cells (ATII) have key roles in innate immune response, surfactant production and as precursors for ATI cells (Mason RJ, Respiratology, 2006). To obtain insight in gene regulatory networks specific for ATI we established a method for negative isolation of ATI cells and investigated their microRNA (miR) profiles.

Methods: Single cell suspensions were prepared from whole lungs of female C57BL6 mice (6-12w) using dispase and mechanical dissociation. ATI were obtained by sorting (BD FACs Aria II) CD45-CD31-alkfluorescence-high cells (sATII). Sorted cells were characterized by flow cytometry, immunocytochemistry (ICC) and RT-qPCR. MR profiles were determined using TaqMan® Arrays Cards (ABI). MR profiles of sATII were compared to cells obtained by panning (pATII) according to a standard method (Koenigshoff M et al., JCI, 2009) using negative selection in antibody-coated (CD45, CD16/32) petri dishes.

Results: Up to 99% of sATII cells were CD45-CD31-CD74+. sATII expressed higher mRNA levels for SPC while miRNAs for CD31, CD45, ZO-1 and α-SMA were expressed at lower levels compared to pATII. mRNA levels for CD74, AQPS and SP-A were similar in both populations. ICC confirmed proFiC expression on sATII. MR profiling revealed 11 miRs expressed at equal abundance (~1.5x) in sATII and pATII. 128 miRs were up (+1.5x) and 64 miRs were downregulated (~1.5x) in sATII compared to pATII. In addition, 3 miRs were only detectable in sATII while 14 miRs were unique to pATII.

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P3726

The lung in a dish - A new tool to study interactions of inhaled (nano)materials with lung cells

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The human lung is exposed to a huge number of nanosized materials with each breath. To study the interaction of those materials with the lung, biomimetic cell culture models are needed. The human air-blood tissue barrier consisting of epithelial cells, the basal lamina and endothelial cells is less than 1 μm thick. Conventional cell culture inserts have a thickness of ~10μm which has been a major drawback to establish realistic models. Therefore, a novel ultrathin porous membrane with a thinness of 500nm was developed to refine an established human air-blood tissue barrier model consisting of epithelial cells (A549), monocyte-derived macrophages and dendritic cells by replacing the conventional inserts with the novel membranes but also complement it with endothelial cells (EA.hy926). Epithelial cells seeded on the upper side of the membrane and endothelial cells on the lower side grow to confluence and form a tight bilayer. Immune fluorescence stainings revealed the typical characteristics of epithelial/endothelial cells and specific markers (von Willebrand factor and PECAM) were exclusively detected in the endothelial cell layer. Experiments with all four cell types have been performed and showed that all cell types can be cultured together as a quadruple model on the new ultrathin membrane. Once fully established and characterized, this new system will offer an advanced 3D cell culture model of the human airway barrier and an excellent tool to study the effects of inhalable substances (e.g. nanomaterials) with a realistic lung model. This will significantly reduce the number of animals used to perform inhalation risk assessments and will offer a controlled system for different studies.

P3727

Pulmonary haptoglobin (pHp) is a scavenger system preventing arterial leukages

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Haptoglobin is a long known molecule. The recently discovered pHp variant is a scavenger system which can be a local first line immunoregulatory molecule which could play a crucial role coming into focus in the course of immunoregulatory events in the human lung. Here we describe the fast release of pHp upon different stimuli using a human tissue enriched cell culture system. Furthermore, the pHp in the supernatants of human tissue cultures after stimulation periods as short as 1h is detectable. A hypothesis has been that the pHp release is occurring in the supernatants immediately after stimulation. As nasal NO is increasingly used for screening of PCD, further work assessing the upper airway’s role in the low levels of nasal NO seen is warranted. Data collection continues.

P3729

Epithelial ciliary beating analysis in chronic airway diseases

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Human bronchial epithelial cells (HBEC) activation and increased mucus production are constant features of epithelium in chronic airway diseases. However, the mechanisms and involvement of mucociliary component are poorly understood in these diseases. We used an in vitro model of bronchial epithelial cell culture in air-liquid interface obtained from bronchial biopsies of asthmatic patients (mild and severe) or COPD patients. We questioned the regulation of mucociliary couple in this system using an original approach combining biology and physics. Methods: HBEC were obtained after processing biopsy were expanded on tissue culture-treated plastic and then, were plated on uncoated nuclepore membranes in air-liquid interface for 21 days to obtain a mucociliary phenotype. For each epithelium re-differentiated in vitro, we first measured thickness and cilia beating frequency (CBF). We used fast videomicroscopy (37°C). The effect of mucus presence on cilia beating was assessed by measuring frequency before and after addition of PBS. Results: Preliminary results are presented in table 1 and are expressed as median (min-max). Conclusion: At present we did not find any major change in the velocity of cilia beating according to the airway diseases in our air-liquid interface system. The contribution of mucus should be better investigated.

P3730

Air liquid interface culture can alter ciliary beat pattern in epithelium from primary ciliary dyskinesia patients

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Introduction: Primary Ciliary Dyskinesia (PCD) is a rare inherited heterogeneous disorder of cilia, impairing mucociliary clearance. PCD is diagnosed by low nasal nitric oxide concentration, abnormal airway ciliary function with corresponding ultrastructural defects, excepting atypical cases. PCD may be differentiated from secondary dyskinesia by assessing differentiated ciliated epithelium at air liquid interface (ALI). Aim: To evaluate ciliary beat pattern (CBP) on PCD airway epithelium before and after ALI culture. Methods: Ciliary function of nasal brushing epithelium from 9 PCD patients with ultrastructure defects confirmed by TEM, was analysed (n=10 cell clusters) at 37°C by high-speed video microscopy (100x objective). Confluent basal ep-
In vitro culture of human airway epithelial cells in asthma

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Introduction: The airway epithelium is considered important in the pathogenesis of several respiratory conditions including asthma. While studies of airway epithelial cell (AEC) cultures obtained from adults and children have provided valuable insight into the role of these cells in airway disease, little is known about how neonatal AEC phenotype impacts on respiratory disease in later life. We describe a novel method for culturing nasal AEC within days of birth.

Methods: Nasal swabs from healthy, unsedated infants within 72 hours of birth by gently brushing both nostrils with an interdental brush. Brushes were agitated in specialised AEC growth media and primary cell monolayers grown to confluence before sub-culture. IL-8 concentrations were measured in supernatants of transient passage AEC monolayers at rest and after exposure to IL-1β & TNF-α (both at 10ng/ml).

Results: Sampling was acceptable to parents and there were no adverse effects. Primary cultures were successfully established in 74/82% of 90 neonates sampled. Epithelial lineage of the cells was confirmed by morphological analysis and positive immunostaining for cytokeratin 19 and negative staining for potentially contaminating cell types. Constitutive IL-8 secretion was observed and was not affected by cytokine treatment.

Conclusion: We describe a safe, minimal invasive and reproducible method of culturing AEC from neonates suitable for functional cell analysis and amenable to large population based studies. This novel technique offers a unique opportunity to study "naive" AEC not yet exposed to the confounding effects of environmental pollutants and pathogens and may prove useful in elucidating the early origins of respiratory disease.

P3733

CSE exposure abrogates regulatory effects of the bronchial epithelium on B cell survival and IgA production in a coculture system. A pivotal role of TACI

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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 COPD is mostly related to cigarette smoking, only a minority of smokers develops this disease and factors of cigarette exposure susceptibility remain not clear. Even though peribronchial lymphoid follicles have been described in severe COPD, it remains unknown whether B-cell conditioning is altered in this disease, especially after CSE (Cigarette Smoke Extract) exposure.

Objectives: In this study, we report on CSE exposure data using a coculture model of B cells with human primary bronchial epithelium (re)differentiated in vitro in air-liquid interface.

Methods: IgA synthesis was studied following CSE exposure in CD19+ B cells (purified by immunomagnetic sorting from healthy blood donors) after co-culture for 13 days with a bronchial epithelium from severe COPD patients. B cells were also assessed by flow cytometry for cell activation and survival.

Results: In four independent experiments, we observed that IgA production and cell survival were upregulated in B cells cocultured with the bronchial epithelium, as compared to B cells cultured alone. CSE exposure of the epithelium abrogated these effects, and this was associated with the suppression of TACI induction upon co-culture.

Conclusion: These data suggest that a crosstalk exists between B cells and the epithelium with respect to COPD, which could be mediated at least in part through regulation of TACI.

P3734

A novel method for harvesting and culturing airway epithelial cells from neonates

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Introduction: The airway epithelium is considered important in the pathogenesis of several respiratory conditions including asthma. While studies of airway epithelial cell (AEC) cultures obtained from adults and children have provided valuable insight into the role of these cells in airway disease, little is known about how neonatal AEC phenotype impacts on respiratory disease in later life. We describe a novel method for culturing nasal AEC within days of birth.

Methods: Nasal swabs from healthy, unsedated infants within 72 hours of birth by gently brushing both nostrils with an interdental brush. Brushes were agitated in specialised AEC growth media and primary cell monolayers grown to confluence before sub-culture. IL-8 concentrations were measured in supernatants of transient passage AEC monolayers at rest and after exposure to IL-1β & TNF-α (both at 10ng/ml).

Results: Sampling was acceptable to parents and there were no adverse effects. Primary cultures were successfully established in 74/82% of 90 neonates sampled. Epithelial lineage of the cells was confirmed by morphological analysis and positive immunostaining for cytokeratin 19 and negative staining for potentially contaminating cell types. Constitutive IL-8 secretion was observed and was not affected by cytokine treatment.

Conclusion: We describe a safe, minimal invasive and reproducible method of culturing AEC from neonates suitable for functional cell analysis and amenable to large population based studies. This novel technique offers a unique opportunity to study "naive" AEC not yet exposed to the confounding effects of environmental pollutants and pathogens and may prove useful in elucidating the early origins of respiratory disease.

P3735

A reliable and long shelf-life in vitro cell model for studying goblet cell metaplasia in the human airways

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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 COPD is mostly related to cigarette smoking, only a minority of smokers develops this disease and factors of cigarette exposure susceptibility remain not clear. Even though peribronchial lymphoid follicles have been described in severe COPD, it remains unknown whether B-cell conditioning is altered in this disease, especially after CSE (Cigarette Smoke Extract) exposure.

Objectives: In this study, we report on CSE exposure data using a coculture model of B cells with human primary bronchial epithelium (re)differentiated in vitro in air-liquid interface.

Methods: IgA synthesis was studied following CSE exposure in CD19+ B cells (purified by immunomagnetic sorting from healthy blood donors) after co-culture for 13 days with a bronchial epithelium from severe COPD patients. B cells were also assessed by flow cytometry for cell activation and survival.

Results: In four independent experiments, we observed that IgA production and cell survival were upregulated in B cells cocultured with the bronchial epithelium, as compared to B cells cultured alone. CSE exposure of the epithelium abrogated these effects, and this was associated with the suppression of TACI induction upon co-culture.

Conclusion: These data suggest that a crosstalk exists between B cells and the epithelium with respect to COPD, which could be mediated at least in part through regulation of TACI.

P3736

Goblet cell metaplasia, induced mainly by TH-2 cytokines like IL-13 and IL-4, is a common feature of several respiratory diseases such as asthma, COPD, and Cystic fibrosis. Recent clinic trials demonstrated that blocking IL-13 signaling seems to be an effective therapeutic strategy. In order to develop more efficient drugs, a reliable and reproducible in vitro cell model would be invaluable. Epithelium has developed a high quality in vitro cell model of the human airway epithelium (MucilAir) which can be maintained at a functional and homeostatic state for a year, allowing long term tests of drug candidates. In order to create an in vitro
cell model of the airway goblet cell metaplasia, Muc1Air was treated with IL-13 at different concentrations, ranging from 0.3 to 30 ng/ml. Using in situ Alcian Blue staining, as well as histological analysis, we demonstrated that Muc1Air showed an increased goblet cell density after 14 days of IL-13 treatment, in a dose dependent manner. Furthermore, ELISA analysis revealed a concomitant increase of Eotaxin and Peristin released in the culture media as a function of IL-13 concentration. Despite some subtle morphological differences of the goblet cells between donors, the results from several different batches of Muc1Air are very similar and therefore reproducible. Taken together, Muc1Air is a relevant and reliable model for studying Goblet cell metaplasia, and for assessing the efficacy of drug candidates.

P3736
Do characteristic airway epithelial change precede the development of lung fibrosis? Ectopic epithelial marker protein expression in bleomycin induced fibrosis replicates that seen in bronchiolized epithelium in IPF fibrosis? Ectopic expression of the gel forming mucin, MUC5B was recently described as a specific marker for the bronchiolized epithelium seen in IPF and IPF-like conditions. We have shown that it is co-expressed in this region with LPLUNC1 but not with other airway submucosal gland proteins, including Zinc-alpha2-glycoprotein and Proline-rich protein 4. To shed light on a temporal association of expression of these markers, we have developed a mouse model of airway remodeling events. This mouse model is induced by the pro-fibrotic agent bleomycin (Bleo). MUC5B and LPLUNC1 were co-expressed in a population of goblet cells in the airways of mice within 3-7 days of Bleo exposure, prior to the onset of a fibrotic process. Continued expression is seen during the development of fibrosis between 14-21 days post treatment. In contrast, in mice treated with PBS neither protein was seen (due to mouse airways being essentially free of goblet cells). Staining was absent from the fibrotic regions and the lung parenchyma, as is the case in IPF. Our data show that the ectopic expression seen in human IPF is mirrored by that seen in the Bleo mouse model. Furthermore it suggests that these epithelial remodeling events precede the development of lung fibrosis and these can be studied in mice.

P3737
A unique session of aerobic exercise does not decrease pulmonary inflammation in a murine model of asthma
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Recent studies have shown that long term exercise training reduces airway inflammation. However, there is a lack of evidence of the effects of a single session of exercise. Objective: To evaluate the effects of a single session of aerobic exercise in the airway inflammation. Moreover, there is a lack of evidence on the effects of a single session of exercise. Methods: Thirty two mice were divided in Groups (n=8): Control (CT), Aerobic Training (AT), OVA, and OVA+AT. Groups OVA were sensitized by intraperitoneal injections of OVA/500µg/mice in the days 0, 14 and 28 followed by 30 min of 1% OVA inhalation (days 21th, 23th, 25th and 28th). CT and AT groups received saline. Exercise (AT groups) was performed in the day 28th for 60 min at 50% intensity of maximal capacity. Bronchoalveolar fluid (BALF), lung tissue and blood were collected in the day 29th. It was evaluated: total and different cells in BALF, IgE and IgG1 titers, peribronchial eosinophils, and airway remodeling (smooth muscle, collagen and elastic fibers, and mucus expression). Eotaxin, RANTES, VEGF, ICAM, VCAM, IL-1ra, NF-kb and Foxp3 in the airways were also evaluated. Statistical significance was evaluated by two way ANOVA followed by Bonferroni or Newman-Keuls. Results: OVA increased IgE; and IgG1 levels, total and eosinophil cell counting, and all remodeling features (smooth muscle, collagen and elastic fibers, and mucus expression) (p<0.05). In addition, OVA increased the expression of oestotxin, RANTES, VEGF, ICAM, VCAM, NF-kb and Foxp3 (p<0.05). On contrary, a single bout of aerobic training did not changed any of these effects (p>0.05). Conclusion: A single exercise session seems do not have any anti-inflammatory effect in a murine asthma model.

P3738
Aerobic training inhibits leukocytes production of oxidants, pro-inflammatory and pro-fibrotic factors reducing asthmatic phenotype
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Aerobic training results in beneficial effects to asthmatic patients and also in animal models of asthma. However, the studies have not evaluated yet the effects of aerobic training on the peribronchial leukocytes activation. This study evaluated the effects of 4 weeks of low intensity aerobic training on the expression of inflammatory and fibrotic mediators by peribronchial leukocytes. 32 BALB/c mice divided in 4 experimental groups: Control, Exercise, OVA and OVA+Exercise were sensitized on days 0, 14, 28 and 42 and challenged with aerosolized OVA 1% for 3x/week, beginning on 21st day for 4 weeks. Low intensity aerobic treadmill training started on day 22nd for 4 weeks. 72 hours after last OVA challenge mice were assessed to lung inflammation, levels of IL-5 and IL-10 in BAL fluid by ELISA and for quantitative analysis of peribronchial leukocytes activation. The results showed that aerobic training in sensitized animals resulted in significant decrease of total cells and eosinophils in BAL fluid, decreased level of IL-5 and increased level of IL-10 in BAL fluid (p<0.01), decreased expression of IL-4, IL-5, IL-13 (p<0.001), CCL5, CCL10 (p<0.001), ICAM-1 and VCAM-1 (p<0.05), GP91phox and 3-nitrotyrosine (p<0.001), NF-kb and TNFα (p<0.001), while increased the expression of IL-10 (p<0.001). Concerning the airway remodeling, aerobic training in sensitized animals resulted in decreased expression of TGF-beta, IGF-1, VEGF and EGF (p<0.001). We conclude that aerobic training in sensitized animals results in a direct effect on peribronchial leukocytes reducing the expression of important factors related with the airway inflammation and remodeling.

P3739
Involvement of oxidative and nitrosative stress in the development of proteolytic pulmonary emphysema
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Our aim was to investigate the participation of oxidative stress in elastase-induced pulmonary emphysema. C57BL/6 mice were submitted to pancreatic porcine elastase (PPE) instillation (0.05U or 0.5U) per mouse (i.t.) to induce pulmonary emphysema. A separated group of mice were treated with amonoguanidine 1% (AMG). Lungs were collected on days 7, 14 and 21 after PPE instillation. Control group was sham-injected. We performed BAL, biochemical analyses of oxidative stress, and lung stereology and morphometry. Emphysema was histologically characterized at 23 days after 0.5 U of PPE, presenting increased alveolar linear intercept and volume density of airspaces in comparison with the control group. TNF-α was elevated at 7 and 14 days after PPE 0.5 U, concomitant with reduction of IL-10 levels at IL-10 levels at the same time-points. Myeloperoxidase was elevated in all groups treated with 0.5 U of PPE. A contribution of oxidative stress at early stage of emphysema was observed with increased levels of nitrite, malondialdehyde and superoxide dismutase activity at 7 days after PPE 0.5 U. Glutathione peroxidase activity was increased in all groups treated with 0.5 U of PPE. With iNOS inhibition by AMG 1%, emphysema was attenuated. Furthermore, the proteolytic stimulus by PPE enhanced expression of iNOS and nitrotyrosine, PPE stimulus also induced eNOS expression, but AMG reduced it. Our results suggest a pathway of oxidative and nitrosative stress by nitric oxide production via iNOS expression in pulmonary emphysema.

P3740
The serotoninergic receptor subtype 5-HT1RB contributes to the pathogenesis of allergic airway inflammation
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In addition to its well described role in the nervous and cardiovascular system, 5-HT1B, also known as serotonin-1B receptor (5-HT1B), has also shown to influence immune responses and the immune-regulatory properties. Furthermore, elevated levels of free serotonin have been detected in the serum of symptomatic asthmatics. However, the exact serotoninergic receptor subtype involved have not been elucidated, yet. In this study we questioned whether the subtype 5-HT1RB is involved in the pathogenesis of experimental asthma. Expression of 5-HT1RB receptors in lung tissue was analyzed by immunohistochemistry. Allergic airway inflammation was studied in the classical OVA-alum model and in a model of house dust mite (HDM) induced airway inflammation. The experimental induction of allergic airway inflammation led to an increased...
5-HTR1B expression in the lungs of animals sensitized to OVA and challenged with OVA-aerosols. 5-HTR1B expression was even higher in animals with chronic OVA-aerosol challenge as depicted by reduced bronchoalveolar lavage eosinophils and lymphocytes, by reduced perivascular and peribronchial inflammation, as well as by reduced production of Th2 cytokines by re-stimulated mediastinal lymph node cells. The intratracheal application of NAS 181 had also protective effects in HDM-induced asthma. Here we provide evidence that 5-HTR1B receptors modulate asthmatic airway inflammation. Therefore, 5-HTR1B receptors might be promising targets for the development of new anti-asthmatic drugs.

P3741
The antimicrobial peptide CRAMP protects against emphysema

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Rationale: COPD is one of the most prevalent causes of death worldwide and is associated with an ongoing destruction of pulmonary structures that finally lead to the development of emphysema. Antimicrobial peptides (AMP) are a part of the innate immune system. The AMP CRAMP is expressed in the murine homologue of the human calcium dependent antimicrobial peptide (nCAP-18/LL-37). It plays an important role in angiogenesis, cancer and chemotaxis. This work will show that CRAMP is important in lung function in an elastase-induced model of lung destruction.

Methods: Lung destruction was initiated by two times intratracheal administration of elastase. Ten days after the last administration lung function was measured. Cytokines in BAL were measured by ELISA. The lungs were resected and fixed for stereological analysis. Lung tissue was also used for immunohistological staining and RNA-extraction.

Results: Elastase treated CRAMP-ko animals had significantly higher neutrophil influx, more IL1ß and TNF-α in their BAL as the controls. 30 days after the first elastase treatment CRAMP-ko had a higher mean linear intercept and a significantly decreased pulmonary system resistance and elastance. MMP-9 expression and activity was increased and the concentration of VEGF was decreased in the elastase treated CRAMP-ko as compared to the elastase treated wildtype mice.

Conclusion: This work shows that the antimicrobial peptide CRAMP has a protective function in a model of elastase induced lung destruction. CRAMP-ko animals showed more inflammation, a higher degree of lung destruction as well as a higher expression and activity of MMP-9. The concentration of VEGF was significantly lower in the elastase treated ko animals.

P3742
Importance of the receptor for advanced glycation end products in the respiratory mechanics

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Background: There is an increasing clinical interest in studying the receptor for advanced glycation end products (RAGE) and its soluble forms in pulmonary diseases. Interestingly, RAGE and its soluble forms are preferentially expressed in alveoli thereby challenging the pathophysiological role of RAGE. As we have already shown the importance of RAGE as an adhesion molecule in alveolar cells, this study aimed to investigate the age-dependent physiological significance of RAGE in respiratory mechanics.

Methods: Lungs of young (1-6 month), adult (6-9) and old (>24) RAGE knockout (ko) and wild-type mice were analyzed ex vivo using the perfused isolated lung system with negative-pressure ventilation at weight-matched constant tidal volume. Elastin expression was assessed by gene array and histochemistry. Results: Dynamic lung compliance increased gradually with the age in RAGE ko as well as in wild-type mice. Independent of age, the lungs of RAGE ko mice showed higher compliance than that of the wild-type. In this context, old wild-type and young-adult RAGE ko mice had similar lung dynamic compliance. According to the effect of RAGE deficiency on lung compliance, we determined a reduced collagen mRNA and protein expression in the lung tissue of RAGE ko mice. However, lack of RAGE had no significant effect on airway resistance and epithelial layer permeability.

Conclusion: Our study suggests the physiological importance of RAGE and its function in mediating an appropriate lung compliance in which its/their impact on the elastin expression might play a critical role.

P3743
Long-term exposure to tobacco smoke on alveolar macrophages phenotype with regard to genetic and age predisposition

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Core role of tobacco smoke as a risk factor in chronic obstructive pulmonary disease (COPD) is proved, but COPD develops not in every smoker. Since long-term tobacco smoke is a functional phenotype of alveolar macrophages (AM) with regard to genetically determined macrophages phenotype while aging.

Methods: Experimental COPD reCOPD was simulated in vivo in two genetic mouse strains:C57/Bl6 (n=40)-predominant M1 phenotype, and Balb/c (n=40)-M2 phenotype. ECOPD groups included 30 mice, control-10 mice. Tobacco smoking lasted for 6 months-2 cigarettes i.d. COPD was verified histologically. AM functional phenotype was assessed by nitric oxide production (NO) spectrophotometrically.

Results: COPD was confirmed histologically in both eCOPD groups, changes were more expressed in C57/Bl6. There was no significant difference in basal NO production (nBO) in eCOPD groups, but induced NO production (nSO) significantly decreased during 6 months and was much lower in C57/Bl6 than in Balb/c: 3.80±0.21 vs 5.53±0.29 mM (p<0.05). There were no differences in initial nBO in both controls; nSO significantly decreased in both controls during 6 months. Aging decreased INO in both controls - from 26.40±3.2 to 6.60±0.45 mM in C57/Bl6, and from 19.21±1.20 mM to 7.57±0.72 mM in Balb/c, changes were more expressed in C57/Bl6.

Conclusions: We elicited genetic predisposition to COPD risk factor - tobacco smoke, associated with M1 macrophages phenotype and age-related transformation of AM phenotype toward anti-inflammatory M2, increasing with long-term inhalation of tobacco smoke and more expressed in M1 phenotype.

P3744
Cell therapy with adipose tissue-derived stem/stromal cells for elastase-induced pulmonary emphysema in rats

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Background: Studies demonstrating lung repair by stem cells or growth factors have been reported in animal emphysema. We focused on adipose tissue-derived stromal/stem cells (ASC) for regenerative medicine, since it has a high potential to secrete multiple angiogenic factors and differentiate various kinds of cells. Aim: To demonstrate the therapeutic impact of ASC transplantation and to elucidate mechanisms of the effects in rat emphysema models.

Methods: ASC were isolated from rat subcutaneous adipose tissue. Emphysema was induced by intratracheal instillation of porcine pancreatic elastase (PPE). One week after PPE, cell transplantation was performed intravenously. One and 2 weeks after transplantation, we assessed pulmonary function and histopathological changes and measurement of chemokine levels in lung tissue.

Results: ASC transplantation restored pulmonary function to near normal levels and enlargement of the alveolar airspaces was also inhibited. Immunohistochemical analysis revealed some transplanted ASC were localized at damaged alveolar spaces. Vascular endothelial growth factor (VEGF) was significantly reduced by PPE. After ASC transplantation, VEGF level was not reduced. Hepatocyte growth factor (HGF) and cytokine-induced neutrophil chemoattractant-1 (CINC-1) levels were significantly higher than PPE.

Conclusions: Transplantation of ASC for emphysema rats improved pulmonary function and inhibit enlargement of the airspaces. Secretion of HGF, VEGF, and CINC-1 by surviving ASC after transplantation may have contributed to lung repair. Cell therapy with ASC may be a new therapeutic strategy to improve pulmonary function and inhibit alveolar destruction.

P3745
Differential effects of atorvastatin, pravastatin, rosuvastatin and simvastatin on lungs from mice exposed to cigarette smoke

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Short-term cigarette smoke (CS) exposure leads to acute lung inflammation through its influence on oxidants/antioxidants imbalance, but lately studies have shown anti-inflammatory and antioxidant effects. Therefore, we aimed analyzing the effects of four different statins on the lungs of mice exposed CS. Male C57Bl/6 mice were divided into six groups (n=8 mice/group). Mice exposed to the smoke from 12 cigarettes/day/5 days (CS group); exposed to smoke from 12 cigarettes per day for 5 days.
days plus aortovasctam (10 mg/kg/day; CS+A group), or pravastatin (5 mg/kg/day; CS+P group), or rosuvastatin (5 mg/kg/day; CS+R group) or simvastatin (20 mg/kg/day; CS+S group), control group was sham-smoked. One day after the last CS exposure, mice were sacrificed, the bronchoalveolar lavage fluid (BAL) was performed and the lungs were removed for histological analysis and homogenized for biochemical analyses. Oxidant levels were reduced in CS+S (p < 0.05); DPHP levels were increased in CS+A, CS+R and CS+S (p < 0.05); nitrite levels were reduced in CS+P, CS+R and CS+S (p < 0.05). MCP-1 levels were reduced in CS+R and CS+S (p < 0.01); hydroperoxide levels were reduced in CS+R, CS+S and CS+P (p < 0.001); catalase activity was reduced in CS+A, CS+P (p < 0.01) CS+R and CS+S (p < 0.05) when all compared with CS group. These results suggest that simvastatin is the best treatment for acute lung injury induced by CS due to reduction of inflammatory and oxidant markers.

P3746 Pulmonary function, oxidative stress and inflammatory markers in LPS-induced acute lung injury: Differential effects of aortovasctam, pravastatin and rosuvastatin

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The present study was designed to determine what statin could attenuate acute lung injury (ALI) induced by lipopolysaccharide (LPS) in C57BL/6 mice. Young male mice (n = 23) were divided into 5 groups (n = 6 each): injected with LPS 1p. (10 mg/kg), LPS plus aortovasctam (10 mg/kg/day; LPS+A group) or pravastatin (5 mg/kg/day; LPS+P group) or simvastatin (20 mg/kg/day; LPS+S group). Control group received saline (p.). In a separated group of mice (n = 5) the sum of pulmonary arterial and venous systolic pressures (DeltP) and static elastance (E(st)) were measured. One day later (24 h), the animals were sacrificed, BAL performed and lungs were removed for histopathological analysis and homogenized for biochemical analyses. The amount of leukocytes was lower in LPS+P (p < 0.01) and LPS+S (p < 0.05). Cytokine levels of MCP-1 was lower in LPS+P (p < 0.01) while IL-6 was lower in LPS+P (p < 0.01) and LPS+S (p < 0.05). Redox markers (superoxide dismutase and catalase) were lower in LPS+A (p < 0.01). Lipid peroxidation (malondialdehyde and hydroperoxides) were lower in all treated groups (p < 0.05). Myeloperoxidase was lower in LPS+P (p < 0.01). DeltaPtot and E(st) was significantly higher in the LPS group than in the other groups. Our results suggest that aortovasctam, but not simvastatin, exhibits anti-inflammatory and antioxidant actions in LPS-induced ALI.

394. Fibrogenesis between epithelial injury and fibroblast proliferation

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Alveolar fibroblasts are key cells to the process of alveolar septation as PDGFRα knock-out prevented alveolar myofibroblast differentiation and completely blocked secondary septation formation. Lipofibroblasts have been proposed to be essential for septation, peak in number during septation and regress significantly thereafter. Whether PDGFRα expressing precursors are deriving both lineages of fibroblasts is unsolved.

For identification of active PDGFRα expression, PDGFRα-GFP knock-in mice were used. Immunofluorescence staining revealed a co-expression of PDGFRα-GFP and uSMA in the bronchial compartment as well as in the alveolar space. The expression of ADRB co-localizes with the precursor marker in a subset of cells. The same pattern of expression could be observed in the constitutive PDGFRαCre and the conditional PDGFRαCreER mice. PDGFRα-GFP mice showed that PDGFRα-expressing precursor cells are differentiating into myo- as well as lipofibroblasts. The constitutive PDGFRαCre and conditional PDGFRαCreER mice revealed restriction of PDGFRα signalling to bronchial smooth muscle cells and alveolar fibroblasts in the lung. Lineage tracing with conditional PDGFRαCreER mice could confirm that postnatal PDGFRαCreER cells derive lipofibroblasts and myofibroblasts.

P3748 Nr2f is closely related to enhance bleomycin induced airway inflammatory responses caused by diesel exhaust particles in mice

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Diesel exhaust particles (DEP) induced oxidative stress play an important role in proinflammatory reaction on airway. Nr2f is involved in the transcriptional regulation of many antioxidant genes. In the present study, we investigated the effect of DEP on an experimental model of bleomycin (BLM)-induced airway inflammatory responses in both Nr2f+/+ and Nr2f−/− mice. BLM was administered IV to Both Nr2f+/+ and Nr2f−/− C57BL/6d mice at a dosage of 80 μg/kg body weight on day zero. Mice were exposed to 1mg/m3 DEP for 8 hrs/day and 5 days/week. We designed two experimental groups as follows: group 1, BLM alone, clean air; group 2, BLM plus pre-4wks-DEP exposure. Cell populations in BALF were examined at 10 days after BLM injection. We also examined cytokines and chemokines.

In the DEP exposed group, the percentage changes from BLM alone group in the total number of cells and macrophages remarkably increased in the both Nr2f+/+ and Nr2f−/− mice. BLM was administered IV to Both Nr2f+/+ and Nr2f−/− C57BL/6d mice at a dosage of 80 μg/kg body weight on day zero. Mice were exposed to 1mg/m3 DEP for 8 hrs/day and 5 days/week. We designed two experimental groups as follows: group 1, BLM alone, clean air; group 2, BLM plus pre-4wks-DEP exposure. Cell populations in BALF were examined at 10 days after BLM injection. We also examined cytokines and chemokines.

These findings suggest that DEP might be an important factor on the BLM induced lung injury, and Nr2f might be an important genetic factor in the determination of susceptibility to BLM induced lung injury caused by DEP via regulating the macrophages defense mechanisms in mice.

P3749 Inhibiting CXCR4/CXCL12 axis attenuates lung fibrosis both in vitro and in vivo

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Background: Lung fibrosis is characterized by fibroblast proliferation and collagen deposition. CXC chemokine receptor 4 (CXCR4), which binds the stromal cell-derived factor 1 (SDF-1/CXCL12), has been shown a critical role in cell proliferation. Here, we aim to examine the exact modulatory effects of CXCR4/CXCL12 on the fibroblast proliferation and lung fibrosis.

Methods: In vitro, primary human lung fibroblasts (HLF) was isolated from patients with idiopathic pulmonary fibrosis and primary spontaneous pneumothorax for thoracoscopy with stapling of any air leak. CXCR4 protein level was assessed by indirect immunoblotting. MTT was used for the proliferation assay of bleomycin stimulated normal HLF in the presence or absence of AMD3100, an antagonist of CXCR4. In vivo, C57BL/6 mice were injected intraperitoneally with saline or AMD3100 (200μg) 1 day before intratracheal instillation of bleomycin (5mg/kg). Survival rate, lung fibrosis and pulmonary function will be assessed.

Results: The basal level of CXCR4 expression was higher on fibrotic HLF. Bleomycin could promote the proliferation of normal HLF, which could be significantly attenuated by AMD3100 pretreatment. AMD3100 administration significantly increased the survival rate of mice on day 2i compared with bleomycin treatment alone. According to the histology, pulmonary fibrosis was attenuated by AMD3100 pretreatment in later stage of bleomycin injury. However, no significant differences in total lung capacity and airway resistance were observed between these groups.

Conclusion: Collectively, our data suggest that AMD3100 could significantly attenuate lung fibrosis both in vitro and in vivo through inhibiting CXCR4/CXCL12 axis.
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alveolar epithelial cells and suppressing lung inflammation

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Acute lung injury (ALI) is a critical illness syndrome consisting of acute respiratory failure with bilateral pulmonary inflammatory response that is refractory to current therapies. ALI is characterized by injury of the alveolar capillary barrier, neutrophil accumulation, and induction of pro-inflammatory cytokines followed by devastating lung fibrosis. Ghrelin, an acylated peptide produced in the stomach, increases food intake and growth hormone secretion, suppresses inflammation, and promotes cell survival. We investigated the pharmacological potential of ghrelin in the treatment of ALI by using a bleomycin-induced ALI model in mice. Ghrelin or saline was given to mice daily starting 1 day after bleomycin administration. Ghrelin-treated mice showed a definitively higher survival rate than saline-treated ones. They also had smaller reductions in body weight and food intake.

The amelioration of neutrophil alveolar infiltration, pulmonary vascular permeability, induction of pro-inflammatory cytokines, and subsequent lung fibrosis were notable in ghrelin-treated mice. Additionally, ghrelin administration reduced the injury-induced apoptosis of alveolar epithelial cells. Our results indicate that ghrelin administration exerts a protective effect against ALI by protecting the alveolar epithelial cells and regulating lung inflammation, and highlight ghrelin as a promising therapeutic agent for the management of this intractable disease.

P3751
A longitudinal characterization of lymphangiogenesis in bleomycin-induced pulmonary fibrosis mouse model
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Background: The roles of lymphangiogenesis in the pathogenesis of pulmonary fibrosis has been studied; however, it has not been associated with this condition in human.

Objective: To clarify longitudinal characteristics of lymphangiogenesis in bleomycin-induced pulmonary fibrosis mouse model.

Animal and methods: Pulmonary fibrosis was induced in C57BL/6 female mice by intratracheal injection of 3.0 U/kg of bleomycin. Three mice were sacrificed in each group at days 0, 7, 14, 21, 28, and 35 days after. Formalin fixed and paraffin embedded lung tissues were used for immunohistochemical and morphometric analyses. Antibodies specific for Vegfr-3, Cd31 and type 1 collagen were used to detect lymphatics, blood vessels and collagen, respectively.

Results: The dilatation of the existing lymphatics around bronchus and large blood vessels was observed on Day 7, and numerous lymphocytes were organized around them. The lymphatics were newly formed in fibrotic lesions on Day 14, although capillaries were barely detected in the lesions. In Masson Trichrom staining, connective tissue was most prominent on Day 21, and loose after that. The area densities of interstitium and hydroxyproline concentration in lung homogenates were maximally increased on Day 21. The existing and the newly formed lymphatic densities were significantly increased on Day 21, respectively (p < 0.05).

Conclusion: In the early stage, the existing lymphatics may play a role in the organization of lymphoid structure, which possibly facilitate the fibrogenesis. In the later stage, the newly formed lymphatics may be associated with the tissue resolution.

P3752
Bioavailability of vascular endothelial growth factor (VEGF)? A role in pulmonary fibrosis?
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Vascular endothelial growth factor (VEGF) is both a growth factor and permeability factor, involved in tissue repair and as such, has been proposed to have a role in the pathogenesis of pulmonary fibrosis. VEGF is generated as multiple isoforms of two families, VEGFxxxb and VEGFxxx, and mediates its effects through specific receptors, VEGFR-1 and VEGFR-2 co-receptors, neuropilin-1 and neuropilin-2. We hypothesised that these receptors, co-receptors and isoforms would be differentially expressed in normal versus fibrotic fibroblasts. Normal fibroblasts (NF) and fibrotic fibroblasts (FF) (from patients with proven UIP) were extracted from lung samples using the explant method. Expression of VEGFR-1, 2, and NRPI-1, NRPI-2, and VEGF isoforms was established at the protein level using western blotting whilst receptor expression was confirmed with immunofluorescence staining of cells in culture.

Both NF and FF expressed VEGFR1 and 2. NRPI-1 and 2 and VEGFxxx,xxxb isoforms did not significantly differ in VEGFR-2 and NRPI-1 expression between NF and FF fibrast. However, both fibrast expression of VEGFR-1 and NRPI-2 were significantly reduced in NF versus FF (p<0.05, non-paired t-test).

VEGF receptors, co-receptors and isoforms are expressed differentially in NF and FF. This suggests a potential role for changes in VEGF bioactivity in the development of pulmonary fibrosis.

P3753
Erythropoietin (EPO) attenuates the expression of its receptor (EPO-R) in bleomycin (BLM)-induced pulmonary fibrosis (PF) in rats
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Bleomycin (BLM)-induced pulmonary fibrosis (PF) in rats

Objective: To investigate the pharmacological potential of RKT in the treatment of ALI by using a bleomycin-induced ALI model in mice. Ghrelin, an acylated and orexigenic peptide, produces predominantly in the stomach. We previous studies have reported that RKT increases plasma level of ghrelin, an antidiabetic and anti-inflammatory peptide.

RKT administration was investigated the pharmacological potential of RKT in the treatment of ALI by using a bleomycin (BLM)-induced lung fibrosis, and highlight the potential role for changes in VEGF bioactivity in the development of pulmonary fibrosis.

P3754
Rikkunshito ameliorates bleomycin-induced lung injury in mice
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Acute lung injury (ALI) is a critical illness syndrome consisting of acute respiratory failure with bilateral pulmonary infiltrates that is refractory to current therapies. ALI is characterized by injuries of the alveolar epithelial barrier, infiltrations of neutrophils into lung parenchyma, and induction of pro-inflammatory cytokines followed by devastating lung fibrosis.

Rikkunshito (RKT), a traditional Japanese medicine, consists of several kinds of flavonoids which have been shown to have anti-inflammatory effects. In addition, previous studies have reported that RKT increases plasma level of ghrelin, an acylated and orexycoric peptide, produced predominantly in the stomach. We investigated the pharmacological potential of RKT in the treatment of ALI by using a bleomycin (BLM)-induced lung injury model in mice.

RKT or distilled water was given to mice orally and daily starting from the day of BLM administration. RKT-treated mice showed a definitively higher survival rate than distilled water-treated ones. They also had smaller reductions in body weight and food intake compared to the controls. Additionally, RKT-treated mice showed reduction of pulmonary epithelial permeability, neutrophil alveolar infiltration, and subsequent lung fibrosis.

RKT administration resulted in increase in plasma levels of ghrelin in BLM-treated mice. However, RKT administration also exerted protective effects against BLM-induced ALI response on ghrelin-deficient mice in addition to ghrelin-competent mice. Our results indicate that RKT administration exerts a protective effects on BLM-induced lung injury in mice, independently of the effects of ghrelin, and highlight RKT as a promising therapeutic strategy for the control of the ALI.
P3755
Leukotriene (LTC4) aggravate bleomycin-induced pulmonary fibrosis in mice
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Background: Synthesis of cysteinyl leukotrienes (cys-LTs) is thought to cause inflammatory disorders such as bronchial asthma and allergic rhinitis. Recent reports have suggested that LTC4 is an important regulator of pulmonary fibrosis. This study examined the effect of LTC4 in LTC4 synthesize-overexpressed transgenic (Tg) mice with bleomycin-induced pulmonary fibrosis. We also focused on the function of lung-derived fibroblasts in the Tg mice.

Methods: To administration of bleomycin, pranlukast hydrate, a cyst-LT1 receptor antagonist, was intratracheally instilled. Concentrations of IL-4, -13, and TGF-β1 mRNA was measured by real time PCR. Results: The levels of IL-4, -13, and TGF-β1, and pulmonary fibrosis were greater in Tg than in WT mice. The reduction of LTC4 function in Tg mice could be decreased both these cytokines and pulmonary fibrosis. Furthermore, continuous LTC4 secretion from fibroblasts was higher in Tg than in WT mice, while reduction of LTC4, by pranlukast in fibroblasts from Tg, but not in those from WT mice, decreased cell viability and expression of TGF-β1 mRNA.

Conclusion: These findings first suggest that overexpression of LTC4 by pranlukast in fibroblasts from Tg, but not in those from WT mice, to mimic epithelial-mesenchymal interactions in the human lung.

Distal airway epithelial cells differentiate into ATII-like cells as suggested by morphological changes as well as increased expression of differentiation markers AQP3, SP-A, SP-C in the 3D model. Wnt11 was identified in the model and in human lung explant cultures as one of the main regulators of ATII differentiation. Added Wnt11 increased the expression of ATII markers, while silencing of Wnt11 resulted in elevated levels of EMT markers N-cadherin and S100A. We conclude that the 3D lung model is applicable for studying epithelial-mesenchymal interactions in the lung. Our finding may mark Wnt11 as a potential therapeutic target in lung regenerative therapy.

P3756
LSC 2012 Abstract – Wnt11 is identified in 3D human lung tissue model as regulator of distal airway epithelial cell differentiation
Demokos Barthe1, 2, Veronika Csongei2, Vijay D’Souza1, David R. Thickett1, Judith E. Pongracz2.

Methods: Prior to administration of bleomycin, pranlukast hydrate, a cyst-LT1 receptor antagonist, was intratracheally instilled. Concentrations of IL-4, -13, and TGF-β1 mRNA was measured by real time PCR. Results: The levels of IL-4, -13, and TGF-β1, and pulmonary fibrosis were greater in Tg than in WT mice. The reduction of LTC4 function in Tg mice could be decreased both these cytokines and pulmonary fibrosis. Furthermore, continuous LTC4 secretion from fibroblasts was higher in Tg than in WT mice, while reduction of LTC4, by pranlukast in fibroblasts from Tg, but not in those from WT mice, decreased cell viability and expression of TGF-β1 mRNA.

Conclusion: These findings first suggest that overexpression of LTC4 by pranlukast in fibroblasts from Tg, but not in those from WT mice, to mimic epithelial-mesenchymal interactions in the human lung.

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P3758
LSC 2012 Abstract – Imaging Wnt/beta-catenin signalling in an ex vivo tissue culture model of lung repair
Franziska Uhl, Melanie Königshoff, HMGU, Comprehensive Pneumology Center, Munich, Germany

Emphysema is a pathophysiological hallmark of COPD and characterized by airspace enlargement and impaired alveolar repair processes. Recently, Wnt/beta-catenin signalling has been linked to epithmesenchymal changes in human disease and animal models thereof. Here, we aim to further decipher the underlying mechanisms and image structural changes involved in lung repair processes. We applied an ex vivo tissue culture model from wildtype (C57Bl/6) and Wnt reporter mice (Bat-/-TopGal) subjected to elastase treatment or PBS. Tissue slices (300 μm) generated using a vibratome were viable in culture for up to 7 days ex vivo (WST-1: d1: 21 ±6 vs. d7 41 ±67%). Structural integrity of control (C) and epithmesenchymal (E) lung slices was determined by qPCR and immunofluorescence microscopy. Functional Stipc was decreased in E lung slices compared with control and further decreased over time shown by ELISA (d1: 135±19 ng/ml C vs. 82±17 ng/ml E). Wnt signalling activation by Lef1 led to an increase in Stipc expression accompanied by increased β-galactosidase staining in alveolar regions and upregulated target gene expression, such as Axin2, Dkk2 or Lef1. Epithmesenchymal tissue slices closely reflect COPD-like changes in vivo. Lung slices are viable up to 7 days ex vivo allowing determination of structural changes and cell fate in the diseased lung upon signal pathway modification.

P3759
Proliferation of alveolar type II pneumocytes is stimulated by Jagged-1 in vivo
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Notch is an ancient cell-signaling system that regulates the specification of cell fate. Recently, Notch was found to confer antigen presenting cell function on mast cells and induce histamine release in human basophils and regulate migration and survival of eosinophils. In acute lung injury, alveolar type II cells activate macrophages, secrete soluble mediators, migrate and spread in response to the injury. Additionally, Notch stimulates myofibroblast differentiation and migration of cultured RLE-6T7 cells. However, until now, nothing is known on the role of Notch activation regarding proliferation of rat alveolar type II cells. Rat alveolar type II cells (RLE 6T7) were obtained from the American Type Culture Collection (ATCC no. CRL-2300; Manassas, VA, USA) and were cultured in DMEM/Ham’s F12 containing 10% fetal calf serum and L-glutamine. Cell proliferation was measured by direct cell count and the fluorometric proliferation assay EZ4U basing on tetrazolium salt reduction. Cells were incubated with the test substances in medium containing 0.5% fetal calf serum for 24h at 37°C and 5% CO2. Jagged-1 significantly stimulated proliferation of alveolar epithelial cells within a wide concentration range [5μg/ml to 100μg/ml]. The maximum effect was observed at 100ng/ml. To show specificity of the observed effect, rat alveolar type II cells were preincubated (45 min) and co-incubated with the specific gamma secretase inhibitor DAPT [107 M] which completely abolished the effect of Jagged-1 (10μg/ml).

Hence, we report for the first time that the Jagged-1/Notch signalling pathway is affecting rat alveolar type II cell proliferation in vitro.

P3760
Wnt11 inhibits epithelial-mesenchymal transition induced by TGFb1 in human type II alveolar epithelial cells
Demokos Barthe1, 2, Vijay D’Souza1, Judith E. Pongracz2, David R. Thickett1.

Methods: Wnt11 inhibits epithelial-mesenchymal transition induced by TGFb1 in human type II alveolar epithelial cells.

Increased activity of TGFβ1 plays a crucial role in the pathogenesis of idiopathic
pulmonary fibrosis (IPF). Alveolar type II cells (ATII) undergo EMT expressing mesenchymal markers when exposed to a high concentration of TGFβ1 in both in vitro and in vivo models. Mesenchymal signals might contribute to the differentiation and regeneration of pulmonary epithelium. Wnt11 is a secreted glycoprotein known to be expressed in the mesenchyme of the embryonic lung. We constructed a 3-dimensional (3D) human tissue model of primary human pulmonary cells to mimic epithelial-mesenchymal interactions in the lung. Our results indicate that human lung fibroblasts are a source of Wnt11 in the lung tissue model. ATII cells isolated from human lung samples were treated with recombinant TGFβ1 and/or Wnt11. Expression levels of the EMT markers Vimentin, alpha smooth muscle actin (αSMA) and SLUG were determined by qPCR and immunofluorescence. We found that Wnt11 inhibits EMT induced by TGFβ1 in ATII monolayers and in 2D and 3D ATII/fibroblast co-cultures. Wnt11 treatment resulted in decreased expression of EMT markers compared to TGFβ1 treated cell cultures.

**Conclusion:** Our data suggest that mitochondrial metabolism plays an important role in the phenotypic activation of lung fibroblasts in both TGFβ1 stimulated cells in vitro and bleomycin-induced fibrosis in vivo.

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**Figure 1.** Human ATII cells subjected to TGFβ1 and Wnt11 treatment.

We propose that the pulmonary mesenchyme might contribute to the homeostasis of epithelial cells by secreting Wnt11. This finding that effects of TGFβ1 can be antagonized by Wnt11 may mark it as a potential therapeutic target in the fibrotic diseases of lung.

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**P3761 Epithelial Pten controls acute lung injury and fibrosis by regulating intercellular junctional integrity and EMT.**

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Injury to alveolar epithelial cells (AECs) and its repair process are integral to the pathogenesis of acute lung injury (ALI) and idiopathic pulmonary fibrosis (IPF). Disruption of AECs integrity and its reconstitution are crucial for ALI progression. In addition, myofibroblasts, key effector cells in IPF, partially originate from AECs through epithelial-mesenchymal transition (EMT). However, the regulation mechanisms of AECs integrity remains unclear. We explored the role of epithelial Pten in lung injury by generating a postnatally and lung epithelium-specifically Pten-null (SOPten) mouse strain. Sixty percent of SOPten mice died of hypoxia, whereas all control mice survived after bleomycin insult. SOPten mice demonstrated aggravation of ALI and lung fibrosis with enhanced disruptions of intercellular junctional complexes of AECs and degradation of basement membranes. Epithelial-derived myofibroblasts were increased in epithelium-specific Pten-deficient mice. Lung sections of bleomycin-treated SOPten mice showed increased pAkt, pS6K, Snail and MMP expression. Reduced claudin-4, E-cadherin, and laminin-beta1 expressions. Systemic Akt inactivation definitively saved SOPten mice through amelioration of bleomycin-treated SOPten mice showed increased pAkt, pS6K, Snail and MMP expression. Reduced claudin-4, E-cadherin, and laminin-beta1 expressions. Systemic Akt inactivation definitively saved SOPten mice through amelioration of bleomycin-treated SOPten mice showed increased pAkt, pS6K, Snail and MMP expression. Reduced claudin-4, E-cadherin, and laminin-beta1 expressions. Systemic Akt inactivation definitively saved SOPten mice through amelioration of bleomycin-treated SOPten mice showed increased pAkt, pS6K, Snail and MMP expression. Reduced claudin-4, E-cadherin, and laminin-beta1 expressions.

**Methods & results:** Using an epithelial mesenchymal transition (EMT) model, immunoblotting demonstrated up-regulation of E-cadherin and suppression of Fibronectin expression by TLD extract, thereby reversal of EMT in the treated A549 cells. Additional experiments displayed that TLD can inhibit hyper-expression of p-ERK 1/2, p-Akt, p-STAT3, NF-κB, and α-SMA in lung fibroblasts of nonspecific interstitial pneumonitis (NSIP) and HMGB1-stimulated up-regulation in those of normal or NSIP, concomitant with reduced levels of inflammatory cytokines. Alzet osmotic minipumps application of TLD extract to Bleomycin/BLM-challenged mice significantly decreased acute inflammation and pulmonary fibrosis. Mucosal application of TLD extract to native mouse trachea by Ussing chamber recordings suggested activation of Cyt secretion by increasing cAMP. These effects were mimicked by a mix of isolated components.

**Conclusion:** We suggest that the extract from TLD may provide a novel and effective treatment for interstitial lung fibrosis through multi-ingredient synergistic regulation of cAMP signaling.

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**P3764 Chemokine profiles of A549 human alveolar epithelial cells that underwent epithelial-mesenchymal transition by TGF-β and/or TNF-α.**

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Epithelial-mesenchymal transition (EMT) is supposed to be implicated in the pathogenesis of lung fibrosis through enhanced TGF-β1 signaling. TNF-α has also been implicated in tissue fibrosis. Recently, TGF-β1 induced EMT is augmented by TNF-α, suggesting that enhanced EMT by TNF-α may be important in the pathological processed of lung diseases. However, the mechanism of enhanced EMT by TNF-α has not been fully elucidated. Therefore, we evaluated the cytokine/chemokine profiles of the cells that underwent EMT by TGF-β1 and/or TNF-α.

**Methods:** A549 cells were incubated for 48 hours with 5 ng/ml of TGF-β1, 10 ng/ml of TNF-α, or TGF-β1 and TNF-α to undergo EMT. After 48 hours incubation, growth medium was changed to serum-free medium, and the supernatants were collected at 48 hours. Cytokine/chemokine array was performed using Ray Bio human cytokine array V. Relative values were quantitated by densitometry, and normalized to that obtained in non-treated sample.

**Results:** TNF-α induced production of inflammatory chemokines, such as RANTES and MCP-1. TGF-β1 induced production of inflammatory chemokines, including GM-CSF, GRO, GRO-A, MCP-2, and MCP-3. Simultaneous stimulation with TNF-α and TGF-β1 reduced production of GM-CSF, GRO, GRO-A, IL-6, MCP-1, RANTES, and these effects were enhanced on the production of GRO, GRO-A, IL-8, and MCP-1.

**Conclusion:** The cells treated with TGF-β1 or TNF-α have different chemokine profile, and the effect on chemokines production was enhanced by the combination with TGF-β1 and TNF-α. This study might contribute to understanding mechanism of EMT enhanced by TNF-α and pathogenesis of lung fibrosis.
CONCLUSION: This study showed that PF is able to decrease pulmonary fibrosis (11.13 to 15.67) and PQ+antioxidant (11 95%CI 7.77 to 14.23) groups. The not decrease the lung fibrosis (p=0.413). Life expectancy decreased in PQ+NS (11 of ALI

The role of pre-receptor glucocorticoid metabolism in regulating the severity of ALI

The role of pre-receptor glucocorticoid metabolism in regulating the severity of ALI

P3764

Hyperoxia increased lung resistance and decreased compliance, total lung capacity and forced expiratory flow. After recovery, resistance, compliance and total lung capacity had normalized whereas forced flows remained low. Sphingolipids, including ceramides, were significantly increased after hyperoxia. Ceramides were still increased after 2 weeks of recovery, but normalized to control values after 4 weeks. Addition of D-sphingosine during the first 5 days of recovery reduced ceramide levels at 2 weeks and partially reversed the hyperoxia-induced increase in alveolar size and arrest in alveolarization at 4 weeks, although no further improvement in lung function parameters was observed.

Aim: To characterize lung function and BAL sphingolipid profile of newborn mice during hyperoxia exposure and recovery in room air, and to examine the effect of D-sphingosine supplementation during recovery.

Methods: Newborn mice were exposed to 80% O2 for 4 weeks and allowed to recover in room air for another 4 weeks. Lung function measurements, histological and morphometrical analysis of lung tissue was performed and BAL fluid was collected during hyperoxia and after recovery with and without D-sphingosine supplementation. Sphingolipids in BAL were quantified by tandem mass spectrometry.

Results: Hyperoxia increased lung resistance and decreased compliance, total lung capacity and forced expiratory flow. After recovery, resistance, compliance and total lung capacity had normalized whereas forced flows remained low.

Molecular pathogenesis of Idiopathic Pulmonary Fibrosis (IPF) remains unclear. We recently demonstrated a key role for the PI3K pathway in both proliferation and differentiation into myofibroblasts of lung fibroblasts treated with TGF-β. In this study we assessed the expression of Class I PI3K p110 isoforms in IPF lung tissue and fibroblast cell lines. Moreover, we investigated the in vitro effects of the selective inhibition of p110 isoforms on IPF fibroblast proliferation and fibrogenic activity.

To evaluate expression levels of PI3K p110 isoforms, IHC as well as Western blot and Flow Cytometry analysis were performed on normal and IPF tissue sections. No significant differences between normal and IPF tissue/cells were observed for the expression of PI3K p110 α, β and δ isoforms whereas p110γ resulted overexpressed in both IPF lung homogenates and ex-vivo fibroblast cell lines. The IHC results show a strong immunoreactivity for p110γ in myofibroblasts of IPF lungs. Moreover, in pathologic bronchiolar structures of IPF lungs, basal cells exhibited a pronounced nuclear expression of p110γ which was hardly detectable in normal lung tissues. Furthermore, as a consequence of both p110γ pharmacological inhibition and gene silencing, a significant inhibition of proliferation rate and α-SMA expression were observed in IPF fibroblasts whereas no effects were found on normal cells.

Our data indicates that PI3K p110 γ isoform can be a novel pharmacological target.
Inhibition of the sonic hedgehog pathway at the primary cilium prevents the effect of TGF-beta 1 on alveolar epithelial cells.

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Introduction: The mesenchymal differentiation of alveolar epithelial cells induced by Transforming Growth Factor beta-1 (TGF-beta1), also called Epithelial Mesenchymal Transition (EMT), may contribute to Locidpathic Pulmonary Fibris (IPF). The Sonic Hedgehog (SHH) pathway is involved in epithelial cells-fibroblasts interaction during fetal lung development and lung fibrogenesis in adult lung. Previously, our laboratory has demonstrated that the SHH pathway is necessary to the action of TGF-beta 1 in human pulmonary fibroblasts (Cigna et al. in revision).

Aims: We hypothesized that the SHH pathway could play a role in mesenchymal differentiation of alveolar epithelial cells induced by TGF-beta 1.

Methods: We assessed the effect of TGF-beta 1 (1-5 ng/ml) for 48h in serum-free medium. The expression of E-cadherin, N-cadherin, and fibronectin was evaluated by real-time PCR, Western blotting and immunocytochemistry. The migratory capacity of A549 is also measured in these conditions.

Results: Inhibition of the pathway via SMOGLI abolishes the effect of TGF-beta 1 on the migration of epithelial cells but does not influence the effect of TGF-beta 1 on cell differentiation. By contrast, the inhibition of the HH pathway in the primary cilium with HPI-4 prevents and reverses the effect of TGF-beta 1 on epithelial cell differentiation.

Conclusions: Our results indicate that the primary cilium controls the effect of TGF-beta 1 on A549 cells in vitro.

Protective effect of mesenchymal stem cells (MSC) on hypoxia-induced epithelial-mesenchymal transition of alveolar epithelial cells (AEC)

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Background: Epithelial-to-mesenchymal transition (EMT) of AEC induced by TGF-β1 or hypoxia (HX) may contribute to pulmonary fibrosis. In animal models of lung fibrosis, administrated fibroblastic MSC reduced fibrosis and mortality by an unknown mechanism. We hypothesized that MSC may favor alveolar wound healing by preventing hypoxia-induced EMT. We tested in vitro the paracrine effect of MSC on the phenotypic changes of AEC induced by HX.

Methods: Rat AEC cultured on Transwell filters were exposed to HX (3 or 1.5% O2) for up to 12 days in the presence/absence of human MSC on the bottom of well. Epithelial electrical resistance (TER) as well as epithelial markers (E-cadherin, ZO-1, TFP-1) and mesenchymal markers (smooth muscle α-actine, vimentin) were assessed by ohm-meter, immunofluorescence and Western blot at days d1, d2, d7, d12.

Results: Exposure of AEC to HX resulted in a dose- and time-dependent decrease of TER and of epithelial marker expression, together with an increase in mesenchymal marker expression. These effects were reproduced by treatment with cobalt chloride and were partially prevented by anti-oxidant drugs (Euk134 or α-tocopherol). By contrast, with 100 μM vitamin E and C, hypoxia with 100 μM vitamin C, hypoxia with 100 μM vitamin C and hypoxia with a combination of vitamins E and C (10-7, 10-6 M respectively) TER measurement, immunofluorescence staining of ZO-1 and RT-PCR to detect IL8, IL6, TNF-α and ZO-1 expression were used.

Results: The reductions of the TER in hypoxic groups (hypoxia and hypoxia with antioxidants) were associated with the reduction in the ZO-1 thickness and downregulation of ZO-1 expression compared with the control. In contrast, the expression of IL-8, IL-6 and TNF-α was upregulated in the hypoxic groups compared with the control.

Conclusions: Hypoxia-induced barrier permeability dysfunction represented by the decrease in TER and the reduction of ZO-1 levels is associated with an increased expression of pro-inflammatory cytokines IL-8, IL-6 and TNF-α. The antioxidant vitamins E and C had only a slight protective effect against hypoxia damage.
originating at the initiation of oxidation amino acid rests of protein at the exacer-
beration (0.05±0.01U/mg) and remission stage (0.03±0.00U/mg) than in control
subjects (0.01±0.00U/mg) (p<0.05). COPD patients had a decreased amount of
carbohydrate derivatives at the stage of elongation of the process. This may be due to
the considerable protein destruction. We have shown low level of reduced thiol at
the exhaustion of antioxidant system. The data received correlate with disruption
of pulmonary function and oxygen saturation in COPD patients.

Purpose of the study: The evaluation of the IV-type collagen level dynamics in
BALF of patients with 3rd stage COPD during the treatment with Roflumilast.

Materials and methods: The contents of the IV-type collagen in BALF was evalu-
ated in 39 patients with III stage COPD in a random stage using enzyme-linked
immunosorbent assay before and after 3 months of treatment with the inhibitor of
phosphodiesterase 4 – Roflumilast, 500 mg per day, inside, together with the basic
local 3rd stage COPD treatment (GOLD, 2010).

Results of the study: The contents of the IV-type collagen in BALF before the
treatment in patients with 3rd stage COPD was (69±3±12) ng/ml, which is in 7.4 times higher than in almost healthy people, whose contents consisted of (9±0.5±54) ng/ml. After the second examination in 90 days, the
above-mentioned indicator in patients fell down by 2.45 times and was equal
(28±2±2.3) ng/ml.

Conclusions: The depression of IV-type collagen levels demonstrate the ability to
slow down pneumosclerosis progression in patients with III COPD who are treated
with Roflumilast.

The depression of IV-type collagen levels demonstrate the ability to
slow down pneumosclerosis progression in patients with III COPD who are treated
with Roflumilast.

The effect of intravenous immunoglobulin on oxygen-dependent metabolism
of blood cells in patients with community acquired pneumonia

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Active oxygen forms (AOF) determine the microbicidal activity of phagocytes.

Their low generation may be one of the reasons of latent inflammatory process.

The aim was to study the effect of i.v. immunoglobulin immunovenin (IMV) on the
production of AOF in in-vitro experiments and in patients with community-
acquired pneumonia (CAP).

Methods: The method of chemiluminescence (CLL) registration was used to study
the effect of various doses of IMV (0.005 mg/ml, 0.03 mg/ml, 0.05 mg/ml) on the
production of AOF in the blood of healthy subjects. In the clinical part of the
research AOF generation was studied in 35 patients with CAP. 17 patients with
CAP received standard therapy. In 18 patients IMV was added to the treatment

Results: In in-vitro experiments IMV dose of 0.05 mg/ml increased CLL inten-
sity of blood by 18.4±0.3% (p<0.05) the doses of 0.01 mg/ml and 0.05 mg/ml
increased CLL intensity by 48.6±2.1% (p<0.05) and 64.5±3.4% (p<0.05)
respectively. In comparison with normal findings CLL intensity of blood in pa-
tients with CAP has been found to be reduced by 1.5 times. The use of IMV in patients has increased production of AOF in blood and resulted in positive
dynamics of clinical findings. In the case of standard therapy low CLL intensity of
blood maintained, the inflammatory process often had a prolonged course.

Conclusion: IMV may be used in the treatment of patients with CAP owing to
its influence on AOF. It allows to increase AOF production by phagocytes and
decrease the incidence of latent inflammatory processes.

Converse airway effects of nicotine in vitro and in vivo

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Cigarette smoke, which contains high concentrations of nicotine and endotoxin
(LPS), plays a pivotal role in the development of asthmatic airway inflammation
and hyperreactivity (AHR). But the mechanisms behind this are poorly known.
The present study examines the effects of nicotine and LPS on murine airways
both in vitro and in vivo.

In the in vitro model, murine tracheal segments were cultured in presence of
nicotine (10 μM) and/or LPS (10 μg/ml) for 4 days. Smooth muscle contractility
was assessed with myograph and inflammatory mediator expressions measured
with real-time PCR. In the in-vivo model, mice were exposed to nicotine (24
mg/kg/day) via osmotic pumps for 28 days followed by intranasal (i.n.) LPS
(1 mg/ml) instillation during the last 3 days. Airway resistance was measured
using FlexiVent® after i.v. methacholine challenge and inflammatory cells in
the bronchoalveolar lavage fluid were counted. In vitro, nicotine increased contractions to Bradykinin (BK) and des-Arg9-BK. Carb cholactons only increased after combined nicotine and LPS exposure.

Moreover, nicotine specifically up-regulated Toll-like receptor 2 and 4 as well as
inflammatory mediators COX-2 and MCP-1 in vivo, micro- and macrophages,
but i.n. LPS caused both AHR and acute pulmonary neutrophilic inflammation.

28-days of in-vivo nicotine exposure suppressed the LPS-induced AHR both in
central and peripheral airways and prevented pulmonary neutrophil infiltration.

It is interesting to note that the local smooth muscle effect of nicotine differs
markedly from the in-vivo effect which involves a much more complex system
of inflammatory cells and mediators. This is important to acknowledge when
evaluating the toxic effect of nicotine.
P3780 Effect of stress on free radical indices in bronchial asthma

Elena Zaprudnova1, Svetlana Soodaeva2, Igor Klimanov2

Effect of stress on free radical indices in bronchial asthma

We investigated the influence of stress on the levels of some free radical indices in exhaled breath condensate (EBC) at people with asthma (BA) compared with healthy people.

The control group (n=57) included healthy, young people aged 20 - 23 years. The second group (n=62) included young people who suffer from BA (remission) aged 20-23 years.

The levels nitrate/nitrite, metabolites NO, and malondialdehyde (MDA) were determined at rest and under stress in both healthy and in people with BA. Stress state of subjects formed on the background of the educational process, as exam stress is one of the first places among the causes of mental stress in students.

The study found that people suffering from BA, there is increased production of NO in the lungs, which is reflected in increased levels of NO metabolites in EBC by 1.3 times compared with control. Patients with BA most sensitive to stress conditions in comparison with healthy young people, resulting in a higher level (1.3 times) in their production of NO metabolites during stress (5.8±0.03 mM in patients with BA during stress and 4.5±0.05 mM in healthy under stress, p <0.05). In patients with BA as an increase in basal level of MDA in a 1.6 times (p <0.05) in EBC in comparison with control. Under conditions of stress has been increased increase of lipid peroxidation, as evidenced by increased concentrations of MDA in EBC of 1.5 times in normal and 1.7 times in patients with BA. Thus, the most active enhancement of free radical processes in the lungs leads to the conclusion that patients with BA most sensitive to the stress associated with the educational process.

P3781 Regulation of VEGF receptors and co-factors by hypoxia and hyperoxia

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VEGF exerts its biological effect through specific receptors, VEGFR-1 and VEGFR-2 and co-receptors, neuropilin-1 and neuropilin-2, leading to a complex regulatory system. The presence of hypoxia in lung disease and its treatment by high flow oxygen have been proposed to contribute to lung injury. We hypothesised that hypoxia and hyperoxia may lead to changes receptor and co-receptor expression and hence regulation of VEGF bioactivity.

A549 (ATCC) as a model for lung epithelial cells and Human pulmonary microvascular endothelial cells (HMVEC-li) were obtained and cultured in 24 hours in a PROXO chamber in normoxic (N), hyperoxic 90% O2 (H), hypoxic conditions were represented by culture in the presence of Cobalt chloride (CoCl2). The cells were then lysed for protein or RNA extraction. Expression of VEGFR1, 2 and NRP-1, NRP-2 was established at both mRNA and protein level by q-PCR, immunofluorescence and Western blotting.

These findings evidence the beneficial role of NO and VIP pathways in preventing the lung inflammatory response to hypoxia and indicating their protective potentials against the subsequent development of airway hyperresponsiveness.

Grant support: OTKA K81179. The first author is a laureate of the long-term ERS fellowship.

P3784 Protective effects of erythropoietin and N-acetyl cysteine on methotrexate-induced lung injury in rats

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Objective: To evaluate the effects of P3784(Erythropoietin) on the expression of plasmaglobulin activator inhibitor (PAI-1) in lipopolysaccharide(LPS) induced acute lung injury(ALI).

Methods and results: ALI was induced in P3784(-/-) and C57BL/6J mice 4hrs or 24hrs after intratracheal instillation of LPS(5mg/kg), characterized by inflammation in morphology, higher wet/dry ratio, elevated protein concentration and increased neutrophils in bronchial alveolar lavage fluid(BALF), which were more significantly in P3784(-/-) mice. After LPS administration, PAI-1 mRNA expressions were markedly increased in a time-dependent manner and the PAI-1 concentration in BALF were markedly increased by 4hrs and decreased nearly to baseline at 24hrs in P3784(-/-) mice compared to C57BL/6J mice. Autoaphagy was significantly enhanced with higher expression of LC3B in P3784(-/-) mice compared to C57BL/6J mice. Primary cultured macrophages were stimulated by LPS (100ng/ml) for 4hrs. The level of reactive oxygen species(ROS) in macrophages from P3784(-/-) mice was significantly higher than that from C57BL/6J mice. The release of PAI-1 was significantly increased in macrophages from P3784(-/-) mice compared to wildtype mice after LPS instillation. PAI-1 release was partially suppressed by extracellular signal-regulated kinase(ERK) and p38 mitogen-activated protein kinase inhibitor(MAPK) but not by c-Jun N-terminal kinase inhibitors.

Conclusions: In LPS-induced ALI, P3784(-/-) mice increased PAI-1 expressions of partially dependent on enhanced autophagy in lungs and p38 MAPK and ERK in macrophages. Thus, P3784 predicts against fibronolytic activity under inflammation by regulating autophagy.

P3783 Prevention of hyperoxia-induced lung injury: Counterbalancing the deleterious effects of endothelin-1 in rat lungs

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Rationale: Endothelin (ET-1) plays a major role in the hyperoxia-induced pulmonary hypertension leading to lung damage. We determined the role of the ratio of oxygen NO/ET-1 pathway in the lung function decline changes following hyperoxia exposure in rats.

Methods: Airway resistance (Raw);respiratory tissue damping (G) and elastance (H) were obtained by forced oscillations at baseline conditions and following incremental doses of iv methacholine (MCH) in 4 groups of 28-day-old rats. Animals were exposed for 3 days to: room air (Group C, n=6), hyperoxia (> 95% O2, Group HC, n=5); hyperoxia with concomitant administration of vasoactive intestinal peptide (VIP 150 μg/kg/day iv, Group HV, n=4) or oral sildenafil citrate (20 mg/day, Group HS, n=4).

Results: Hyperoxia led to significant increases in G (38.66%, 62.63%, 38.41% in groups HC, HV, HS respectively, p<0.05) and in H (59.91%, 67.3%, 70.85%, p<0.05) in all groups, while Raw did not change. Airway hyperresponsiveness to MCh was observed in rats of Group HC, which was prevented by treatments with VIP or sildenafil.

Conclusions: These findings evidence the beneficial role of NO and VIP pathways in preventing the lung inflammatory response to hyperoxia and indicating their protective potentials against the subsequent development of airway hyperresponsiveness.

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(MTX), EPO group was administered, SC of 5 mg/kg MTX and 2000 IU/kg EPO, and NAC group was given 5 mg/kg MTX and 200 mg/kg NAC once daily for 4 consecutive days. At the fifth day, the right lungs were extracted. Oxidative damage was evaluated by measuring the malondialdehyde (MDA) level and superoxide dismutase (SOD) and catalase (CAT) activities. Histological damage was evaluated by inflammation and congestion scores.

Results: In MTX group MDA levels were significantly higher, CAT and SOD activities were significantly lower than those in the Sham, EPO and NAC groups (P < 0.05). In EPO group MDA levels, CAT, and SOD activities were higher, but not significant higher than in group NAC. In group MTX both scores were significantly higher than in group sham (P < 0.05). The congestion score of group MTX was significantly higher than those in group EPO and NAC (P < 0.05). When the group EPO was compared to the group NAC, the difference was not significant (P > 0.05).

Conclusion: EPO and NAC have significant preventive effects on methotrexate-induced lung damage in rats.

396. Various issues in clinical physiology

P3785 Acute effects of volume-oriented incentive spirometry on chest wall kinematics in patients chronic stroke Ellis Linn, Gardêna Ferreira, Tânia Campos, Rodrigo Melo, Elis Emanuelle, Renato Targino, Figueiredo, Physiotherapy, Physical Therapy, Federal University of Rio Grande do Norte, Natal, RN, Brazil

To study the acute effects of incentive spirometry (IS) volume-oriented on chest wall kinematics in chronic stroke patients and healthy subjects. Volume of chest wall (CW), abdominal (ab), abdominal rib cage (RC) and pulmonary rib cage (RCp) compartment were assessed in 20 chronic stroke patients (experimental group,EG) age 56.9±7.3 years old, FVC%:81.5±10.9% and FEV1/FVC:80.5±9.7 and 20 age-matched healthy subjects (control group,CG), age 56.5±3.0 years old, FVC%:95.6±8.8% (p=0.0026) and FEV1/FVC:80.5±8.4 by bidimensional Plethysmography. Protocol comprise 3 moments: quite breathing (QB), volume-oriented IS (3 series/10 repetitions) and recovery quite breathing (rQB). The tidal volumes of chest wall in EG was lower compared to the CG, in QB (0.05±0.01L), IS (1.8±2.3 L) and rQB (0.4±0.5 L) (< p<0.001). The tidal volume increase in chest wall 75% in EG and 73.3% CG during IS. Different pattern of breathing were found in tidal volume in EG compared to CG on ab compartment: QB(54.1% vs 43.7%), IS(43.3% vs 40.9%) and rQB(48.9% vs 46.2%); RCp compartment, QB(30.7% vs 37.9%), IS(37.7% vs 39.9%) and rQB(32.9% vs 37.3%). Right and left hemithorax volume were different in EG, in QB (2.1±0.6 ml) and rQB (0.4±0.5 ml) independent of stroke side impairment. Increase in chest wall 75% in EG and 73.3% CG during IS. Different pattern of breathings were found in tidal volume in EG compared to CG on ab compartment: QB(54.1% vs 43.7%), IS(43.3% vs 40.9%) and rQB(48.9% vs 46.2%)

Method: Twenty one subjects aged from 18 to 30 years were examined. After being examined at the low altitude (Bishkek, 700 m above sea level) all subject were transported to 3200 m. At the HA patients were repeatedly examined in the 7th, 14th and 21st days of the surgery. Group Bishkek HA-7 HA-14 HA-21 Descent Normoresponders 43,7±1,7 40,4±1,1 41,0±1,6 41,6±1,9 46,5±1,7 Hyperresponders 45,8±2,1 38,6±1,5 42,4±2,5 44,1±2,8 48,4±3,0

Conclusion: At Bishkek the 1st group had the higher max VO2 value, but after the ascent at HA the max VO2 significantly decreased at that group (from 45.8 to 38.8 ml/kg/hr, p < 0.01), while the 2nd group demonstrated the nonsignificant max VO2 reduction. Later these differences disappeared. Obtained data can denote the presence of the interrelation between sPAP response to HA hypoxia and decrease of the physical capacity at HA. This supposition may be tested on a largersample of volunteers.

P3787 Slowly adapting stretch receptors upregulate mixed cough responses in the rabbit Chayra Abdou, Sissi On, Brune Demoulin, Odile Ruckebusch, Anne-Laure Leblanc, Noëlle Bertin, François Marchal, Silvia Varechova, EA 3450 Laboratoire de Physiologie, Faculté de Médecine, Vandoeuvre les Nancy, France

Rationale: Inhibition of slowly adapting stretch receptors (SIRS) inhibits the cough reflex (CR), but it is not clear whether SIRS stimulation facilitates CR and/or expiration reflex (ER). The issue is relevant to the long term understanding of chronic cough because those mechanisms that regulate cough are poorly understood.

The aim of the study was to determine whether SIRS stimulation by continuous positive airway pressure (CPAP) alters CR and/or ER in the rabbit.

Method: 5 rabbits were anesthetized and tracheostomized. The trachea was exposed to punctuate mechanical stimuli at control and with 4.5 cmH2O CPAP. 24 stimulations were aimed in each condition in each animal. CR and ER were identified from airflow and volume signals, diaphragmatic and abdominal muscle electrical activity. The reflexes were defined as a forced expiratory effort preceded (CR) or not (ER) by an augmented inspiration. Mixed responses were differentiated from the pattern of the first breath as ER/CR.

Results: 241 stimulations, evenly distributed in inspiration and expiration, were obtained at control (n = 121) and on CPAP (n = 120). The overall incidence of positive responses significantly increased from 66% at control to 85% on CPAP (p = 0.0005). Incidence of ER, CR or ER/CR was not significantly altered. In control, the mixed ER/CR response significantly increased from 14% at control to 38% on CPAP (p = 0.0005).

Conclusions: SIRS stimulation up regulates airway defensive reflexes, namely ER/CR. Thus SIRS appear to sensitize preferentially those ER-facilitated coughs. It is speculated that a proper identification of airway defensive responses in patients may be relevant to a better understanding of chronic cough.

P3788 The effects of inspiratory muscle fatigue on swallowing physiology in healthy young adults: Preliminary results Joanna Malizia, Carol E. Garber, Georgia Malandraki, John H. Saxman, Biobehavioral Sciences, TC, Columbia University, New York, NY, United States

Introduction: Fatigue of the respiratory muscles has been associated with swallowing disorders in many respiratory and neurological diseases, however, the mechanism with which fatigue affects the swallowing function remains unclear.

Aims: The aim of the present pilot study was to examine the effects of respiratory muscle fatigue on swallowing physiology in healthy adults.

Methods: Participants included 10 healthy young adults randomly assigned in two groups: an expiratory and an inspiratory muscle group. Respiratory and electrophysiological measurements were obtained during the following tasks: three abdominal water swallows, b100nl continuous water swallows and cold swallow test (cracker), at three time points: at baseline, immediately post exercise-induced fatigue, and finally, after a 15-min rest period. A loaded breathing device was used to induce fatigue. Surface electromyography was employed to capture muscle activity of the submental and the infrahyoid muscles during swallowing.

Results: Electromyographical findings showed that, for the submental muscle, the integral was found to be significantly higher during the immediate post-fatigue condition compared to both the baseline and post-rest conditions (p < 0.05) in all tasks for both the inspiratory and expiratory groups.

Conclusion: These preliminary results suggest that fatigue of the expiratory muscles has an effect on selective electrophysiological measures of swallowing. The greater impact of the submental muscles during swallowing compared to the infrahyoids could be a compensatory strategy, given the fatigue of the lower respiratory muscles.

P3789 Orthodeoxia in hypoxaemic morbid obesity reverts one year after bariatric surgery Eva Rivero1, Ebyham Arismendi2, Ana Tejedor1, Yolanda Terriola,1, Concepcion Gustillo,2, Felip Burgos1,2, Salvador Delgado1,2, Jaime Balsa1,1, Robert Rodriguez-Roizm1,2, Anaesthesiology, Hospital Clinic, Barcelona, Spain;2 Respiratory Diagnostic Center, Hospital Clinic, Barcelona, Spain;1Gastrointestinal Surgery, Hospital Clinic, Barcelona, Spain

Introduction: In morbid obesity (MO), pulmonary gas exchange (GE) abnormalities are influenced by postural changes that are known to improve after bariatric surgery (BS).

Objective: To unravel the determinants of GE in MO at upright (U) and supine...
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Time-dependence of lung recovery after a 4-week exposure to traffic and sugar cane burning air pollutants
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Exposure to particulate matter from urban air pollution (UP) or biomass burning (BP) has been associated with lung impairment. We investigated the time-dependency of lung functional recovery in BALB/c mice exposed to UP or BP particles. During 4 weeks they received 3 nose-only instillations of 15 μL of distilled water (C) or UP or BP (15 μg/μL of saline). Mice were weighed weekly. 1 (C1, UP1, BP1), 2 (C2, UP2, BP2), 7 (C7, UP7, BP7) or 14 (C14, UP14, BP14) days after the last instillation, pulmonary mechanics, FRC and histology were measured; catalase and superoxide dismutase activities were evaluated in lung homogenates. Body mass gain was similar among the groups. Pulmonary elastance and its viscoelastic component (cmH2O/mL), resistive and viscoelastic pressures (cmH2O) were higher in UP1 (31 ± 1.6, 14 ± 0.8, 1.5 ± 0.1), respectively) and BP1 (30 ± 0.4, 16 ± 0.8, 1.4 ± 0.1) than in C1 (23 ± 4.3 ± 0.1, 0.6 ± 0.4, 0.8 ± 0.1, respectively). These parameters returned to control values at day 2, except for resistive pressure that normalized at 7 days. Alveolar colage (S) was larger in UP1 (21 ± 8.5) and BP1 (23.2 ± 1.9) than in C1 (17 ± 3.0) and returned to baseline at 7 days, while bronchocostriction index and alveolar and bronchial lesion scores increased in UP1 (2.3 ± 0.3, 3 ± 0.3) and 3.2 ± 0.4, respectively) and BP1 (2.3 ± 0.3, 2.8 ± 0.3 and 2.3 ± 0.4, respectively) in relation to C1 (1.5 ± 0.2, 1.0 ± 0.3 and 0.8 ± 0.4, respectively) and normalized in 2 days. No differences were found in FRC and oxidative stress. Thus, a 4-week exposure to UP and BP induced lung impairment that resolved 7 days after the last exposure. Supported by FAPERJ, CNPq, MCT.

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Exposure to hypercapnia and muscle function
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Hypercapnia has been proposed as one of the systemic factors participating in muscle dysfunction occurring in COPOD. Aim: To assess the effects of acute and chronic exposure to hypercapnia on peripheral and respiratory muscle function.

Methods: Two subgroups of 8 Wistar rats each were submitted to either a hypercapnic gas mixture (FICO2 0.5) or room air, 2 h for 15 days. Maximal inspiratory pressure (MIP), lower limb dymanometry (LDD), breathing pattern, work of breathing, Po1 and arterial blood gases were determined at the beginning and at the end of each exposure.

Results: Acute exposure to hypercapnia (1st single bout) did not involve changes in muscle function. However, chronic exposure to hypercapnic bouts resulted in a lower weight gain, and a decrease in both MIP (% ref) and LDD (% ref) in hypercapnic animals when compared with control (C) group. Interestingly, acute exposure to hypercapnia in the last (15th) day also involved a decrease in both MIP and LLD. Acute hypercapnia resulted in increases in respiratory rate (RR) but minute ventilation (VE) and P0.1 remained constant. Chronic exposure to hypercapnic bouts did not change breathing pattern nor ventilatory drive.

Conclusions: Although a single acute exposure to hypercapnia did not induce changes in muscle function, repeated exposures resulted in both a loss in muscle strength and an increase in susceptibility to a further impairment with new hypercapnic bouts. The similar behavior of respiratory and limb muscle strength, both normalized by rat anthropometry, indicates that the loss of force is the result of hypercapnicia and not a consequence of either the increase in ventilatory work or the decrease in weight gain. Supported by ERS short fellowship, SEPAR and J.Grau Grants.

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Disturbance of airway patency is accompanied by a decrease of exhaled breath temperature in asthmatics
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Introduction: Allergy in asthmatics is accompanied with the increase of exhaled breath temperature. The correlation of this parameter with airway patency is known to be about.

Aim: To study the correlation between bronchi patency and exhaled breath temperature in patients with bronchial asthma.

Methods: The exhaled breath temperature (T*°C) during quiet breathing using a device “X-halo” (Delmedica Investments Pte Ltd), lung function (FEV1, FVE1,FVC) and the level of hydrogen peroxide (H2O2) in exhaled breath condensate (EBC) were studied in 82 patients with bronchial asthma (the mean age 35.0±1.1 years).

Results: The patients were divided into two groups according to the presence of airway patency impairment or its absence (FEV1, 80.8±2.69 and 108.3±2.09%; p<0.001, FEV1/FVC 68.3±1.37 and 77.8±1.23%; p<0.001, respectively). In the group of patients with airway patency impairment there were a significant decrease of exhaled breath temperature (34.0±0.14°C) and the increase of H2O2 level (1.18±0.08mmole/ml) in EBC in comparison with the group of patients with out lung function changes (34.5±0.14°C; p<0.05; 0.89±0.08 mmole/ml; p<0.05, respectively). There was found the correlation between the exhaled breath temperature and FEV1 (r=0.02; p<0.05) and the bronchodilation response to β2-agonist SABR FEV1 (r=0.41; p<0.01), as well as between the level of H2O2 in EBC and FEV1 (r=0.64; p<0.01).

Conclusion: The decrease of exhaled breath temperature in asthmatics is associated with the disturbance of bronchi patency and reversibility of bronchial obstruction.

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Central alterations during prolonged exercise in normoxia and hypoxia
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Introduction: Prolonged cycling exercise in normoxia (N) induces fatigue due to both peripheral and central alterations. Interestingly, it has been reported that cerebral perturbations are greater during short-duration isolated exercise in hypoxia (H) compared to N. The purpose of this study was to test the hypothesis that central alterations are accentuated in H compared to N during prolonged whole-body exercise.

Methods: Ten subjects performed two sessions consisting of 3 80-min cycling bouts at 45% of their relative maximal aerobic power in N and H (FIO2 < 12%). Before exercise and after each bout, transcranial magnetic stimulation was used to assess cortico spinal excitability (motor evoked potential; MEP) and intracortical inhibition (cortical silent period; CSP) of knee extensors. Femoral nerve electrical stimulation was used to measure muscle characteristics. Voluntary activation was added for all but two of the three conditions.

Results: A significant but similar torque reduction was observed at the end of the exercise in N and H. With the exception of CSP, a significant time effect was observed for all parameters. CSP was longer and the reduction of twitch peak torque was lower in H than in N. No other significant differences were observed between N and H.

Discussion: Fatigue level was found to be similar between N and H when exercise is performed at the same relative intensity. Even if the brain is importantly affected by hypoxia2 as shown by the greater intracortical inhibition, this does not appear to further affect central motor drive.

References:

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Regional lung ventilation distribution among individuals with chronic heart failure after an inspiratory muscle training program: A randomized controlled trial

Objectives: To evaluate regional lung ventilation distribution in patients suffering (S) while breathing ambient air, in random order, before and one year after BS.

Methods: 15 (14 females; 51±SE72 yrs; BMI, 47±2 kg/m2) hypoxemic -H (PaO2, 73±5 mmHg) and normoxic N- (PaO2, 80±4 mmHg), matched for age, sex and BMI were studied before and after BS. GE measurements, including ventilation-perfusion (V/AQ) distributions were performed.

Results: Before BS, H patients at U exhibited moderate V/AQ imbalance (low V/AQ of distal areas compared to S). In addition, PaO2 at U was improved by (±9.15±0.2 mmHg), (p<0.03, each). Moreover, H patients at U improved PaO2 by (±6.7±0.6 mmHg) compared to S and V/AQ imbalance postural differences between Pre and Post BS also improved (p<0.02).

Conclusions: Hypoxemic morbid obesity is associated with orthoadoxia. This novel finding may be related to a gravitational heterogeneous redistribution of pulmonary blood flow and a chronic systemic inflammatory. Sarcopenia ingenion reverts completely this phenomenon.

Supported by FIS (PI00831108), Esteve and CIBERES.

References:
P3795 Does SpO2 correlate with SaO2 in stable COPD patients? 
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Background: Pulse oximetry is commonly used to measure oxygen saturations (SpO2) in assessment of patients with stable COPD. This is considered to be equivalent to oxygen saturations measured on a blood gas analyser (SaO2). The ATS, ERS and GOLD guidelines for COPD define suitability for long term oxygen therapy with PaO2 less than 7.3kPa or SaO2 of less than 88%.

Aim: To establish if SpO2 correlates to SaO2 in stable COPD patients.

Methods: Retrospective study of patients with stable COPD attending oxygen clinics in an acute teaching hospital.

Results: N=73, Male 29%, Mean Age70 (range 53 - 93), Mean FEV1 0.89 L, current smokers 29%, 26% on oxygen, mean MRC grade 4, mean BORG score at rest 2 and mean h��cotat (HCT) 0.41. On’t paired testing in all patients, no statistically significant difference was noted between SpO2 and SaO2 (p value: 0.972), the mean SpO2-SaO2 is -0.012% (95% CI of -0.71 to 0.69).

However, in current smokers subgroup (N=21) high variation between these values was noted, with the mean SpO2-SaO2 1.067%. There was a tendency for SpO2 to be lower than SaO2 (95% CI of -1.03 to 3.17).

Conclusions: As the difference between SpO2 and SaO2 is high in current smokers, SpO2 reading using pulse oximetry might not be reliable. Further studies with larger sample size are needed to evaluate this further.

P3796 Breathing patterns in mountaineers climbing to extreme altitude (7546m)
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Background: We investigated breathing patterns and oxygenation in mountaineers climbing to extreme altitude (7546m) and correlate it with functional capacity and quality of life. The present study also analyzed the changes in arterial and predicted MIP, higher MLFHzq score and greater distance walked in the 6MWT, as well as a reduction in the BORG scale after the 6 MWT in relation to the control. For the OEP, IMT group members exhibited higher values for total chest wall volume (Vcw), abdominal rib cage volume (Vrc,a) and abdominal volume (Vab) when compared to the control.

Conclusions: For patients with COPD, IMT proved efficient in improving muscle strength, functional capacity and quality of life. The present study also analyzed the changes in arterial and predicted MIP, higher MLFHzq score and greater distance walked in the 6MWT, as well as a reduction in the BORG scale after the 6 MWT in relation to the control. For the OEP, IMT group members exhibited higher values for total chest wall volume (Vcw), abdominal rib cage volume (Vrc,a) and abdominal volume (Vab) when compared to the control.

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thus causing the water level in the smaller section to alternately rise and fall, simulating diaphragmatic movement. FRC, tidal volume (Vt) and respiratory rate (RR) were adjusted by altering the volume of water within the phantom lung and the ventilator settings. We performed MBW on the phantoms lung at a variety of values of FRC, Vt and RR. Each experiment was performed in triplicate. Measured FRC was then compared to the true FRC in each case.

**Results:** Measured FRC was within 5% of true FRC in all but one experiment. The intraoperator correlation coefficient for the triplicate measurements was 0.999, suggesting that the MBW technique is highly repeatable.

**Conclusion:** We conclude that MBW performed using an Innocor gas analyser is highly repeatable and accurate. Simple one-compartment lung phantoms appear to be a promising method for the validation of MBW systems.

**Methods:** This cross-sectional study was conducted in 2011 at the University Hospital of Basel, Switzerland. Patients with COPD stages I to IV were investigated. Functional exercise capacity was measured by the six-minute walk test according to the guidelines of the American Thoracic Society. Spirometry was performed according to current guidelines. Health status was assessed by the CAT. A forced entry multiple regression analysis was calculated. The regression included 6MWD, forced expiratory volume in one second in % of predicted (FEV1%,predicted) and Body-Mass-Index (BMI). The dependent variable was the CAT-score.

**Results:** Complete data were available for 73 individuals (age 67 ± 9.8 years, 58.9% males). FEV1%predicted 69.7 ± 22.7%, 6MWD 434.7 ± 99.1 m, CAT-score 12.5 ± 6.8, BMI 25.7 ± 5.5. Age and 6MWD significantly contributed to the model (β = -0.49 respectively p = 0.46, p < 0.01). BMI and FEV1%predicted did not significantly influence the CAT-score (β = 0.14 respectively p = 0.8).

**Conclusion:** The association of the 6MWD and the CAT-score indicates that higher physical fitness level is related to improved health status and thus decreased impact of COPD on an individual's life.

**P3801**

**Respiratory disability and reproducibility of arterial stiffness by pulse wave velocity (PWV) in stable COPD patients**

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**Background:** Pulse wave velocity, a validated method for assessment of arterial stiffness, is widely used in studies evaluating cardiovascular risk and/or efficacy of new bronchodilators for improving arterial stiffness in COPD patients. However, PWV reproducibility studies are lacking in this population.

**Methods:** 38 stable COPD patients (79% men, 63 ± 10 years, FEV1 = 53 ± 17% of predicted values) were included. Using the Complior™ device, the carotido-femoral PWV was measured at baseline (d0), after 2 weeks (d15) and 6 weeks (d42). Pearson coefficient and Spearman coefficients and Kendall's Coefficient of Correlation (ICC) allowed comparing PWV at d0 vs. d15 (short-term reproducibility) and d42 (middle-term reproducibility). The relationship between PWV and inflammatory status (CRP, TNF and ILE) were also investigated.

**Results:** Mean PWV values were 11.10 ± 9.11, 11.05 ± 12.17 and 11.24 ± 2.52 m/s at d0, d15 and d42, respectively. For short-term reproducibility (d0 vs. d15), Spearman coefficient was r = 0.78, p = 0.001 and ICC = 0.790 (range 0.632-0.885). For middle-term reproducibility (d0 vs. d42), Pearson coefficient of correlation was r = 0.76, p = 0.001 and ICC = 0.749 (range 0.567 - 0.861). There was no significant link between PWV and inflammatory markers neither for baseline values nor for between-sessions differences, suggesting that minor changes in inflammatory status did not influence the reproducibility of PWV.

**Conclusion:** Using the Complior™ method, PWV measurements had good reproducibility in stable COPD patients. Such assessment of arterial stiffness can be properly used as objective outcome for randomized trials.

**P3802**

Early oxygen desaturation is related to acute mountain sickness (AMS) development during acute high altitude (HA) exposure

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Early oxygen desaturation during HA exposure (both in the field and during HA simulated test) has been reported to be significantly related to AMS development. Aim: Monitor oxygen saturation (SpO2) and AMS during the ascent from Alagna (1200m) to Capanna Regina Margherita (4559m) with an overnight stay in Gnifetti Hut (3647m).

**Methods:** 66 subjects (55M, 18-67 yrs), intending to climb M. Rosa, were recruited at the cable care station in Alagna, equipped with a 24-h data memory pulse oximeter (Pulsion-35s, Minolta) and asked to fill the Lake Louise questionnaire for AMS diagnosis. 25 subjects (37.8%) showed a LL score ≥ 3 (AMS+ group), 41 were in AMS-group.

**Results:** SpO2% in AMS+ and AMS- was similar in Alagna (94.6 ± 1.9 vs 95.1 ± 2.2) but was lower in AMS+ during HA exposure: at 3257m, after 30-40 min. of cable ascents 95.5 ± 1.3 vs 97.7 ± 3.5, *p* < 0.001, and in Gnifetti Hut at rest (94.6 ± 1.2 vs 98.6 ± 2.4, *p* < 0.001) and during the night (76.9 ± 4.6 vs 79.3 ± 5.7, *p* < 0.001). AMS+ spent more time with lower SpO2%: time (%) at rest in Gnifetti Hut with SpO2% < 80 (15.8 ± 13.8 vs 7.2 ± 7.7, **), and during the night with SpO2 80-95%, and < 70 (33.2 ± 32.9 vs 15 ± 18.5, **; 11.8 ± 19.3 vs 2.7 ± 6.2, *. *). Only 34 subjects (26m) climbed to Capanna Regina Margherita (14AMS+); AMS+ maintained SpO2% < (73.4 ± 5.1 vs 76.8 ± 8.3, *. * and > time (hours) spent with SpO2% < 80 and > 75 (3.5 ± 1.2 vs 2.7 ± 0.9, *; 2.5 ± 1.4 vs 1 ± 0.8, *; ) *p < 0.05, ** *p < 0.01.

**Conclusions:** Lower SpO2% in AMS+ occurs very early at the beginning of HA exposure after 30-40 min. of ascent. Subjects which subsequently develop AMS always spend more time with SpO2% significantly lower than healthy subjects (AMS-).
The estimation of respiratory muscles (RM) status by echodensitometry in men with chronic obstructive pulmonary disease (COPD)

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Aim: Investigate the RM status.

Material and methods: We obtained the indices: homogeneity (H), structural density (SD), echogenicity (E) and dispersion (D) of the internal oblique abdominal muscle (intOAM) by ultrasonic scanner. We carried out histological research of intOAM. Research was made in 20 COPD pts: 1st group (10 – 1st stage); 2nd group (10 – 2nd stage). Control - 12 healthy subjects.

Results: There have been areas of myolysis, cell proliferation of periurium, “megroth” of fatty tissue between myobrills (MF). There is interstitial sclerosis, sections “contractions” of MF. Among the relatively preserved MF was found deep dystrophic one with protein granules of different sizes in the appearance of the sarcoplasm. The H in pts of the 1st and 2nd groups was 20.8 and 19.3 respectively (p < 0.05). The E also was different in pts of the 1st and 2nd groups (3.7 and 4.8). The D was increased in the 2nd group 18.6 vs. the 1st group 17.5. The SD had the tendency to decrease. Increasing of COPD severity was associated with significant enhancing of “contractions” (p=0.72), destruction of MF (p=0.69) and proliferation of fibroblasts (r=0.52). We detected the presence of negative correlations between H, SD and sclerosis (r=0.39 and r=0.51 respectively). Meanwhile the E was higher in these pts and correlated directly (r=0.48; p<0.05). The D was increased in the presence of fragmentation of MF (p=0.52). The E correlated in the 2nd group with fat mass (r=0.62). This may indicate the accumulation of intramuscular fat in the second stage.

Conclusion: The proposed echodensitometric parameters reflect the degenerative processes occurring in the RM.

397. Metabolic and cardiovascular consequences of OSA I

P3804
Positive effect of CPAP therapy in OSA patients on A-FABP, CRP and triacylglycerol levels and diastolic blood pressure

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Aim: The influence of CPAP therapy on A-FABP, CRP and triacylglycerol (TAG) levels and diastolic blood pressure (DBP)

Subjects and methods: Eighty-one patients (70 males, a mean age of 53.9 ± 24.8 years) diagnosed with OSA and indicated for CPAP treatment. Anthropometric, DBP and blood serum levels of A-FABP, CRP and TAG were measured before and after 3 months of CPAP treatment

Results: There were significant differences in A-FABP, CRP, TAG levels and DBP between the 1st and 2nd groups. A-FABP levels reached a mean value of 39.7 ± 27.7 (p<0.001) in the 1st group and 21.7 ± 14.2 ng/mL (p<0.001) in the 2nd group. CRP levels were 5.3 ± 9.2 (p<0.05) in the 1st group and 2.1 ± 1.3 ng/mL (p<0.05) in the 2nd group. TAG levels were 1.7 ± 0.8 (p<0.001) in the 1st group and 1.5 ± 0.7 mmol/L (p<0.001) in the 2nd group. DBP was 77.3 ± 5.3 mmHg (p<0.001) in the 1st group and 70.7 ± 4.3 mmHg (p<0.001) in the 2nd group.

Conclusion: A-FABP, CRP and TAG levels significantly decreased after CPAP therapy. DBP decreased significantly after CPAP therapy.

P3805
Evaluation of renal function in a cohort of patients affected by obstructive sleep apnea

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Introduction: Obstructive sleep apnea (OSA) has been linked to chronic kidney disease (CKD). We investigated the renal function (GFR) of a cohort of non-CKD patients admitted to our Sleep Medicine Unit for suspected OSA.

Materials and methods: 374 subjects underwent a cardiorespiratory polysomnography (PSG) and a blood collection for GFR. Oronasal airflow, respiratory efforts and oxyhaemoglobin saturation were recorded. PSG was scored according to AASM rules. GFR was calculated trough the MDRD equation. Descriptive statistics, analysis of variance (ANOVA), linear regressions were performed. A p value < 0.05 was considered significant.

Results: Patients were 53 ± 12 years old, with a mean BMI > 30. Estimated GFR was 95.1 ± 19 mL/min/1.73 m². The population was suffering from severe OSA (AHI=45.8 ± 19.7; min spO2=72 ± 10.9%; T90 <90% 24 ± 26.6%). No differences were seen in baseline GFR according to AHI and ODI. A significant difference in GFR according to T90% (p=0.005) and min spO2 (p=0.017) was observed. These results were attributable to higher levels of GFR in more hypoxemics. GFR showed no correlation with AHI, ODI or T90%, but it was related to min spO2. These results were confirmed in univariate linear regressions, but not in multivariate regression analyses. However, when mild to moderate OSA cases were excluded, spO2 turned out to be the first independent predictor of GFR.

Conclusion: In severe OSA cases, GFR seems to be inversely related to the severity of oxygen desaturation, but not to the common OSA’s indexes. These findings may be due to nephropulmonary compensatory mechanisms against chronic hypoxia that need to be studied in a longitudinal way.

P3806
Treatment of central sleep apnea in patients with heart failure: A retrospective observational study

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Introduction: In patients with heart failure (HF) and central sleep apnea syndrome (CSAS) different therapeutic options, such as continuous positive airway pressure (CPAP), bi-level PAP (BiPAP) and adaptive servoventilation (ASV) are available. All are potentially effective in improving heart function and in reducing apnoe-hypopnea index (AHI), while ASV is generally considered to be most effective.

Aim: To assess how HF-patients with CSAS (AHI > 15) respond to the different treatments in terms of AHI.

Methods: CPAP was given first, and when ineffective or when patients still experienced SAS related complaints, followed by BiPAP and/or ASV. Efficacy was assessed by a sleep study under treatment. Treatment was considered effective when AHI reduced <15% or reduced at least 50% from the baseline AHI to a value <20/hour.

Results: 14 males (70 y) were assessed.

Figure 1. Overview of the efficacy of the treatments.

Conclusions: Although ASV seems to prove to be most effective in HF-patients with CSAS, CPAP and BiPAP together are still effective in 57% of the patients.
Obstructive sleep apnea in patients with typical atrial flutter: Clinical, prognostic and therapeutic implications

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Background: The clinical yield of successful cavo-tricuspid isthmus (CTI) radiofrequency ablation for the treatment of atrial flutter (AF) is limited by a high incidence of atrial fibrillation (AFib) in the long term. The association of obstructive sleep apnea (OSA) could favor an incomplete arrhythmia control in this setting. We assessed the impact of continuous positive airway pressure (CPAP) therapy in reducing the occurrence of AFib after CTI ablation.

Methods: A cohort of consecutive patients undergoing successful CTI ablation for typical AF was screened for OSA and followed-up during 12 months. Upon diagnosis of severe OSA, CPAP therapy was initiated. Relationship of the following variables with the occurrence of AFib during follow-up was investigated: CPAP therapy initiation, hypertension, body mass index, underlying structural heart disease, left atrial diameter and previous AFib documentation prior to CTI ablation.

Results: We included 56 patients (age 66±11 years, 12 female), 27 of whom (48%) were diagnosed from severe OSA. Twenty-one patients (38%) had AFib during follow-up. Freedom from AFib prior to ablation was associated with a lower incidence of AFib after this procedure (from 67% to 34% of cases; p=0.019). Additionally, CPAP therapy initiation in those patients never being diagnosed from AFib resulted in a reduction of AFib episodes during follow-up (from 46% to 6% of cases; p=0.025).

Conclusions: Severe OSA is a prevalent condition in patients with typical AF, and its treatment by means of CPAP therapy results in a lower incidence of new-onset AFib after CTI ablation.

Obstructive sleep apnea syndrome (OSAS) is a frequent disease associated with increased risk of cardiovascular disorders. The aim of this study was the evaluation of changes in osteoprotegerin serum levels and in body composition parameters in patients with sleep apnea syndrome.

We examined 47 patients with OSAS (mean age 55.42±7.91, mean AHI 32.76±19.98) and 29 persons from control group (mean age 49.48±13.68). All subjects underwent bioelectrical impedance analysis with a single-frequency bioimpedance analyzer (Model BIA 101 Akem) and polysomnography Grass Aura Lite. The osteoprotegerin serum level was measured using a ELISA kit: Human Osteoprotegerin (R&D Systems).

We didn’t show either differences in osteoprotegerin serum levels between OSAS patients and control group (4,496 vs 4,631 pmol/l, p=0.680) nor correlations between osteoprotegerin and AHI (p=0.484, R=0.08). Moreover we didn’t find changes in osteoprotegerin levels in OSAS patients with diabetes (p=0.251, with hypertension (0.911) or ischemic heart disease (0.876).

We observed higher BMI in OSAS patients (p=0.009), but from all body composition parameters we revealed only lower phase angle in OSAS patients (5.65, vs 5.87, p=0.047). We evaluated the relationships between osteoprotegerin and body composition parameters and we found only tendency, that osteoprotegerin level correlated negative with muscle mass percentage (MMF) (p=0.069, R=0.299) and positive with fat mass percentage (FM). CRP was significant higher in OSAS than in control group (6.59 vs 3.85, p=0.006) R=0.198, p=0.08), but we didn’t find correlations between osteoprotegerin and CRP (p=0.929, R=0.010).

Our study didn’t show changes in osteoprotegerin in OSAS patients.
defined using a full polysomnography study. The glucose metabolism was investi-
gated by oral glucose tolerant test. Blood glucose and IRI were determined on the 0, 60th, 120th, 180th min. 18 patients were with newly diagnosed IGT. 12 patients had NBG. Resistin (RayBio) and FFAs (Wako) were determined in both groups. IRI was 25.29 μIU/ml in IGT patients. In patients with NBG, IRI was 21.3 mlU/l. BMI did not differ significantly between patients with IGT and NBG. BMI was 40.42 ± 11.5 and 41.21 ± 10.9 in those with NBG. AHI (60.8%) was higher in patients with NBG compared to those with IGT – 50.6. Patients with NBG had also higher plasma levels of FFAs – 0.360/mmol/l compared to patients with IGT – 0.210/mmol/l. Only resistin was higher - AHI ≥ 30. IGT patients compared to NBG – 3.98 ng/ml. IRI in IGT patients was 25.29 μIU/ml and correlated best to the levels of resistin (p<0.05).

The commonly used clinical parameters – BMI, AHI, FFAs were higher in patients with OSA and NBG. They are not reliable clinical markers for the early detection of impaired blood glucose metabolism in OSA patients. Only resistin correlated to the levels of IRI and could be applied as a predictor and early detection marker of impaired blood glucose metabolism in OSA patients.

P3812

The need of higher CPAP pressure in a population with obstructive sleep apnea (OSA) and refractory hypertension (RHT) versus controlled hypertension-a retrospective study

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Rationale: RHT is common in obese patients, refractoriness among them is frequently caused by OSA. A previous study held in our clinic showed that patients with RHT had higher CPAP failure rate.

Methods: After exclusion criteria (central/mixed SAS, obesity-hyperventilation/orlap syndrome, obstructive/restrictive respiratory dysfunction, CPAP failure) applied to 214 SAS patients with HT, we studied 34 patients with controlled HT and RHT/demographics, anthropometrics, symptoms, comorbidities, sleep study’s: Chi test,TTest, Pearson. The 2 groups were similar in terms of smoking habit and antihypertensive treatment.

Results: Controlled HT-27 patients (79.4%); 14 men (77.8%), 8 women (20.6%); RHT-7 patients (20.6%); 4 men (57.1%), 3 women (42.9%). RHT patients were younger: 49.6 ± 8.8 vs 58.4 ± 12.1 years, p<0.04, morbid obesity: 45.5% vs 7.4% (p<0.01), higher Epworth score: (12.6 ± 5.1 vs 6.4 ± 2.4, p<0.005) and more comorbidities (ischemic heart disease: 33.3% vs 7.6%, p<0.02, dyslipidemia: 83.3% vs 28.6% (p<0.02). Also RHT patients needed higher pressure to correct respiratory events (1.7 ± 1.2 vs 9.8 ± 1.7 cm H2O), even if they had mild OSA in a higher range(57.1% vs 22.2%, p<0.05). There was no linear dependence between BMI and CPAP pressure variables, after CPAP/AHI, minimum Sao2 and BP values (Pearson, p<0.5).

Conclusions: After CPAP failure exclusion, patients with OSA and RHT still need higher CPAP pressure. Rich does not correlate with obesity. RHT patients will cost more the health system due to their cardiovascular comorbidities, young age and sleepiness. Further studies have to elucidate the need of higher CPAP pressures in RHT patients.

P3813

Left ventricular function assessment in patients with obstructive sleep apnea syndrome

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Background: There are conflicting data on the effect of obstructive sleep apnea syndrome (OSAS) on the cardiac structure and function in human subjects.

Aims: To assess the left ventricular functions in patients with OSAS.

Patients and methods: Forty patients with OSAS, diagnosed by full polysomnography, underwent ECG and echocardiography using conventional mode and doppler tissue imaging to assess the function of the left ventricle.

Results: 11 patients had mild OSAS, 11 patients had moderate OSAS and 18 patients had severe OSAS. The three groups were matched in age, gender, BMI and incidence of hypertension. Severe OSAS had significantly higher AHI, lowest oxygen saturation, average oxygen saturation, and desaturation time % of total sleep time (<90%). Pulmonary hypertension and left ventricular diastolic dysfunction were significantly higher in moderate and severe OSAS groups. No difference between groups was found in LV systolic function. Diastolic dysfunction parameters were better correlated with AHI and lowest oxygen saturation during sleep.

Conclusion: Assessment of left ventricular function is mandatory in OSAS patients even if they have no cardiac symptoms. Severer obstructive sleep apnea syndrome may result in left ventricular diastolic dysfunction. Doppler tissue imaging is a better echocardiographic tool for assessment of left ventricular diastolic dysfunction. Severity of left ventricular diastolic dysfunction is correlated with AHI and lowest O2 saturation during sleep.

P3814

Serum aminotransferase levels in patients with severe obstructive sleep apnea

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Background: Obstructive sleep apnea (OSA) is one of the most common sleep disorders with a plethora of complications. Currently the impact of hypoxia due to OSA on liver function is targeted growing attention. This study evaluated the association between serum aminotransferase levels as accepted predictive factor for liver injury and factors connected with OSA severity (apnea hypopnea index (AHI), lowest oxygen saturation level, oxygen desaturation index (DI), percent of time below 90% saturation (T<90%)).

Materials and methods: 66 patients with BMI ≥ 30, who their OSA was confirmed by PSG, were divided equally into two groups based on AHI. 33 patients in control group with 5 ≤ AHI < 15, and 33 patients in case group with AHI ≥ 30 event/hours were enrolled. We compared serum level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with OSA severity factors in each group.

Result: Mean DI was (56.5 ± 26.9) (14.0 ± 10.4) in case and control group respectively (P-value <0.001). T<90% was (33.1%) and (14.2%) in case and control group respectively (P-value <0.001). A significant different in mean DI level and T<90% were observed in case and control group, respectively mean levels of AST (21.3 ± 8.6), (21.5 ± 9.39) and ALT (24.2 ± 14.07), (19.8 ± 9.74) were not significantly different (P-value =0.935) (P-value = 0.142). Pearson correlation showed there is a weak relation between mean DI<90%, AST (0.069) and ALT (P=0.837).

Conclusions: This study showed there is no significant correlation between serum aminotransferase levels and OSA severity.
Methods: We compared age and body mass index (BMI) matched non-to-moderate and severe OSA in the 239 male subjects hospitalized for examination of OSA. We analyzed the relationships between fat areas by computed tomography, comorbidity, polysomnographic data, arterial and venous blood data. Results: Of the 239, 52, 67 and 94 had mild, moderate and severe OSA. We compared all the 94 severe OSA with 85 of the 143 non-to-moderate OSA matched with age and BMI. While waist circumference was the same, severe OSA had a significantly larger VFA. Between the 2 groups, arterial oxygen partial pressure (PaO2), HbA1c and fibrinogen differed significantly. Multivariate modeling of these determinants revealed that both VFA and AHI independently determined PaO2 (contribution rate ($R^2$)=6.5% and 6.7%) and fibrinogen ($R^2$=7.5% and 4.4%), while HbA1c associated independently with AHI ($R^2$=3.7%), not VFA. Conclusions: Severe OSA had a significantly larger VFA, lower PaO2, higher HbA1c and fibrinogen than non-to-moderate OSA. Larger VFA in severe OSA suspect that VFA increase would be a key factor related to body composition in OSA becoming severe. PaO2, HbA1c and fibrinogen were independently predicted by VFA and AHI. Thus, control of OSA would decrease VFA, and in turn, a decrease in VFA and OSA might improve HbA1c and fibrinogen.

P3817
The inflammation and insulin resistance in obstructive sleep apnea
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Objectives: The association between obstructive sleep apnea (OSA) and insulin resistance (IR) remains controversial. Sleep apnea and obesity may increase IR and inflammation by different mechanisms. This study investigated the relationship between sleep apnea and obesity with IR, and pro-inflammatory state.

Methods: A total of 133 consecutive subjects who were referred for polysomnography. 112 were documented to have OSA defined as apnea-hypopnea index (AHI) >5 and 21 control subjects with normal sleep. Inclusion criteria: male, at least 18 years old and able to cooperate. Exclusion criteria: other sleep disorders, OSA with or without comorbidities, other chronic diseases, pregnancy, and BMI >30 kg/m2. Controls were selected based on their BMI. AHI was calculated by the Actigraphy AH16 device. IR was measured using the homeostasis model assessment IR (HOMA-IR).

Results: IR was higher in the obese patient with OSA than in the non-obese patients with OSA as independent of each other in all subjects according to multivariable linear regression analysis. AHI and BMI were the determinants of IR in the moderate and severe OSA groups. BMI divided into the following two groups based on the body mass index (BMI) as BMI $\leq 30$ and BMI $>30$.

Conclusion: In the non-obese group, BMI was the only determinant of IR. However, AHI and BMI were the determinants of IR in the obese patients with OSA. However, AHI and BMI were the determinants of IR in the non-obese group. The inflammation and insulin resistance in OSA are independent of each other in all subjects according to multivariable linear regression analyses. AHI and BMI were significantly higher in the obese patients with sleep apnea than in the control group. However, AHI and BMI were also the determinants of IR in the non-obese group.

P3818
Glucose metabolism abnormalities in obstructive sleep apnoea (OSA) patients
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Objectives: Obstructive sleep apnea is associated with disturbances in glucose metabolism and increased risk of type 2 diabetes. The aim of this study was to assess relations between OSA and diabetes. We studied 1164 OSA pts (876 males and 298 females), mean age $\pm$ 56.4 $\pm$ 10.4 years, AHI $\leq 5$ were selected upon polysomnography. Control group has been accepted as A Group. In addition, patients with OSA were divided into the following two groups based on the body mass index (BMI) as non-obese (B group) (BMI $<30$) and obese (G group) (BMI $\geq 30$).

Methods: All of inflammatory cytokines (CRP, hs CRP, TNF-α) were significantly higher in the obese patients with sleep apnea than in the control group. All of inflammatory cytokines showed significant associations with BMI while did not AHI, AI, ESS.

Results: Of the 239, 52, 67 and 94 had mild, moderate and severe OSA. We compared the 239 male subjects hospitalized for examination of OSA. We analyzed the relationships between fat areas by computed tomography, comorbidity, polysomnographic data, arterial and venous blood data. Results: Of the 239, 52, 67 and 94 had mild, moderate and severe OSA. We compared all the 94 severe OSA with 85 of the 143 non-to-moderate OSA matched with age and BMI. While waist circumference was the same, severe OSA had a significantly larger VFA. Between the 2 groups, arterial oxygen partial pressure (PaO2), HbA1c and fibrinogen differed significantly. Multivariate modeling of these determinants revealed that both VFA and AHI independently determined PaO2 (contribution rate ($R^2$) = 6.5% and 6.7%) and fibrinogen ($R^2$ = 7.5% and 4.4%), while HbA1c associated independently with AHI ($R^2$ = 3.7%), not VFA. Conclusions: Severe OSA had a significantly larger VFA, lower PaO2, higher HbA1c and fibrinogen than non-to-moderate OSA. Larger VFA in severe OSA suspect that VFA increase would be a key factor related to body composition in OSA becoming severe. PaO2, HbA1c and fibrinogen were independently predicted by VFA and AHI. Thus, control of OSA would decrease VFA, and in turn, a decrease in VFA and OSA might improve HbA1c and fibrinogen.

P3819
Correlations between cardiovascular diseases and diabetes in obstructive sleep apnoea (OSA)
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Objectives: Obstructive sleep apnea is associated with disturbances in glucose metabolism and increased risk of type 2 diabetes. The aim of this study was to assess relations between OSA and diabetes. We studied 1164 OSA pts (876 males and 298 females), mean age $\pm$ 56.4 $\pm$ 10.4 years, AHI $\leq 5$ were selected upon polysomnography. Control group has been accepted as A Group. In addition, patients with OSA were divided into the following two groups based on the body mass index (BMI) as non-obese (B group) (BMI $<30$) and obese (G group) (BMI $\geq 30$).

Methods: All of inflammatory cytokines (CRP, hs CRP, TNF-α) were significantly higher in the obese patients with sleep apnea than in the control group. All of inflammatory cytokines showed significant associations with BMI while did not AHI, AI, ESS.

Results: Of the 239, 52, 67 and 94 had mild, moderate and severe OSA. We compared the 239 male subjects hospitalized for examination of OSA. We analyzed the relationships between fat areas by computed tomography, comorbidity, polysomnographic data, arterial and venous blood data. Results: Of the 239, 52, 67 and 94 had mild, moderate and severe OSA. We compared all the 94 severe OSA with 85 of the 143 non-to-moderate OSA matched with age and BMI. While waist circumference was the same, severe OSA had a significantly larger VFA. Between the 2 groups, arterial oxygen partial pressure (PaO2), HbA1c and fibrinogen differed significantly. Multivariate modeling of these determinants revealed that both VFA and AHI independently determined PaO2 (contribution rate ($R^2$) = 6.5% and 6.7%) and fibrinogen ($R^2$ = 7.5% and 4.4%), while HbA1c associated independently with AHI ($R^2$ = 3.7%), not VFA. Conclusions: Severe OSA had a significantly larger VFA, lower PaO2, higher HbA1c and fibrinogen than non-to-moderate OSA. Larger VFA in severe OSA suspect that VFA increase would be a key factor related to body composition in OSA becoming severe. PaO2, HbA1c and fibrinogen were independently predicted by VFA and AHI. Thus, control of OSA would decrease VFA, and in turn, a decrease in VFA and OSA might improve HbA1c and fibrinogen.

P3820
Left and right ventricular function in obstructive sleep apnea patients
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Objectives: Obstructive sleep apnea is associated with right ventricular dysfunction including preload and afterload abnormalities. Right ventricular contractility remains difficult to assess due to the complex RV geometry. Echocardiographic speckle tracking strain analysis of CPAP therapy effects may offer new insights into understanding of regional contractility.

Methods: We assessed the hypothesis that RV dysynchrony exists in OSA patients and can be reversed by CPAP therapy.

Results: Logistic regression analysis revealed significant correlation between diabetes and cardiovascular diseases and obesity (BMI $>30$ vs $\leq 30$ kg/m²).

Conclusion: Diabetes was frequent ($>20\%$ of subjects) in moderate and severe OSA patients. Cardiovascular diseases and obesity were the independent predictors of diabetes in this group.

P3821
left and right ventricular function in obstructive sleep apnea patients
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Objective: Obstructive sleep apnea is associated with right ventricular dysfunction including preload and afterload abnormalities. Right ventricular contractility remains difficult to assess due to the complex RV geometry. Echocardiographic speckle tracking strain analysis provides a better understanding of regional contractility. We tested the hypothesis that RV dysynchrony exists in OSA patients and can be reversed by CPAP therapy.

Methods: Prospective study including patients with a confirmed OSA diagnosis.

Conclusion: Diabetes was frequent ($>20\%$ of subjects) in moderate and severe OSA patients. Cardiovascular diseases and obesity were the independent predictors of diabetes in this group.
Echocardiographic (TTE) measurements were obtained at baseline and after one month of CPAP therapy. We measured usual TTE parameters: left ventricular ejection fraction (LVEF), transmural pulsed Doppler including E and A waves velocity and Doppler tissue imaging. The speckle tracking analysis was used to generate 6 segmental RV strain curves. Time to peak strain was determined with dysynchrony defined as the difference between earliest and latest segments. Global strain was calculated.

Results: 36 patients (M: 69% mean (SD) age 56(11) yrs, body mass index 35.1(7.38) kg/m2, respiratory disturbance index 46(18.8)) were included. At baseline 56% had high blood pressure, 22% had a chronic heart disease, with a normal LVEF: 61.8%. Speckle tracking strain analysis showed RV dysfunction with a decreased RV global strain: 13.8(5.8) % and RV dysynchrony: 174 (89) ms. After one month of CPAP, RV function was significantly improved and dysynchrony was reversed: 125 (82) ms (p=0.03).

Conclusion: We observed RV dysynchrony at baseline in OSA patients. RV dysynchrony was improved after one month of CPAP therapy.

3P823

Relationship between sleep apnea syndrome, plasma myeloperoxidase levels and cardiovascular risk

Cystatin C (Cys C) is a protease inhibitor synthesized in all nucleated cells. Lately it has been proposed as an indicator of early dysfunction in glomerular filtration rate. NT-proBNP is a hormone secreted by ventricles in response to heart overload. The aim of this study was to assess Cys C plasma level in patients with OSA and its relationships with OSA-associated cardiovascular diseases. Cys C and NT-proBNP were also compared as predictors of cardiac abnormalities.

We studied 238 consecutive patients with OSA: mean age=56.87±9.97yrs, BMI=33.5±5.84.kg/m², mean AHI=38.97±21.71, mean ODI=44.85±27.85. Elevated level of cystatin C (under 50yrs: CysC<0.92mg/L, over 50yrs: CysC<1.10mg/L) was found in 40% of cases. Comparison of pns with normal and elevated level of Cys C is shown in a table below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elevated Cys C&lt;sub&gt;≤&lt;/sub&gt; 0.92mg/L</th>
<th>Normal Cys C&lt;sub&gt;≥&lt;/sub&gt; 0.92mg/L</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Hypertension (%)</td>
<td>77 (79%)</td>
<td>104 (74%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Coronary Artery Disease (%)</td>
<td>34 (35%)</td>
<td>22 (14.6%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>17 (17.5%)</td>
<td>4 (2.8%)</td>
<td>0.00009</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>9 (16.3%)</td>
<td>19 (22.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated NT-proBNP (%)</td>
<td>28 (15.9%)</td>
<td>21 (18.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cys C&lt;sub&gt;≤&lt;/sub&gt; 0.92mg/L</td>
<td>61 (62.9%)</td>
<td>79 (56.4%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Logistic regression analysis (LRA) revealed that CAD (OR=5.2; 95%CI=1.31-19.48, p=0.005) and HF (OR=5.2, 95%CI=1.9-19.9, p=0.001) were associated with increased CysC level. Association of increased NT-proBNP level with cardiac disorders in OSA pts was also confirmed (for CAD OR=2.5, 95%CI=1.1-5.3, p=0.01, for HF OR=4.9, 95%CI=1.6-14.9, p=0.004).

Conclusions: Increased Cys C level is strongly associated with cardiac diseases in pts with OSA. Cys C seems to be a better indicator of HF than NT-proBNP in OSA pts.

398. Clinical predictors of OSA, adherence to CPAP and psychology

3P824 Plasma levels of TNF-alpha in obstructive sleep apnea syndrome (OSA) before and after surgical intervention

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Background: Prior studies have shown that biomarkers of inflammation, including TNF-alpha, are raised in patients with sleep apnea. TNF-alpha is one of the important risk factors for atherosclerosis, stroke and Cardiovascular disease in OSA patients.

Aim of the study: To determine whether TNF-a blood levels is elevated in OSA syndrome and whether they are reversible after surgical intervention.

Methods: Among the patients who had visited the ENT clinic for evaluation of sleep problems, 70 subjects were selected. Polysomnography (PSG) and morning venous blood serum for levels of TNF-a were performed in all the subjects and 35 patients were diagnosed as having OSA. All patients with OSA had surgical intervention according to individual cases. Laser assisted uvulopalatoplasty (LAUP), extended LAUP (LAUP and laser assisted tonsillar ablation), or laser assisted uvulopalatoplasty were done using a CO2 laser. Sleep apnea monitoring, clinical evaluation and TNF-a level were then compared before and 3 months after intervention.

Results: We compared thirty five patients with OSA(21 males and 14 females), mean age(46.6±12.4), with 35 control subjects(11males and 24 females),mean age (34.2±9.6).The mean (SD) plasma levels of TNF-alpha was significantly higher in patients with OSA than in control group (5.77±4.046 vs. 2.24±1.59g/L (p<0.039)) respectively, and TNF-alpha level significantly decreased (to 3.22±3.4g/L (P = 0.001)) after treatment Also TNF-alpha levels showed a statistical correlation with the AHI before treatment, and with neck circumference after treatment.
Conclusion: Our results suggest that TNF may be a prognostic factor for comparing patients with OSAS before and after treatment.

P3825
Prescription, subjective and objective compliances in patients with obstructive sleep apnea syndrome using positive airway pressure
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Gold treatment for obstructive sleep apnea syndrome(OSAS) is continuous positive airway pressure(CPAP). We aimed to assess prospectively prescription,subjective and objective compliances in OSAS patients recommended PAP treatment.factors effecting compliance,648 patients (69.6% men,30.4% women/recommended to use PAP in January 2005-June 2011,were included. Patients using PAP were questioned for adverse effects and assessed with ESS/Epworth Sleepiness Scale/at follow-ups.Prescription,objective and subjective compliances were assessed.Relationship between compliance and demographic data,PSQI(polysonomography) findings,ESS scores,adverse effects were analyzed.The mean age was 51.29±4.97 and mean BMI(body mass index) was 33.52±6.56.In the first night PSG mean AHI(apnea-hypopnea index) was 54.16±26.41 and Al/apneare index)was 31.46±26.95 24h/38.3%cases attended follow-ups,246 (37.9%) were followed by phone visits and 154(23.8%) couldn’t be reached.Patients using PAP for at least 4 hours per night for at least 70% of the days monitored were regarded as compliant and who didn’t meet this criteria were considered as noncompliant. In the population 63.9%obtained PAP machine/prescription). In 248 cases attending follow-ups,subjective compliance was 85.1%-objective compliance was 64.5%.Higher ODI(oxygen desaturation index) and lower SpO2(oxygen saturation) at the first night PSG were found to positively affect prescription (p<0.05).Improvement in ESS score and satisfactory sleep were significantly correlated with objective compliance(p<0.05).Chest discomfort,difficulty falling asleep and sleep disturbances were significantly higher in noncompliant group (p<0.05).

P3826
Association between obstructive sleep apnea (OSA) and depression and the effect of continuous positive airway pressure (CPAP) treatment
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Background: Obstructive sleep apnea (OSA) is a relatively common disorder which has a negative impact on the psychological well-being of affected individuals.
Objective: To assess the association between OSA and depression as well as the effect of treatment with continuous positive airway pressure (CPAP).
Methods: A total of 37 newly diagnosed individuals with OSA underwent an overnight polysomnography and were assessed using the Epworth Sleepiness Scale (ESS), the Hamilton Depression Rating Scale (HDSRS), and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients were assessed before and after 2 months of CPAP use.
Results: Of the 37 patients included in the study, 21 (56.7%) had clinically relevant depression as indicated by a score 10 on the HDSRS and eleven patients (29.7%) met the diagnostic criteria for a major depressive episode using the Structured Clinical Interview. Scores on the HDSRS were correlated with the Apnea Hypoaxia Index, ESS scores, and oxygen saturation. Patients showed a significant reduction in depressive symptoms and improvement in ESS scores after CPAP treatment.
Conclusion: Patients with OSA should be screened carefully for depressive disorders. CPAP should be tried first before starting other treatment modalities for depression.

P3827
The psychological burden of OSAS patients is not correlated with apnea-hypopnoea index
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Introduction: Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of upper airway obstruction during sleep, which leads to the presence of excessive daytime sleepiness. Regarding the psychological comorbidity in patients diagnosed with OSAS, previous studies focused mainly on depressive and, secondarily, to anxiety symptoms.
Aims and objectives: To record the prevalence of the occurrence of depressive symptoms and of alexithymic characteristics in a sample of OSAS patients and to investigate their relation to respiratory parameter (Apnea - Hypopnoea Index, AHI) of polysomnography.
Methods: The study was conducted in a certified sleep laboratory. 35 randomly selected patients were examined for anxiety, depression and alexithymia using the Spielberger Trait Anxiety Inventory (STAI), the Beck Depression Inventory (BDI) and the Toronto Alexithymia Scale (TAS-20), respectively.
Results: A high prevalence of anxiety (41.4%) and depressive symptoms (55.2%) and of alexithymic characteristics (41.4%) was observed in OSAS patients. Although the control group showed a higher prevalence of anxiety (66.7%) and depression (83.3%) symptoms, there were no differences between the two groups (t-test p>0.05). With regard to severity, no differences were observed between subgroups (mild, moderate and severe OSAS, ANOVA p>0.05). Women showed higher scores in BDI and STAI compared to men (t-test p<0.05). Finally, no correlation was observed between psychometric scores and AHI (Pearson correlation p>0.05).
Conclusions: This study supports the presence of a high degree of psychological burden in patients diagnosed with OSAS, regardless of the severity, as determined by the AHI.

P3828
Continuous positive airway pressure in patients with obstructive sleep apnea: Independent predictors of adherence
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Background: Although continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea (OSA), long-term adherence is challenging. Therefore, the identification of adherent patients is necessary to determine independent adherence predictors.
Methods: In a retrospective data analysis we studied 4263 German patients (age = 54.4±11.2 years; 82.4% male) treated with the CPAP device S8i (ResMed, Sydney, Australia). We analysed AHI, mean airway pressure, mean leakage, hours of use per night and efficiency (days of use/total days). Data of the last 156.7±3.53 months of treatment (range 30-180 days) were collected. Logistic regression was used for determining independent predictors of CPAP adherence.
Results: Mean therapy duration was 3.5±±3.6 years. Independent predictors for poor CPAP adherence (<3/month) were female gender, leakage and therapy duration. Odds ratio (OR) for female gender was 1.63, OR for leakage increment per 0.1% was 1.13, and OR for therapy duration increment from (starting from 15 years) per 1 year was 1.15. Furthermore, age, therapy duration, mask pressure and leakage were independent predictors for excellent CPAP adherence (>7/month): OR for 5-year increment of age was 1.06, OR for therapy duration increment per 1 year was 1.10, OR for mask pressure increment per 1 cmH2O was 1.08, and OR for leakage increment per 0.1% was 0.86.
Conclusion: Independent predictors for poor CPAP adherence (<3/month) were female gender, short-term therapy and higher leakage, whereas independent predictors for excellent adherence (>7/month) were higher age, long-term therapy, increased mask pressure and lower leakage.

P3829
The relationship between obstructive sleep apnea syndrome and two common urological disorders
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Erectile dysfunction (ED) and Lower Urinary Tract Symptoms (LUTS) associated with benign prostate hyperplasia (BPH) usually occur in older men. The aim was to investigate the relationship between Obstructive Sleep Apnea Syndrome (OSAS) and two urological common disorders.
Between January 2007 and April 2010, the men over the age of 50 admitted to the outpatient department of pulmonary diseases with suspected OSAS were selected. All patients had polysomnography analysis. A total of 29 patients having moderate and severe OSAS with apnea-hypopnea index (AHI)=15-30 (11 patients) and AHI>30 (18 patients), respectively were included in the first group.21 patients with AHI<5 constituted the control group. Voiding symptoms were evaluated by using International Prostate Symptom Score (IPSS) and uroflowmetry. ED was investigated by administering International Index of Erectile Function (IIEF). Both groups were comparable with regard to age, PSA, prostate volume, and prostate size by digital rectal examination, IPSS values and uroflowmetry results. On the other hand, nocturia and IIEF results were remarkably different between two groups. The average number of nocturia was 1.47, and the mean score of IIEF was 15.48 in patients with OSAS. Those were 0.88 and 19.90 in the control group, respectively (p<0.05).
In this study, IPSS and uroflowmetry values showed no difference between patients with and without OSAS. On the other hand, nocturia and IIEF results were both remarkably different in OSAS patients. As a result, OSAS was shown to be associated with nocturia and ED. Therefore, the patients with complaint of either nocturia or ED should be investigated for OSAS.
P3831 Sleep behavior and disturbance in high school students: a cross-sectional study in Jeddah, Saudi Arabia

Rosh Meraldi1, Siraj Walli2, Douaa El Derwi2, Ayman Krayem2, Rawan Nassif1

Methods: A cross sectional study was carried out from January to May 2011 on a random sample of high school students. Participants completed a questionnaire which included the Pittsburgh Sleep Quality Index (PSQI), Perceived Stress Scale (PSS) and Epworth Sleepiness Scale (ESS).

Results: 947 students were recruited, of whom 55.6% were female with a mean age (±SD) of 15.6±1.17 years. Marked delay of mean sleep week (04:58) and rise (12:04) time was identified. The total hours of sleep on school nights was 6.97±2.72, with an average estimated sleep latency of 25 minutes. Ten percent of students reported using medications within the last month to help them fall asleep. Disturbed sleep (PSQI score >5) was found in 56% of the study participants. Excessive daytime sleepiness (EDS) defined as ESS score of >10 was found in around one third (33%) of students. Fifty-five percent were identified as psychologically distressed based on PSQI. No significant difference was identified in PSQI global score between stressful and not stressed groups (p=0.590), or between different GPAs (p=0.129).

Conclusions: A high frequency of EDS was found among OA pts (38%), which was underdiagnosed and undertreated. These pts had more severe OSA than patients with NIgER; their nasal symptoms severity was associated with higher AHI. The evaluation of IgEAR in OA pts may contribute to improve these patients’ clinical approach.

P3834 Infections complications associated with the use of CPAP in patients with sleep apnea-hypopnea syndrome

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Introduction: CPAP systems can be contaminated by microbes, increasing the risk of respiratory infections. Humidifiers can add a higher risk. Our study evaluates among respiratory tract colonization and respiratory diseases related to CPAP with or without humidifier.

Objectives: A prospective study was designed. 100 CPAP-users were randomized: Group A (CPAP without humidifier): 50 patients (43 men, 7 women) between 41 and 98 years (average, 62). Patients were instructed of respiratory infection symptoms. Swabs were taken from pharyngeal exudates in all patient, and from masks and tubes in Group B.

Methods: 16 Pharyngeal exudates cultures were positive in Group A and 5 in Group B (32% versus 5%; RR 6.59, 95% CI: 1.37-32.66). Streptococcus pyogenes group A: 6 in Group A and 1 in Group B; Streptococcus beta-hemolytic group C: 3 in Group A, 2 in Group B; Staphylococcus aureus: 1 in Group A; Strepoytococcus group C: 2 in Group B. Respiratory infection symptoms: 3 patients in Group A, 5 in Group B (6% versus 10%). Swabs from masks and tubes in Group B: 31 microbial flora, 2 multiple fungal flora, 3 Turboponas candida, 1 Aeromona hidrophila, 1 Rodotoru raburi, 1 Serratia marensiens and 1 Pseudomonas aeruginosa.

Conclusion: Upper respiratory airways colonisation has been lower in the humidifier group, even though CPAP systems contamination has been common. Respiratory infection symptoms were low in both groups. Humidifiers have not significantly increased infections.

P3833 Snoring at sitting position is a good predictor of sleep apnea in Chinese patients

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Background: Snoring is a common symptom among adults population, and it is the most common complaint in patient with obstructive sleep apnea(OSA) syndrome. Patients who have snoring in sitting position during nap or sleep should have narrower upper airway. The aim of this study was to evaluate if the snoring in sitting position is a predictor of OSA patients.

Method: We prospective enrolled 51 male and 23 female patients. All the participants received questionnaires as well as a standard polysomnography thereafter.

Results: Patients who have self-reported snoring of sitting position (with tilt position for over 45°, 55%+ group) have higher body mass index as well as higher circumference of neck and waist, higher level of Epworth sleepiness scale.
During polysomnographic study, SS group have more percentage of S1 and less percentage of S2 sleep. Besides, SS group have more severity of apnea-hypopnea index (AHI), as well as higher AHI during REM or non-REM sleep. More oxygen desaturation index and arousal index were also noted. The sensitive and specificity of the SS group for OSA defined as AHI ≥5 were 0.77 and 0.52, with positive predictive value and negative predictive value were 0.8 and 0.48. The likelihood ratio value was 1.3. In the other hands, the sensitive and specificity of the SS group for moderate to severe OSA (defined as AHI ≥15) were 0.78 and 0.42.

Conclusion: In the present study, the symptoms of self-reported snoring of sitting position can be a useful predictor of Chinese OSA patients.

P3835
5-years APAP adherence in OSA patients
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Introduction: Although continuous positive airway pressure (CPAP) is effective in the treatment of obstructive sleep apnoea (OSA), inadequate adherence remains a major cause of treatment failure.

Objective: To determine long term adherence to auto-adjusting-CPAP (APAP) and its influencing factors. To evaluate initial compliance and its relation to long-term adherence.

Methods: 83 male patients with moderate to severe OSA were enrolled. After beginning, APAP patients' compliance (% of usage and hours per night) was recorded during medical appointments, after 12 days, 6 months and then annually for at least 5 years.

Results: Patients mean age was 53.8±10.8 years, mean apnoea-hypopnoea index of 25.2±0.1/h and mean Epworth sleepiness scale of 12.4±1.5. Mean follow-up time was of 65.0±1.2 months, 63 patients (75.9%) are still using APAP (73.4±7.7 months) having a mean percentage of use of 92.6±2.8 for 06:55:01±3:55 per day. Twenty patients (24.1%) abandoned treatment after 25.4±17.5 months, on average.

Conclusions: Patients who abandoned treatment during the follow-up period had lower initial compliance. Percentage of use at 12 days and 6th month was 81.7±23 and 65.8±28.5 for non-adherent patients and 96.6±7.4 and 94.3±4.9 for adherents (p<0.01 and p=0.001), mean hours per night were 04:1±1:55 and 04:07±1:57 vs. 06:18±0:28 and 08:14±0:12 (p<0.001 and p<0.001), respectively.

Non-adherent patients were younger (p=0.01). No other differences including employment state, marital status or disease severity and symptoms were found between the groups.

Conclusions: Patients who maintain long-term treatment have very good compliance. Non-adherent patients have significantly lower initial compliance than long-term adherents.

P3836
Obstructive sleep apnea among diabetics in southeastern Nigeria
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Background: Diabetic patients are prone to obstructive sleep apnea (OSAS). OSAS has also been shown to be associated with increased cardiovascular morbidity and mortality. There is a paucity of data on this condition among diabetics in Nigeria. This study was carried out to determine the risk of OSAS among diabetics in Nigeria.

Methods: Diabetics attending the medical outpatient clinic of a tertiary hospital in South Eastern Nigeria were recruited into this survey. A modified version of the Berlin Questionnaire was used to determine the risk for OSAS and also obtain demographic data. Anthropometric and spirometric measurements were also obtained from all subjects. The survey was conducted over a 4 months.

Results: 114 diabetics were randomly recruited for this survey, 54 (47.4%) female and 60 (52.6%) males. 66 (57.9%) of the subjects were hypertensive. The average age of the subjects was 55.5 years and the average duration of diabetes was 7.6 years. 63(55.3%) of the subjects were found to have a high risk for OSAS, there was no gender difference in the risk for OSAS. A high risk for OSAS was associated with increased BMI, increased neck size, hypertension, alcohol use and reduced PEF. The factors that significantly predicted a high risk for OSAS were a history of hypertension (OR 55), alcohol use (OR 9), increasing BMI (OR 2) and poor BP control (OR 2).

Conclusion: OSAS is often not diagnosed among patients with diabetes and the strong association between a previous history of hypertension and OSAS may be the reason for the increased risk of cardiovascular death among diabetics.

P3837
Compliance for NIMV treatment in moderate and severe OSAS patients
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Pulmonology, Bismiamed Yalik University Medical Faculty, Istanbul, Turkey

Aim: In the non-invasive mechanic ventilation (NIMV) using in the treatment of obstructive sleep apnea syndrome (OSAS), compliance problem is a frequently seen difficulty. Aim in this study is to analyze the compliance of the OSAS patients to the NIMV treatment, and to search for the factors affecting the compliance.

Method: The patients given NIMV treatment in the sleep laboratory of the university hospital due to moderate or severe OSAS between 1 January 2011 and 31 December 2011 were included to our study. Polysomnographic findings of the patients were recorded. A questionnaire about compliance to the NIMV that had been set by our clinic applied to the patients by the phone calls.

Results: 75.4% of the included patients were male. The mean age was 49.5±12.3. Mean BMI, Epworth and REM sleep index of the Patients were 32.5±5.9, 10.6±4.6 and 43.2±2.3. Complication related to the NIMV device use was seen in 37 (27%) of the patients. The most frequently seen complications were dryness of mouth, discomfort due to mask, dryness of throat, irritation of the eyes, nasal congestion, bloating, claustrophobia and headache. Sixteen (11.9%) patients was not using the NIMV device due to device discordance. Six of these patients have severe, and 10 of these patients have moderate OSAS.

Conclusion: Compliance to the NIMV in the OSAS treatment is still an important problem. Patients treated with NIMV should be kept under close observation and should be informed about the risks of the disease if not used the device.

P3838
Evaluation of continuous positive airway pressure compliance in a group of obstructive sleep apnea patients
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Currently, the treatment of choice for OSA is nasal CPAP but the documented efficacy of CPAP may be poor because of decreased compliance.

Objective: Objective is to evaluate the CPAP compliance in a group of OSA patients in the state of Kuwait.

Methods: 60 patients proved to have OSA by polysomnography, (ESS) and (FOSS) were done for all patients then follow up for 3 months were done and then patients reassessed again.

Results: Only 45 patients (75%) were compliant on CPAP with a mean runtime of 5.2±0.46 hour/night, CPAP significantly improved the AHI from 44.8±10.85 to 7.5±3.93 (p<0.05), ESS from 17.88±3.2 to 3.47±1.14 and total FOSQ from 83.78±1.67 to 160.9±1.40 (p<0.01), on using correlation study there was significant correlation between the CPAP runtime and the baseline Body Mass Index (BMI), AHI, ESS but on using stepwise regression analysis the only 2 variables showed significant correlation were the BMI and ESS.

Conclusion: In this group of patients the rate of CPAP compliance was considered good (75%) and the only factors that can predict short term CPAP compliance were the BMI and ESS.

P3839
S100B protein: A useful marker in obstructive sleep apnea syndrome
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Aim: Up to now, there have been a few studies performed on serum S100B protein level in patients with obstructive sleep apnea syndrome (OSAS). We aimed to underline the importance of the serum S100B protein as biochemical marker of cerebral damage in patients with OSAS.

Method: Forty-three newly diagnosed OSAS patients [apnea-hypopnea index (AHI): 37.5 (11.3-137), female/male: 18/25] and 25 subjects with AHI value of below 5 [AHI: 4.4 (0.7-4.8), female/male: 9/17] were included in the study. In both groups serum S100B protein level were tested in serum samples taken after polysomnography. Differences in serum S100B protein levels between the OSAS patient group and control group were examined. In addition, association of S100B protein serum level with age, body mass index, AHI, mean apnea time, lowest SpO2 value, percentage time spent at SpO2<90% was analyzed in OSAS patient group. In the control and OSAS patient groups difference between the values was evaluated by parametric independent two samples t test while the relation between the variables and serum S100B protein level in OSAS patient group was evaluated by using Spearman correlation test.

Results: Serum S100B protein level was found to be 133.7 (20.97-230.70) pg/mL in OSAS patient group and 16.1 (10.1-22.9) pg/mL in control group (p=0.000). Serum S100B protein level was not found to be correlated with other variables (p>0.05).

Conclusion: Serum S100B protein level increases in patients with OSAS. This suggests that serum S100B protein may be a useful biochemical marker in determining cerebral damage in patients with OSAS.
Methods: We retrospectively evaluated 134 consecutive patients with moderate-severe OSAS, average age 57±0.10, admitted in a rehabilitation institute for CPAP adaptation, between 2003 and 2009. According to the different provisions of the local health organization before and after 2006, we divided patients in two groups on the basis of the mean length of hospitalization (20 days in Group 1, 7 days in Group 2). CPAP use, numbers of dropout, numbers of patients with discomfort, and numbers of unscheduled visits were assessed at 1 year.
Results: Comparisons are summarized in the table. Data are presented as mean±SD.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=66)</th>
<th>Group 2 (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP use h/night</td>
<td>4.7±2.7 h</td>
<td>4.5±2.8 h</td>
</tr>
<tr>
<td>Dropout (%)</td>
<td>9 (14%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Visits</td>
<td>21 (32%)</td>
<td>23 (38%)</td>
</tr>
</tbody>
</table>

Conclusions: We observed the same adherence to CPAP in terms of mean daily use in the two groups, at one year. However, to obtain the same adherence, the patients adapted in few days had more frequently discomfort, that required a greater number of unscheduled visits.

P3843 Obstructive sleep disorders in children with allergic rhinitis

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Background: Allergic rhinitis (AR) is the most prevalent chronic disease in children, associated with impairments in quality of life, sleep disorders, emotional problems, and impairment in activities. AR can induce medical complications, learning problems and sleep-related complaints, such as obstructive sleep apnea syndrome (OSAS). OSAS is characterized by repeated events of partial or complete upper airway obstruction during sleep. The aim of this study was to estimate the prevalence of obstructive sleep apnea in children with seasonal and perennial allergic rhinitis together with predictive factors.

Methods: We studied children (age 5-17 yrs, N=47) with allergic rhinitis that underwent sleep study using complete polysomnography (PSG) according to standardized protocol. All patients underwent detailed medical and family history, physical examination including ENT examination, and an array of diagnostic tests (skin-prick test, total and specific IgE, cytology of the nasal mucosa, complete and differential blood counts) and Children’s Sleep Habits Questionnaire.

Results: Results from our study showed that almost half (46%) of the examined children with allergic rhinitis suffer from obstructive sleep apnea (88% had obstructive hypopnea). Obstructive sleep apnea was significantly associated with: perennial allergies (p=0.018) and nasal congestion (p=0.026), showing a significantly higher apnea/hypopnea index (AHI) in the group with perennial allergy (p<0.025).

Conclusion: Results of this study indicate that significant number of children with allergic rhinitis may develop obstructive sleep apnea. Perennial AR is an independent risk factor for OSAS in children probably because nasal congestion is the most prevalent symptom of it.

399. Sleep apnoea: clinical topics

P3844 Socioeconomic factors affecting the acceptance of continuous positive airway pressure in sleep apnoea syndrome patients

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Background: CPAP therapy is often associated with suboptimal adherence rates and the assessment of patients’ motivations and barriers is important for the treatment. The aim of this study was to investigate factors which may affect the acceptance of CPAP among patients with SAS.

Methods: We studied 150 consecutive patients with SAS (age 5-80 years, 68% male) who were referred to the Sleep Unit in Thessaloniki, Greece. Patients were divided into two groups: those who had been diagnosed with SAS and prescribed CPAP during the last 2 years did not come to the follow-up visit despite the instructions. We contacted them via telephone and asked about their perception of treatment effectiveness and the adherence to CPAP therapy. Results: From 109 patients, 62 (56.8%) (age 49.2±11.3 years, 93.5% male) were found and answered the questions. Twenty two patients (35.5%) did not purchase the CPAP device (group 1) mainly (50%) due to economic restriction, 12 patients (19.4%) abandoned CPAP therapy after time (group 2) mainly (50%) due to subjective perception of treatment ineffectiveness and 28 patients (45.1%) continue CPAP therapy but ignored the follow-up procedure (group 3). No significant correlations were observed between anthropometric characteristics, severity of SAS, socioeconomic and employment issues and the decision about the CPAP treatment.
in each group, but group 1 had lower education level than the two others (basic level 36.4% vs 16.6%, p < 0.05). No significant differences were noted between the 3 groups with respect to method of CPAP titration, age, BMI, AHI but the ESS was higher in the craniofacial patients and snoring or noisy breathing were favored for an initial PSG to rule out SDB.

Methods: Specific diagnoses and symptoms were: Crouzon’s (n=7), Apert (n=5), Saethre-Chotzen (n=1), Goldenhar (n=1), idiopathic craniosynostosis (n=2), achondroplasia (n=8) and Pierre-Robin (n=2). Their mean age was 5.1 years, none was overweight or obese. Of these patients, 19/26 (73%) had evidence of SDB and 7 (27%) had primary snoring. In patients with SDB, the mean apnea-hypopnea index (AHI) was 10.3 (median = 5.7, range 2.5-65.0). Abnormally increased CO2 was observed in 12/26 (46%). Laboratory results (mean, median, range) were: wide range CRP (7.2, 1.0, 0.1-33.5), total cholesterol (135, 125, 112-180), HDL (40, 37, 23-59), LDL (75, 67, 52-115), tryptophane – normal, fasting glucose and insulin – normal.

Conclusion: The results confirm a high prevalence SDB in children with craniofacial anomalies with a higher rate of cardiovascular lesion. Underlying chronic inflammation also exists in these patients. Metabolic changes were not found.
Objective: This prevalence of excessive daytime sleepiness (EDS) and the association of EDS with respiratory symptoms and large variety of health variables was investigated in two well characterized random samples from the general population.

Methods: Adults aged >40 and living in Reykjavik, Iceland (n=939) and Uppsala, Sweden (n=996), were invited (www.boldstudy.org). Response rates 81, 15% and 62, 2%. In addition, the participants were asked to answer The Epworth Sleepiness Scale (ESS). Short Form-12 and standardised questions about sleep and health, diabetes and hypertension.

Results: In Reykjavik mean (± SD) ESS was 6.0±3.9, compared to 6.1±3.9 in Uppsala. The prevalence of EDS, defined as ESS scores >10, were 18.5% in Uppsala and 18.4% in Reykjavik. EDS was more common among men than women and was more prevalent in age groups >60 years (p<0.001) but not related to body mass index (BMI) or smoking status. Those reporting habitual snoring and apneas scored higher on ESS (p<0.001) and so did also those with respiratory symptoms; wheeze and breathlessness (p<0.05), cough (p<0.001), asthma (p<0.01) and nasal allergy (p<0.02). There were no difference in EDS depending on insomnia, diabetes or hypertension. Mental health scores on SF-12 were significantly lower among those with EDS (p<0.05). There was no difference regarding physical health scores.

Conclusion: Excessive daytime sleepiness is a common complaint in the general population both in Iceland and Sweden. It’s more common among men than women among those who more and have apneas. It is also related to respiratory symptoms, allergy and decreased mental quality of live.
P3855
Gastroesophageal reflux in patients with obstructive sleep apnea syndrome; Value of isolated treatment with pantoprazole
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Objective: To test the value of treatment of gastroesophageal reflux disease (GERD) in improving the obstructive sleep apnea syndrome (OSAS).

Patients and methods: The study included 63 patients diagnosed with OSAS after complete history taking, Ewpoth sleepiness score (ESS), physical examination, and full night polysomnography. Of them 29 patients were diagnosed with concomitant GERD by standardized Reflux Disease Questionnaire (RDQ), upper endoscopy, and 24-hour pH monitoring and receiving Pantoprazole 40 mg once daily for 2 months. The patients were reevaluated by polysomnography, ESS, quality of life SF36 v2 questionnaire.

Results: The twenty- nine patients with OSAS and GERD had significantly higher body mass index (BMI), waist circumference, and reported non significant increase in sleep and daytime symptoms of OSAS. After 2 months treatment with Pantoprazole, there was significant decrease in apnea hypopnea index (AHI), snoring events, arousal index, and ESS. Meanwhile, there was a significant improvement in sleep efficiency, minimum O2 saturation, desaturation index and quality of life parameters (SF 36 v2).

Conclusions: GERD and OSAS are common co morbid conditions. Adequate treatment of GERD with Pantoprazole, 40 mg/day for 2 months was effective in improving many subjective and objective findings of OSAS. In patients with OSAS and history suggestive of GERD, upper endoscopy, pH monitoring and treatment with proton pump inhibitors (PPIs) may be an important adjunct in controlling OSAS symptoms.

P3856
Potential Impact of the economic crisis: Experience of a sleep clinic in northern Greece
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Greece has entered a long period of economic crisis with adverse effects on various aspects of daily life. From 2009, poor countries with International Monetary Fund loans displace aid from public health and report negative effects on community health. A transversal study was to evaluate the impact of the economic crisis on the population visiting a sleep clinic of a tertiary hospital between years 2008 and 2011.

Methods: Comparison of the number of patients, anthropometric data, symptoms and treatment acceptance between 2008 (beginning of crisis) to 2011 (great impact of crisis on salaries, psychology).

Results: The number of patients that visited the sleep clinic was significantly reduced in 2011 (n=127) compared with 2008 (n=463) and 2009 (n=445). The age, BMI and ESS did not differ between the years (mean 52.23 ±13.7 years, 33.67±4kg/m2, and 14.11±5.4 respectively). The main symptom of the patients was daytime sleepiness and the symptoms that were worse in 2011 compared with 2008 were headache (32.4% vs. 49.6%, p<0.001) and nightmares (44% vs. 75.9%, p<0.001). In 2008, 320 (69.1%) patients required treatment for Obstructive Sleep Apnea Syndrome with CPAP and 261(81.5%) of them received CPAP. In 2011, 111 (87.4%) required treatment, but only 68% received CPAP.

Conclusions: By the observation of the population visiting a Sleep Clinic, the economic crisis can be reflected in the number of patients, their symptoms and their perspective in treatment options.

P3857
The frequency of REM related OSA among patients with mild OSA and the relation between apnea and daytime sleepiness among these patients
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Aim: The question if REM related OSA is a specific clinical entity or if it is an early sign of severe sleep disordered breathing as there is high occurrence of REM OSA in mild and moderate cases, recently have attracted the investigators. In this study, we aimed to see the frequency of REM related OSA among patients with mild OSA; and also to evaluate relation between apnea and daytime sleepiness among REM related OSA patients.

Methods: 134 patients with mild OSA (RDI<5-15) among 1267 patients with PSG examination at sleep laboratory of Bismiadem University Hospital between August 2010 and February 2012 were retrospectively evaluated. Patients having REM apnea/Non REM apnea >2 and Non REM apnea <15 are considered as REM related OSA.

Results: 80 of 134 (5.95) patients with mild OSA were considered as REM related OSA. When REM related OSA and Non-REM OSA are compared for age, gender, daytime sleepiness, BMI, neck surround and additional diseases; mean age with REM related OSA group was found only significantly lower. Number of apnea in REM was over 15 at 87.3% of REM related OSA group and over 30 at 39.3% of them. There was no relation between apnea number at REM and daytime sleepiness system (p=0.81).

Conclusion: We may consider the result of lower mean age in REM related OSA group as a supporting result for early sign of severe sleep disordered breathing. We consider to follow up this group of patients to answer the question about subject.
Sixty OSA patients were recruited either into an intervention (n=30) or control group (n=30). Assessments occurred at week 0, week 13 and week 26. The intervention involved supervised exercise sessions, dietary advice and behaviour change counselling between weeks 0 and 13. Changes in body habitus and walking capacity (ISWD) between week 0, 13 and 26 were assessed using a mixed-design factorial ANOVA and 95% confidence intervals (CIs) of the net change in groups over time. At 13 weeks, the intervention group improved body mass (-1.7kg; P=0.001) and body fat percentage (-1.1%; P=0.001) relative to the control group, although CIs between groups over time indicate changes were not clinically important. Changes in resting heart rate (-6 [ -9, -2]) beats min^{-1}; P=0.002) and ISWD (+95 [52, 130] mm; P<0.001) were possibly beneficial. At follow-up, changes in resting heart rate were likely trivial (-3 [ -8, -1]); beats min^{-1}; P=0.250) although ISWD was probably beneficial (+110 [71, 149] m; P<0.001).

These data suggest that a change towards exercise behaviour has occurred. Interventions have potential as part of the holistic management of obese OSA patients compliant with CPAP.

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**400. Metabolic and cardiovascular consequences of OSA II**

P3863

Usefulness of SD-101 for screening of sleep apnea syndrome

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Objectives: The SD-101 is a sheet-like device for screening of sleep apnea syndrome (SAS). It examines sleep disordered breathing by sensing the alterations of body loading corresponding to respiratory movement. Polysomnography (PSG) is the essential monitor for the diagnosis of SAS. However, PSG is not suitable for screening device for all people suspected of SAS. A simple and easy device is needed for screening of many SAS patients. For evaluation of the usefulness of SD-101 in more detail, the accuracies of SD-101 was examined about detection of hypopnea and apnea.

Subjects and methods: Forty four hospitalized patients were enrolled (aged 61.0±13.8, 37 males, Body mass index (BMI) 26.0±4.9kg/m²). They were examined by both PSG and SD-101. They were classified into two group, hypopnea group (Group H, 17 patients) and apnea group (Group A, 27 patients). Group H had hypopnea index accounted for more than 50% of Apnea Hypopnea Index (AHI). Group A had apnea index accounted for more than 50% and equal of AHI.

We evaluated correlation between AHI of PSG with respiratory disturbance index (RDI) of SD-101 in each group.

Result: RDI of SD-101 had very close correlation with AHI of PSG (r 0.886 p<0.001). The sensitivity and specificity of the examination using SD-101 were 80% and 100%, respectively. RDI of SD-101 in Group H had lower correlation with AHI of PSG than RDI of SD-101 in Group A. Group H (r 0.548 p<0.05), Group A (r 0.886 p<0.001). The sensitivity of Group H (66.6%) was lower than that of Group A (88.0%).

Conclusion: RDI of SD-101 has very close correlation with AHI of PSG, however SD-101 may not detect hypopnea exactly in hypopnea predominant patients.

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P3864

Effect of CPAP treatment on blood pressure levels in resistant hypertension.

A multicenter randomized study from the Spanish sleep network (NCT00616265)

Miguel Angel Martinez-Garcia1, Francesco Capote2, Francisco Campos-Rodriguez 3, Patricia Llobreter4, Maria Josefa Diaz de Atauri5, Maria Somozas6, Fernando Masa7, Monica Gonzalez8, Lirios Sicristan9, Ferran Barbé10, Joaquin Duran-Cantolla11, Jose Maria Montserrat12, on behalf of Spanish Sleep Network. 1Pneumology Unit, Villajoiosa Hospital, Alicante, Spain; 2Pneumology Service, Virgen del Rocio University Hospital, Seville, Spain; 3Pneumology Service, València University Hospital, Valencia, Spain; 4Pneumology Service, Servicio de Urgencias de Xarxa, Barcelona, Spain; 5Pneumology Service, Vall Hebrón University Hospital, Barcelona, Spain; 6Pneumology Service, La Fe University Hospital, Valencia, Spain; 7Pneumology Service, Hospital Clinic, Barcelona, Spain; 8Pneumology Service, Raval University Hospital, Barcelona, Spain; 9Pneumology Service, Sant Pau Hospital, Barcelona, Spain; 10Pneumology Service, Geriatric Tarragona, Tarragona, Spain; 11Pneumology Service, Fundació Sant Pau, Barcelona, Spain; 12Pneumology Service, Herrera de Pineda University Hospital, Barcelona, Spain

Background: Only very few small studies have analyzed the role of CPAP treatment on blood pressure (BP) levels in patients with resistant hypertension (RH).

Objective: To evaluate the effect of CPAP treatment on BP levels in patients with RH
Conclusions: Sleep apnea severity was associated with increased cancer mortality. [1.08 to 6.06], p=0.032. When stratified by gender and age (cut-off 65 years), only al-220mor SBP (-7.5 mmHg; p < 0.001). There is a positive correlation between the increase used of CPAP in hours/and the decrease in BP levels (n=0.25; p=0.014). 28% of patients in CPAP group vs 17.5% in control group normalized their BP levels; p=0.045). More patients in CPAP group significantly recovered their dipper pattern, compared with control group (p=0.088).

Conclusions: CPAP treatment significantly decrease SBP and DBP levels and allowed the recovering of normal dipper pattern in patients with RH and sleep apnea. The magnitude of these effects correlate with the number of hours CPAP use.

Conclusions: Sleep apnea syndrome and cancer mortality. Longitudinal multicenter study in 5,467 patients from the Spanish cohort Association between sleep apnoea and cancer mortality. Longitudinal P3865 CPAP treatment significantly decrease SBP and DBP levels and allowed the recovering of normal dipper pattern in patients with RH and sleep apnea. The magnitude of these effects correlate with the number of hours CPAP use.

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Obstructive sleep apnea (OSA) is a sleep disorder characterized by recurrent episodes of upper airway obstruction and interruption of airflow. It is well known that it is associated with severe OSAS. However, the analysis of different parts of the night and of the evolution within sleep stages in OSA patients has not yet been investigated.

Objectives: Evaluate and compare HRV in 3 stages of each sleep stage in overnight polysomnographies in OSA and matched healthy controls. We studied overnight polysomnographies of 6 untreated OSA patients (mean age 50±14 yr, apnea-hypopnea index [AHI] = 9.4±6 events per hour) and 6 matched healthy controls. Time and time-domain analysis of R-R intervals (RRi) was performed for the minimum of the central 5-minute sample of stage II, III and REM sleep that was free of stage shifts, artifacts, arousals and apneas. Subsequently, we analyzed the evolution of these stages between OSA and controls.

Results: Comparing the 3 parts of each stage, we did not observe any difference intragroup (P>0.05). In addition, we only observed significant difference of RMSSD index between OSA and controls (P<0.0001) in the first REM stage. In contrast, when compared the average of 3 central 5-minute samples, we observed significant differences of mean RRi, RR tri index, TINN (ms), SD1 and SD2 between OSA and controls (P<0.05) in all stages.

Conclusions: The preliminary results show that despite of any change in the HRV evolution through 3 intervals of each stage, the number of samples analyzed during the night may influence the results of HRV in overnight polysomnography. Financial support: FAPESP

P3871 Diabetes mellitus and obstructive sleep apnea syndrome in primary care Gustavo Cimbra dos Reis1, Vânia Sacramento1, Vitor Fonseca1, Carlos Alves1, Inês Ferro1, Marta Guedes2, Patricia Quintas1, Rita Marques3, José Cabrita4, António Pinto Saravia5, Serviço de Pneumologia, CHIBM, EPE, Barreiro, Portugal; 2LINDE, LINDE, Lisbon, Portugal; 3UF, Quinta da Lomba, Barreiro, Portugal

Introduction: Obstructive Sleep Apnea Syndrome (OSAS) is a risk factor for insulin resistance and type 2 Diabetes Mellitus and its prevalence is higher on these. An adequate screening instrument for primary care units would be valuable.

Objectives: To evaluate Epworth Scale (ES) and Berlin Questionnaire (BQ), as screening tools of OSAS in a diabetic population of a primary care unit.

Methods: This response could be a protective mechanism against tissue hypoxia caused by repeated episodes of hypoxemia.

Results: Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05). Of the 24 patients studied, 18 were diagnosed from OSA (AHI>10) with a mean AHI of 26.2±9.7. Of these, 16 were highly symptomatic (ESSAPS, p<0.05).
401. Pulmonary circulation: acute and chronic pulmonary embolism

P3875
Cardiovascular regulation effects of CPAP therapy in obstructive sleep apnea patients with and without hypertension during daytime
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Obstructive sleep apnea can cause changes in cardiovascular regulation during the night and during daytime. Altered regulation may not be visible in absolute values of heart rate and blood pressure but in a changed coupling between the heart beat and the respiration. In a controlled randomized study we investigated effects of CPAP therapy on daytime cardiovascular regulation.

Twenty-eight patients with OSA in total, thereof 18 with arterial hypertension and 10 with normal blood pressure, were studied at baseline and at a follow up date with three months of CPAP. The age and sex matched healthy control subjects were investigated using the same protocol. All subjects underwent cardiopulmonary coupling analysis. In addition we recorded 20 minutes quiet breathing at rest and a bicylce ergometry with ECG and blood pressure (Portapres). Cardiorespiratory coupling was investigated using symbolic coupling, new developed technique which can reveal causality between signals.

The stress test showed a significant reduction of the diastolic blood pressure at a work load of 50W and 100W (p<0.05 and p<0.01, respectively) and a decrease of the heart rate recovery time after the stress test (p<0.05).

The results indicate a reduction of vascular resistance and sympathetic activity during daytime. The coupling analysis of the resting periods by means of symbolic coupling analysis showed an effect of the CPAP therapy on the baroreflex reaction in hypertensive patients where influences of the systolic blood pressure on the heart rate changed from pathological patterns to adaptive mechanisms of the normotensive patients (p<0.05).

P3876
Increased risk of obstructive sleep apnea in patients with non-alcoholic fatty liver disease
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Background: Increasing prevalence of Obstructive Sleep Apnoea (OSA) and Non-alcoholic Fatty Liver Disease (NAFLD) are linked through the epidemic of obesity and are both associated with increased cardiovascular risk. Studies have shown higher prevalence of NAFLD in OSA patients, but the impact of NAFLD on OSA remains to be determined.

Aims: To determine whether those with NAFLD had different clinical or biochemical characteristics to the rest of the cohort.

Methods: We conducted a retrospective database and case note review of patients with known NAFLD. The database was reviewed for detailed liver investigations and notes examined for any clinical referral for sleep investigations and outcome.

Results: Liver database and case notes of 385 patients with biopsy proven NAFLD were examined. Forty-seven patients were referred to sleep services on clinical grounds (12%). 38 were found to have OSA, 10% of the whole cohort but 86% of those referred. Analysis of variance showed no difference between groups (those with NAFLD, those without NAFLD and those with no previous sleep investigations) in: baseline liver function, diabetes, body mass index, liver biopsy scores or any characteristics to the rest of the cohort.

Conclusions: In a well-defined population of biopsy-proven NAFLD patients, OSA is common and mostly undiagnosed. There are no differences in the clinical characteristics of those referred for sleep studies and those not, other than ESS.

Aims and objectives: To evaluate the indices of quality of life after PE depending on sex and age and to determine their dynamics under the influence of warfarin.

Methods: Assessment of indices of quality of life was done in 80 patients who had survived PE during their hospital stay and out-patient treatment using the questionnaire MOS SF-36.

Results: Patients of both sexes taking warfarin after PE showed better indices of physical status (PS), psychic status (Pc), general status (GS) during out-patient treatment than during their hospital stay. Females had lower indices of quality of life than males both on the in-patient and out-patient stages of treatment.

Conclusions: Patients aged 45-60 years and over 60 taking warfarin after PE demonstrated significantly higher indices of PS, Pc and GS than those who did not take warfarin.

P3878
Thrombophilias in 60 Bulgarian patients with “idiopathic” venous thromboembolism
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In the last two decades, many inherited and acquired thrombophilias predisposing venous thromboembolism (VTE) have been known. The aim of this real life study is to analyze the frequencies of some thrombophilias in patients with acute VTE, in whom no underlying diseases or triggering-VTE factors are present ("idiopathic" VTE). 60 ethnic Bulgarians (34 men and 26 women, mean age 34.47) with VTE (39 with deep vein thrombosis (DVT) only, 12 with pulmonary PE (PE) only and 9 with both) were examined for: Leiden mutation (FVL), prothrombin factor II mutation (G20210A), plasminogen activator inhibitor-1 mutation (PAI-1), C677T and A1298C of methylenetetrahydrofolate reductase (MTHFR) mutations; deficiency of protein C (PC), deficiency of protein S (PS), deficiency of antithrombin III (AT III) and antiphospholipid antibodies syndrome (APL).

In 48 (80%) of patients (79.48% in DVT, 80.95% in PE patients) were found in total 79 abnormalities. VFTL heterogenous mutation was found in 15 (25% of all patients) and homogenous in 2 (3.3%) patients. FVL presents 21.51% of all abnormalities. PAI-1 was on the 17th place with 11% abnormalities. 11 (18.3%) were homogenous and 6 (10%) were heterogeneous in combination with other abnormalities. 6 (10%) had G20210A mutation and 14 (23%) deficiency of AT III. We also found deficiency of Pr.S in 6, Pr.C in 3; mutations C677T in 4, A1298T in 7 patients. APL was found in 5 patients.

We conclude that most of the patients with "idiopathic" VTE have one or more thrombophilias. In addition to the known role of FVL, as a thrombophilic factor, the PAI-1 mutation presents a prominent frequency in our group.

P3879
The treatment of sub massive pulmonary embolism: Thrombolytic or heparin?
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Introduction: Thrombolytic therapy (TT) decreases mortality and morbidity in the patients with massive pulmonary embolism (PE) when compared to heparin therapy. However the use of TT in patients with sub-massive PE remains controversial.

The aim of these studies is to compare the efficiency of heparin and TT for sub-massive PE.

Material and method: Patients with sub-massive PE who were treated during the last five years were included in this study. Patients who have significant hypoxemia or expansive thrombosis or proximal DVT were given TT and the others were given heparin. These groups were compared for demographics, risk factors and echocardiography findings (72nd hour, 6th and 12th month).

Results: Totally 39 patients (20 female, 19 male) were included. The mean age was 57years, the mean duration of follow up was 3.5 years. There was no difference for age, gender, risk factors between TT (n=20) and heparin (n=19) groups. Mean pulmonary arterial pressure (PAP) was 49mmHg in heparin group and 56mmHg in TT group. PAP at 72nd hour was significantly lower in TT group than the heparin group (p<0.001). PAP at 6th and 12th months were still lower in TT group than heparin group but it was not statistically significant. There was no mortality or major bleeding due to the TT or heparin.

Conclusion: As a result of our study TT decreases PAP significantly at 72nd hour in the patients with sub-massive PE so that TT could be the first choice therapy for these patients.
Dear colleagues: D-dimer is not always necessary – Reduce the cost of your hospital!

Müge Aydogdu
Emergency departments
Wells clinical prediction rule and pulmonary embolism rule out criteria
P3882
PE treatment strategies.
patients with a low sPESI but it no adds prognostic information. Risk stratification
In conclusion, cardiac troponin testing may not be required for the minority of
outcome in the study.
cTnT
point(s) had a higher sensitivity, and a higher negative predictive value than the
patients with sPESI
≥
76 patients (62.8%) to the high-risk category (18 (14.9%) advers events within 30 days diagnosis of PE. The sPESI classified
cause or nonfatal recurrent venous thromboembolism or nonfatal major bleeding.
Discussion: The cost of D-dimer for 1 patient in Albania is $12.6, for 150 patients is $1800.6. Is evident: in 12% of cases D-dimer was negative in patients with confirmed PE. In the other group, the clinical data and high score clinical probability are sufficient as an indication for the angio-CT. So, further laboratory examinations, including D-dimer may be avoided, especially in developing countries, where the cost of these tests is high for the hospitals. D-dimer is necessary in low and medium clinical probability cases.
Conclusion: In patients with high risk factors and a clear anamnesis of PE, D-dimer is not necessary. Avoiding it may reduce the hospital expenses.

P3881
Prognostic role of cardiac troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism
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The new, high-sensitivity troponin T (hsTnT) assay may improve risk stratification of nonemergency patients with acute pulmonary embolism (PE). Simplified Pulmonary Embolism Severity Index (sPESI) has shown prognostic accuracy. We aimed to investigate whether risk stratification by cardiac troponin testing improves the prediction of clinical outcomes in patients with a sPESI. The primary endpoint of the study was adverse 30-day outcome, defined as death from any cause or nonfatal recurrent venous thromboembolism or nonfatal major bleeding. A total of 18 (14.9%) adverse events were observed within 30 days following the diagnosis of PE. The sPESI classified 76 patients (62.8%) into the high-risk category (≥ 1 point). Of patients with low sPESI, hsTnT >0.014 pg/mL was positive in 14/53 (26.6%) patients. hsTnT and D-dimer cTnT <0.014 had occurred non-fatal hemorrhage in a patient. The adverse event rate rose from 0% in patients with sPESI ≥ 1 or positive hsTnT, and further to 14% in those with hsTnT ≥0.014 pg/mL + sPESI ≥1. The adverse event rate rose from 1.6% in patients with sPESI ≥ 1 or positive cTnT and further to 12.4% in those with cTnT ≥0.014 pg/mL + sPESI ≥1. The adverse event rate rose from 0.6% in patients with hsTnT ≥0.014 pg/mL and sPESI ≥1. The adverse event rate rose from 1.6% in patients with sPESI ≥ 1 or positive hsTnT, and further to 14.2% in those with cTnT ≥0.014 pg/mL + sPESI ≥1. Of the 121 study patients, the hsTnT≥0.014 pg/mL + sPESI ≥1 points) had a higher sensitivity, and a higher negative predictive value than the cTnT≥0.014 pg/mL + sPESI ≥1 point(s) combinatorial model for predicting 30-day adverse outcome in the study.
In conclusion, cardiac troponin testing may not be required for the minority of patients with a low sPESI but it adds prognostic information. Risk stratification with the combination of sPESI and cardiac troponin may also serve for aggressive PE treatment strategies.

P3882
Wells clinical prediction rule and pulmonary embolism rule out criteria (PERC) in preventing over investigation of pulmonary embolism in emergency departments
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Background: On the worse outcomes of missed diagnosis of pulmonary embolism (PE), unnecessary diagnostic tests are usually ordered to most of the patients with dyspnea or pleural chest pain.
Aims: To identify rates and causes of overinvestigation for PE in our emergency department (ED) and to search whether it was possible to reduce this overinvestigation by using Wells score and Pulmonary Embolism Rule Out Criteria (PERC) in daily practice.
Methods: A retrospective observational cohort study performed in an ED of a tertiary care university hospital. 108 patients, who had diagnostic tests with the suspicion of PE, were included in the study.
Results: Among the whole study group, 53 (49%) were diagnosed as PE (+) and overdiagnosis was present in 55 (51%) patients i.e., PE (-). The sensitivity of high Wells score was 43%, specificity 78%, positive predictive value 66% and negative predictive value 59% for PE diagnosis. PERC criteria found to be negative (when all of the 8 criteria were fulfilled) in only 5 (15%) patients. The sensitivity of the test was 98%, specificity 7%, positive predictive value 5/50, negative predictive value 98.0. When individual parameters of PERC were evaluated solely for the exclusion of PE, “no leg swelling” and “no leg swelling” were found significantly negatively correlated with the diagnosis of PE (p<0.01, r=-0.325 and p<0.013, r=-0.214 respectively)
Conclusion: Over investigation of PE in EDs still remains as an important problem. In order to prevent this, the clinical prediction rules must be developed further or may be used in combination.

P3883
Predictors of poor outcome in chronic thromboembolic pulmonary hypertension
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Background: Clinical and plasma biomarkers are essential to predict the outcome of pulmonary arterial hypertension (PAH). These markers might also be useful to evaluate the outcome of chronic thromboembolic pulmonary hypertension (CTEPH).
Objective: Assess the cumulative mortality and identify predictors of the patients with CTEPH.
Methods: 108 patients with CTEPH who registered in Beijing chaoqyang hospital between January 2006 and October 2011 were analyzed. The primary endpoint is death, and the second endpoint is worsening WHO functional class.
Results: During the follow-up period (4-58 months), 11 patients died (10.2%), meanwhile WHO functional class of 4 patients was worsened (3.7%). The 1-, 3-year survival rates were respectively 95.1% and 82.1%. BMI (HR 0.708; 95% CI 0.677 to 0.941; P=0.007), leukocyte(HR 1.346; 95% CI 1.145 to 1.582;P<0.001), ESR(HR 1.043; 95% CI 1.010 to 1.077;P=0.011), cardiac output(CO) (HR 0.484; 95% CI 0.243 to 0.962;P=0.039), pulmonary vascular resistance (PVR) (HR 1.002; 95% CI 1.001 to 1.003;P=0.001) were independent predictors for poor prognosis of CTEPH patients. Meanwhile 54 patients with PAH were enrolled, and the 1-, 3-year survival rates of PAH patients were 78.8% and 59.4% respectively.

P3884
Daytime measurements underestimate nocturnal oxygen desaturations in pulmonary arterial and chronic thromboembolic pulmonary hypertension
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Background: Nocturnal hypoxemia is important in precapillary pulmonary hypertension (pPH) as it worsens pulmonary hemodynamics. Whether daytime oxygen saturation (SpO2) predicts nocturnal hypoxemia in pPH patients has not been conclusively studied. Therefore, we investigated the prevalence of nocturnal hypoxemia in ambulatory pPH patients in comparison to daytime SpO2 and disease severity.
Methods: Consecutive patients diagnosed with pPH classified as either pulmonary arterial (PAH) or chronic thromboembolic pPH (CTEPH) had daytime resting and exercice SpO2 (at the end of 6-minute walk), thereafter they underwent
overnight pulse oximetry at home. Functional class, pro-BNP and tricuspid pressure gradient were assessed.

Results: 63 patients (mean age±SD 66±15.43 females) with PAH (414 and CTEPH (194). The resting SpO2, exercise SpO2 and mean nocturnal SpO2 were 94±3, 87±9 and 89±6.4%. 49 patients (77%) spent >10% of the night with SpO2 <90% (sustainers), 33 (52%) spent >50% of the night with SpO2 <90% (sustainers desaturators). The positive predictive values of a daytime SpO2 <91% to predict nocturnal desaturation or sustained desaturation were 75.3% and 47%. Nocturnal SpO2 was negatively correlated with the tricuspid pressure gradient, but not with functional class, 4MW and pro-BNP.

Conclusion: Nocturnal hypoxemia is very common in PAH and CTEPH despite often normal daytime SP02 and reflects disease severity. Nocturnal pulse oximetry should be considered in routine evaluation of PAH patients and research be directed to the treatment of nocturnal desaturation in PH.

P3885
The PESI, the simplified PESI and the shock index for identification of high-risk and low-risk patients with acute pulmonary embolism

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We compared the test characteristics of the pulmonary embolism severity index (PESI), the simplified pulmonary embolism severity index (sPESI) and shock index (SI) for predicting 30-day outcomes in a prospective study of 132 patients with objectively confirmed pulmonary embolism (PE). The primary outcome of the study was 30-day mortality.

Overall, 13 (9.8%) out of 132 patients died during the first month. The SI classified fewer low-risk patients (41, 31.1%) out of 132 patients, compared to sPESI (45, 34.1%) and compared to PESI (57, 43.2%). High-risk patients based on the SI had a higher mortality than those based on the sPESI and PESI (31.7%, versus 22.2% and 20.6%). Low-risk patients based on the SI had a lower mortality than those based on sPESI and PESI (0% versus 3.4% and 4%).

The SI quantified the prognosis of patients with PE better than sPESI and PESI.

P3886
Analysis of the association between protein C gene single nucleotide polymorphism and pulmonary thromboembolism in Chinese population

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Background: We investigated the role of protein C (PC) polymorphism in patients with PTE in order to find out the correlation between its polymorphism and the susceptibility of the Chinese population to develop PTE.

Methods: Sixty three consecutive patients with PTE were enrolled as the investigated group and eighty six healthy people as the control group. CT at the position of 2405 and A/G at the position of 2418 in the PC gene promoter region were detected through polymerase chain reaction-restriction fragment length polymorphism analysis.

Results: (1) The results suggested that the genotype frequencies of the two SNPs when combined together were not significantly different between two group (P>0.05). However, the allele frequency of the C2405T SNP was significantly different between the case and control group. The frequency of T allele in the PTE group was higher. (2) These results suggested that there were six different kinds of genotype distribution (TA - TA, TA - CA, TA - CG, TG - CG, CA - CG, CA - CA) and three different kinds of haplotype (TA, CG, CA).

Conclusions: These results suggest that the two polymorphisms present in the control region of PC gene are associated with an increased susceptibility to PTE in the Chinese population.

P3887
Venous thromboembolism in lung cancer with clinical analysis of 89 cases

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Objective: The aim of this study was to investigate the associated clinical factors and to provide evidences for prevention and therapies of VTE in lung cancer patients.

Methods: We retrospectively reviewed the clinical data of 2,053 lung cancer patients with definite diagnosis by cytology or pathology between July 2008 and June 2010 at Shanghai Pulmonary Hospital. In 2,053 lung cancer patients, 89 were confirmed with VTE. The incidence rate of VTE in adenocarcinoma patients and non-adenocarcinoma patients was 5.65% and 3.02%. The incidence rate of VTE in Stages I-IIIa lung cancer patients was significantly decrease (1.48%) in comparison to that in stage IIb-IV patients (5.74%). Significant difference of incidence rate of VTE was showed in the patients with or without comorbidities (2.70% and 6.73%; P<0.01). The incidence rate of VTE in pretherapy lung cancer patients with normal value of platelet count, D-dimer, IL-1 and TNF was 3.72% (0.31%, 2.44%, 3.27%, respectively, whereas, the rate in pretherapy lung cancer patients with high value was 6.26% (5.91%, 10.26%, 7% respectively) (P<0.05). There were no relations between other clinical factors and the incidence of VTE. Logistic analysis showed adenocarcinoma, comorbidities, high value of D-dimer, IL-1, TNF in blood were the related important factors with increased VTE incidence.

Conclusions: Adenocarcinoma is the most common pathological type in lung cancer patients with VTE. The high risk factors of VTE include comorbidities and increase of D-dimer, IL-1 and TNF in blood. Close attention should be paid to those lung cancer patients with high risk factors of VTE.

P3888
Pulmonary perfusion scan follow-up in patients with acute pulmonary embolism

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Introduction: The role of pulmonary perfusion scan in the follow-up of pulmonary embolism (PE) is not clearly known

Aim: To assess the evolution of pulmonary perfusion after a symptomatic acute PE without high-risk and the role of persisting perfusion defects in assessing the risk of recurrent PE.

Methods: A retrospective analysis (April 2005-May 2010) of patients with symptomatic acute PE for whom a pulmonary perfusion scan follow-up of at least 6 months was available. All scans were read independently by 2 readers whose agreement was calculated by kappa test. Recurrent PE was diagnosed on the basis of the presence of segmental perfusion defects not present at the previous control.

Result: The analysis refers to 252 patients, aged 69±15 years (mean ± SD).

The kappa index ranged from 0.84 to 0.98 for the different times. The number of unperfused segments decreased from 5.8±2.8 (baseline) to 2.1±2.0 (6 months, p<0.0001) to 1.7±1.8 (12 months, ns; ANOVA).

After a month from the diagnosis there were 16 recurrences; the number of unperfused segments at the last scan available prior to recurrence did not differ significantly from the number measured at the standard 6 months control in patients without recurrent PE.

Conclusion: After 6 months from acute PE there is a significant reduction in the number of unperfused segments which does not change significantly afterwards. The persistence of perfusion defects is not predictive for the development of later recurrent PE.

P3889
(Contributing factors to) the diagnostic yield of CT pulmonary angiography: A retrospective study

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Introduction: Pulmonary embolism (PE) is a potentially life-threatening disease which requires quick and reliable diagnosis to start timely treatment. Clinical probability of pulmonary embolism is assessed by using a combination of Wells-score and D-dimer level. In most cases of PE, CT of pulmonary arteries (CTPA) provides a reliable diagnosis. In the Isala klinieken approximately 1000 CTPAs are performed annually, but its diagnostic yield and factors associated with improving it are unknown. In literature diagnostic yield varies from 73.1%.

Aims: To determine diagnostic yield of CTPA in our centre and factors associated with it. Differences between specialities as well as adherence to protocol were investigated.

Methods: All patients receiving a first CTPA for pulmonary embolism in 2010 were included. Data about relevant clinical information and requesting specialty were retrospectively obtained. Differences in diagnostic yield were tested using a Chi-square test. Independent predictors were identified with multivariate logistic regression.

713s
Results: PE on CTPA was found in 224 of the 974 patients (23%). Between specialties, diagnostic yield varied from 19.5-23.9% (p=0.20). Independent predictors of diagnostic yield were: age, sex, D-dimer, chest pain, cough, dyspnea, cardiac history, COPD, atelectasis/consolidation, intrapulmonary mass and/or interstitial pulmonary disease on CT. Wells-scores were poorly documented (n=127, 13.1%). Poor adherence to protocol was also shown by a high amount of unnecessary D-dimer values with a high Wells-score (55 of 58; 58.6%).

Conclusions: The diagnostic yield of CTPA in this study was relatively high. Better adherence to protocol might improve it further.

P3890
Should there be an age adjusted D-dimer cut-off value in diagnosing thromboembolic disease? A retrospective analysis
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Previous studies using the enzyme-linked immunosorbent assay (ELISA) D-dimer in pulmonary embolism have suggested that the D-dimer cut-off should be adjusted for age. (Douma et al. BMJ 2010; 340 c1475) Using a retrospective analysis from our DVT clinic we compared latex agglutination assay D-dimer values for patients without DVT in 10 year age brackets (1696 patients). There was a significant D-dimer level rise (compared to under 50 years) with advancing age.

<table>
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<td>632 (807)</td>
<td>679 (631)</td>
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We analysed the data from positive DVTs to look for an age adjusted D-dimer cut-off. (212 patients)

By generating receiver operating characteristics (ROC) curves we calculated 95% sensitivity D-dimer cut-off limits for the various age brackets. A clear relationship between age and D-dimer cut-off could not be shown.

Our data again showed that D-dimer level rises with advancing age. However, with our assay an age adjusted D-dimer cut-off could not be deduced without reducing sensitivity.

P3891
Prognostic value of red cell distribution width in patients with pulmonary embolism
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Elevated red blood cell distribution width (RDW) has been associated with adverse outcomes of heart failure and pulmonary hypertension. We speculated that a higher RDW would be independently associated with poor clinical outcomes in pulmonary embolism (PE) patients.

A total of 702 consecutive patients with acute PE were evaluated. We collected each patient’s base-line characteristics including RDW. The primary end-point was all-cause in hospital mortality. Receiver operating characteristic (ROC) analysis was performed to determine the optimal RDW cut-off levels with regard to prognosis. We used logistic regression to assess the association between factors for the time of presentation and inhospital mortality after adjusting for patient (age, clinical and laboratory variables) factors.

There was a graded increase in mortality rate with each RDW quartiles: 5.8% in quartile I (<15.6), 9.7% in quartile II (15.7-19.4), 13.1% in quartile III (19.5-22.2) and 20% in quartile IV (>22.3) (p for trends <0.001). Patients who died had higher baseline RDW values (16.1% (11.7-28.3)) vs 14.5% (10.7-32.3) p<0.001. The optimal cutoff value of RDW for predicting inhospital mortality was >15% and the negative predictive value was 93% for mortality. In multivariate regression analysis, RDW remained associated with an increased odds of death. RDW levels may provide a potential marker to predict outcome in PE patients.

P3892
Angiogenesis in chronic thromboembolic pulmonary hypertension (CTEPH)
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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by organized thrombi in the pulmonary arteries leading to right heart failure and death. In a murine venous thrombosis model we were able to demonstrate that endothelial cell-specific deletion of vascular endothelial growth factor receptor 2 (VEGF-R2)/fetal liver kinase-1 leads to misguided thrombus resolution. Following the hypothesis that CTEPH is based on inadequate thrombus resolution, we studied the role of angiogenesis in CTEPH.

Methods: Fibrotic CTEPH thrombi, their red fresh portions, and unthrombosed pulmonary arteries were collected from patients undergoing pulmonary endarterectomy. Real Time PCR, immunohistochemistry, in vitro 3D angiogenesis and proliferation assays were performed.

Results: Biochemical analyses revealed that angiogenic molecules such as angiopoietin-2, VEGF, basic fibroblast growth factor and markers for endothelial cells (ECs) such as VEGF-R2, von Willebrand factor and VE cadherin were decreased in CTEPH thrombi compared with pulmonary arteries and fresh pulmonary clots. However, homogenized CTEPH thrombi promoted angiogenesis in an in vitro 3D angiogenesis assay and stimulated the proliferation of human umbilical vein ECs.

Conclusion: Angiogenic molecules are downregulated in fibrotic CTEPH thrombi compared with parent pulmonary arteries and fresh clots. However CTEPH thrombi appear to promote angiogenesis using ECs from healthy donors. Downregulation of genes involved in angiogenesis and lack of functional ECs in CTEPH thrombi may drive thrombus persistence, while the angiostimulatory effect of devascularized thrombi may attract bronchial artery collateralization in the direction of the thrombus.

P3893
Demographics, clinical characteristics, health resource utilization and cost of patients with CTEPH: Retrospective results from six European countries
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Objective: To describe demographics, treatment patterns, health resource utilization and related costs of patients with chronic thromboembolic pulmonary hypertension (CTEPH) in 6 European countries.

Methods: We reviewed medical charts from patients diagnosed with CTEPH and treated with medications for pulmonary arterial hypertension (PAH): Endothelin
receptor antagonists (ERA), PDE-5-inhibitors (PDE5i) or prostacyclin analogues (PA). Demographic and clinical characteristics, medications, and health resource utilization were retrospectively abstracted from patients’ medical records at specialized PH treatment centers from 6 European countries. Resource utilization was valued using country-specific unit costs; descriptive statistical analyses were performed.

Results: Twenty-one hospitals documented 119 CTEPH patients over 25.4 months time. Patients were inoperable (83.2%) or persistent after surgery (16.0%) with mean age 67.5 ± 12.1 years, 61% female, 6-minute walking distance 297 ± 119 meters, and NYHA class III/IV in 27/59/14%. At baseline, 59.7% patients received ERA, 34.4% PDE5i, and 5.8% PA. CTEPH patients experienced 1.8 ± 2.2 hospitalizations per year accounting for 14.8 ± 26.1 days in hospital. Annual cost of PAH-specific medication was the predominant economic factor averaging $36,768 ± 22,630 per year. Hospitalization costs ($4,490 ± $7,923) and concomitant medications ($2,510 ± $2,503) were lower. Other health care resource items accounted for marginal additional costs.

Conclusion: These data provide clinical characteristics and cost estimates for CTEPH patients receiving off-label therapy with medications that have been approved for PAH.

P3894
Clinical characteristics and outcomes of patients with clinically unsuspected pulmonary embolism versus patients with clinically suspected pulmonary embolism
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Background: The routine use of multidetector computed tomography (MDCT) has led to increased detection of unsuspected pulmonary embolism (UPE). Our aim was to compare the characteristics and prognosis of patients with UPE to patients with suspected PE (SPE).

Methods: We retrospectively reviewed the charts of patients diagnosed with PE in a community-based university hospital between the years 2002-2007. UPE was defined as PE detected on CT scans performed for indications other than PE. We compared patients with UPE to patients with SPE for differences in clinical features, ECG, imaging, and echocardiographic findings. We assessed the long-term outcomes of patients.

Results: Of 500 patients with PE, 408 had SPE and 92 had UPE. Patients with UPE were similar to patients with SPE regarding age and sex distribution. Malignancy was more common in UPE patients (27% vs. 13%, p = 0.00029). The mortality hazard ratio after adjustment for age, sex and malignancy was 1.546 (95% CI, 1.139-2.099, p = 0.0052).

Conclusions: We suggest that UPE is more prevalent in patients with a malignancy and is associated with higher mortality despite a less severe clinical presentation. UPE may be a marker of poor prognosis.

P3896
Diffusing capacity for carbon monoxide and mortality in patients with chronic thromboembolic pulmonary hypertension
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Background: Diffusing capacity for carbon monoxide (DLCO) reflects the ability of gas exchange across the alveolar-capillary interface and is also used as a marker of pulmonary vascular disease. Recently, Chandra et al. reported that DLCO predicts mortality in patients with pulmonary arterial hypertension. However, there is little data about DLCO in chronic thromboembolic pulmonary artery hypertension (CTEPH).

Objectives: The aim of this study is to reveal the correlation between DLCO and other clinical markers and to evaluate DLCO as a predictor of mortality in CTEPH patients.

Methods and results: We performed observational retrospective study of 202 consecutive patients with CTEPH (female 69.8%, age 54.6±12.8 yrs., 99-medial, 103-surgical) who underwent both pulmonary function test including DLCO and right heart catheterization from 1986 to 2011 in Chiba University Hospital. %DLCO showed correlation with age, NYHA, Hugh-Jones classification, oxygen delivery, PaO2, %VC, %FEV1 and 6-minute walk distance. However, no correlation was shown between %DLCO and mean pulmonary artery pressure, pulmonary vascular resistance, PaO2 and AaDO2. Among surgically treated patients, there is no difference about operative mortality between normal %DLCO (>70%) group and decreased %DLCO group (<70%) (11.7% vs. 13.3%, p=0.8166). Among the medically treated patients, decreased %DLCO group showed significantly poor survival than normal %DLCO group (5-year survival 69.1% vs. 86.0% p=0.0263).

Conclusion: Decreased DLCO was associated with impaired quality of life, pulmonary function, oxygen delivery in CTEPH, and predicted the mortality in medically treated patients.

P3897
Mir-17 modulates smooth muscle cell markers, apoptosis and BMPR-II levels in human pulmonary artery smooth muscle cells
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Pulmonary Arterial Hypertension (PAH) is a progressively devastating disease characterized by excessive proliferation of the Pulmonary Arterial Smooth Muscle Cells (PASMC’s). Recently micro RNA (miR) has been shown to play an important role in the pathogenesis of PAH. We describe in the present study the effects of over expression of miR17/92 as a cluster or miR17 alone on human pulmonary artery smooth muscle cells (HPASMC). HPASMC were commercially obtained and were transfected with miR17/92 or miR17 encoding plasmid or control vector by electroporation. Proliferation and apoptosis resistant state of PASMC transfected with miR was assessed by MTS and caspase3/7 Glo assays respectively. RNA and protein levels of important target genes in PAH were measured using Real-time RT-PCR and western blots. HPASMC transfected with miR17/92 or miR17 show decreased cell numbers and showed an increased apoptosis as assessed by

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increased caspase activity. Real-time RT-PCR analysis reveals that proliferation markers such as PCNA and Cyclin D1 are not significantly altered. SMC marker calponin and bone morphogenetic protein receptor β2 levels were down regulated in both MCT and/or H2R1792-miR17 transfected cells. Voltage gated potassium channel (Kv1.5) was up regulated in PASMCs treated with miR17/22 cluster but not miR17 alone indicating that different miRs in the 17/22 cluster differentially may regulate key molecules in the development of PAH.

P3989

**Vasopressin is involved in endothelin receptor antagonist-induced fluid retention in rat. Differential effect of selective ETA and dual ETA/ETB receptor antagonists**

**Marek Vereščagin**, Daniel Strasser, Enrico Vezzali, Anna Stalder, Marc Iglarz, Patrick Hess, Martine Clozel. Drug Discovery, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland

Endothelin receptor antagonists (ERAs) are associated with varying degrees of fluid retention. As endothelin B (ETB) receptors have been involved in naturessis and diuresis, we hypothesized that ETA-selective ERAs cause a significant risk of fluid overload in patients.

Aim of the present study was to understand the contribution of each ET receptor subtype in the mechanism of fluid retention in rats. Changes in fluid balance were assessed after administration of the prototypic ETA-selective sunitan and the dual ETA/ETB receptor antagonist bosantan, by measuring haematocrit (Hct), haemoglobin (Hb), plasma volume (PV), body fluid content and renal excretion function.

Acutely, sunitan caused marked dose-dependent decreases in Hct and Hb, whereas bosantan had a lesser effect. Chronic studies confirmed this difference and showed that sunitan increased PV (+50%) and elevated total body fluid content (+15%) compared with vehicle, while bosantan had a small non-significant effect (+16% for PV and +8% for total body water content). In addition, sunitan, but not bosantan, reduced water excretion and increased plasma vasopressin (AVP) concentration (3-fold increase) compared with vehicle-treated rats. In Brattleboro rats lacking AVP and in Wistar rats treated with either the AVP V2 receptor antagonist tolvaptan, or the ETB-selective antagonist BQ-788, hemodilution induced by sunitan was markedly reduced.

These results demonstrate that ERAs, particularly ETA-selective antagonists cause fluid retention by activating the AVP system via secondary stimulation by endothelin of the unthitiated ETB receptors.

P3999

**A potential new therapy for pulmonary hypertension with the use of compound 21, an angiotensin type 2 receptor (AT2R) agonist**

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Pulmonary hypertension (PH) is a debilitating, chronic lung disease that often leads to right-heart failure and death. Currently available therapies are ineffective in significantly improving the quality of life and reducing mortality rates, thereby necessitating the discovery of novel therapeutic interventions. The renin-angiotensin system (RAS) has been associated with the pathophysiology of PH via increased activity of the deleterious ACE/ANGII/AT1R axis. It has been suggested that AT2R are upregulated in response to cardiovascular injury, and subsequent stimulation of this receptor may oppose the deleterious actions of the RAS axis. However, the role of AT2R in PH has yet to be investigated. We propose that non-peptide AT2R agonist, Compound-21 (C21), will attenuate the progression of monocrotaline (MCT)-induced PH in 8-week-old Sprague Dawley rats.

Four weeks post a subcutaneous injection of MCT (50mg/kg), the rats displayed marked elevation in right ventricular systolic pressure (RVSP, Control: 30 ±10.78; MCT: 82.2±4.5mmHg; p<0.05; n=8-10), with subsequent development of right ventricular hypertrophy (RVH, Control: 0.25±0.05; MCT: 0.61±0.04; p<0.05; n=8-10). C21 treatment (0.3mg/kg/day i.p.) began 2 weeks post MCT-challenge resulted in significant attenuation of RVSP and RVH increases (RVSP: MCT+C21: 64.2±6.2mmHg; RVH: MCT+C21: 0.48±0.04; p<0.05; n=14). Furthermore, C21 significantly attenuated PH-induced right heart dysfunction, in terms of elevated right ventricular end-diastolic pressure and +dP/dt. Our results suggest that AT2R represents a novel therapeutic target in the management of PH, and C21 may serve as a lead beneficial compound.

**Abstract P3990 – Table 1**

<table>
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<tr>
<th></th>
<th>Cost</th>
<th>MCT</th>
<th>MCT+Nil50</th>
<th>MCT+Nil100</th>
<th>MCT+Nil400</th>
<th>MCT+Nil800</th>
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<tr>
<td>RVSP (mmHg)</td>
<td>34.6±1.5</td>
<td>112.2±5.5**</td>
<td>96.0±1.6</td>
<td>85.5±4.3**</td>
<td>98.5±7.6</td>
<td>83.6±7.9**</td>
<td>83.6±6.9**</td>
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<td>mPAP (mmHg)</td>
<td>14.7±0.7</td>
<td>47.5±0.9**</td>
<td>40.2±2.3</td>
<td>34.2±4.1**</td>
<td>42.7±3.1</td>
<td>35.0±3.1**</td>
<td>33.9±2.8**</td>
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<td>CO (ml/min/m²)</td>
<td>110.0±5.5</td>
<td>48.4±3.5**</td>
<td>39.8±1.5</td>
<td>93.6±6.8**</td>
<td>88.2±3.8**</td>
<td>99.2±3.7**</td>
<td>95.4±6.4**</td>
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<tr>
<td>PAI-1 (ng/ml)</td>
<td>0.23±0.01</td>
<td>0.76±0.03**</td>
<td>0.59±0.07**</td>
<td>0.50±0.07**</td>
<td>0.67±0.05**</td>
<td>0.55±0.01**</td>
<td>0.62±0.04**</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>9.6±0.4</td>
<td>15.2±0.7**</td>
<td>12.2±0.5</td>
<td>10.8±0.4**</td>
<td>11.4±0.4**</td>
<td>11.5±0.4**</td>
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</tbody>
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**P3990**

**A dose-response study of nilotinib and imatinib in experimental pulmonary hypertension**

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**Introduction:** Platelet derived growth factor (PDGF) and c-kit are involved in the pathophysiology of pulmonary hypertension (PH). Tyrosine kinase inhibitors (TKI) targeting PDGF receptors and c-kit such as imatinib (Im) and nilotinib (Nil) are currently tested in PH.

**Aims and objectives:** To test the efficacy of Nil and Im in experimental PH.

**Methods:** Sprague-Dawley rats were analyzed, corresponding to controls (Cont), MCT alone, MCT treated with Im at 50 or 100 mg/kg (MCT+Im50-MCT+Im100), MCT and treated with Nil at 40, 80 or 120 mg/kg (MCT+Nil40-MCT+Nil80-MCT+Nil120). TKI were administered from day 21 to 35 after MCT. Serum kinetics concentrations (SKC) of TKI were performed at day 28. At day 35 hemodynamic parameters, right cardiac hypertrophy and pulmonary vascular remodelling were studied.

**Results:** SKC showed that Nil50,Nil40 and Nil80 corresponded to human drug concentrations. A dose-response improvement in hemodynamic parameters and medial wall thickness was observed with Im and Nil.

**Conclusion:** Dose-dependent improvements of experimental PH are observed with Nil and Im.

P3901

**Genistein rescues pulmonary hypertension and attenuates abnormal vasoconstriction in rats lungs**

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**Background:** Recent studies suggest that the deregulation of endothelial nitric oxide synthase (eNOS) is accountable for in the development of pulmonary hypertension (PH). Genistein, a phytoestrogen derived from soybean, has been reported to improve endothelial function.

**Objective:** We hypothesized that chronic treatment with genistein would prevent and reverse of hypoxic PH (HX) by improvement of eNOS function.

**Method:** Daily treatment with either genistein (0.2mg/kg) or vehicle was started. After 3-wk hypoxic exposure, rats were treated with the dual ETA/ETB receptor antagonist bosentan, by measuring haematocrit (Hct), plasma volume (PV), body fluid content and renal excretory parameters and diuresis, it was paradoxical to observe that ETA-selective ERAs cause a significant risk of fluid overload in patients.

**Results:** Genistein treatment prevented the progression of PH to right ventricular failure and restored vascular remodeling in HX. And also, genistein rescued pre-existing PH. These effects were mediated by improvement of eNOS function and restoring the interaction of eNOS and eNOS-related proteins. Furthermore, exogenously administration of genistein rapidly attenuated abnormal vasoconstriction in HX by improvement of eNOS function.

**Conclusion:** These results indicated that genistein not only had protective and reversal effects against the development of hypoxic PH, but also attenuated abnormal vasoconstriction of PH. The underlying mechanism might be related to the improvement of eNOS function.

P3902

**Modified exhaled nitric oxide measurement in monocrotaline-exposed rats to monitor pulmonary hypertension**

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**Background and aims:** Rats exposed to monocrotaline (MCT) are broadly used as animal model for pulmonary arterial hypertension (PAH). In analogy to human disease, right heart catheter (RHC) is the established gold standard for pulmonary pressure monitoring. Although exhaled nitric oxide (ENO) levels have been shown to correlate with pulmonary pressures in humans with pulmonary hypertension, no link between ENO and pulmonary pressures could be established in rats. The
aim of the present study was to test whether a technical modification of the NO measurement process could help generate reliable ENO values that correlate with pulmonary pressures as assessed by simultaneous RPP.

Methods: 23 male Sprague-Dawley rats were studied 28 days after MCT-exposure and unilateral pneumonectomy. Hemodynamic parameters were monitored by an implantable telemetry system (DSI Datascience, St. Paul, MN U.S.A.). ENO was measured by means of chemiluminescence (CLD 66, Eco Physics, Durmrten, Switzerland) in single, conscious, spontaneously breathing rats. ENO values measured by a standard accumulation method (ENO standard) and those obtained after process modification (ENO modified) were correlated with mean pulmonary arterial pressures (mPAP).

Results: After process modification, measuring errors were diminished and potential influencing factors eliminated. There was a clear correlation between ENO modified and mPAP (r=0.007, R=–0.49), while no correlation was observed between ENO standard and mPAP (p=0.236, R=–0.212).

Conclusion: Modified non-invasive ENO measurement may be used to monitor PAC in monocrotaline-exposed rats.

P3903
Bone morphogenetic protein signaling in experimental nitrofen-induced congenital diaphragmatic hernia

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Congenital diaphragmatic hernia (CDH) is a life-threatening cause of lung hypoplasia and persistent pulmonary hypertension of the newborn. As bone morphogenetic proteins (BMP) have been shown to play crucial roles in fetal lung and heart development, we explored the potential implication of this signaling pathway in an experimental model of CDH. Pregnant Sprague-Dawley rats were exposed to either 100 mg nitrofen or olive oil on embryonic day 9.5. On embryonic days 17 and 21, fetuses were delivered by caesarian section, sacrificed, checked for CDH and their lung and heart tissue were harvested for pathological evaluation.

Lung and heart weight-to-body weight ratios decreased by 28% and 35% (P<0.05) on embryonic day 17 and by 12% and 8% (P<0.05) on embryonic day 21. Nitrofen administration resulted in airway septa thickening, together with lower radial alveolar count. The pulmonary expressions of the BMP receptor (BMPR) type 2, BMP4 and BMP7 decreased, while the expression of BMPR1A did not change and the expression of gremlin, a BMP antagonist, increased on embryonic day 17. The pulmonary expression of DNA binding protein 1 (Id1) decreased, together with decreased pro-angiogenic factor Gli1 expression on embryonic day 21. The myocardial expressions of BMP2, BMPR1A, BMP7 and SERCA-2A were decreased, while the expressions of gremlin and noggin increased on embryonic day 17. On embryonic day 21, the myocardial expressions of Id1 and SERCA-2A decreased, while gremlin expression increased.

These results suggest that BMP signaling is downregulated in the lungs and the heart at early and late stages of nitrofen-induced CDH.

P3904
TSC/mTOR pathway promotes hypoxia-induced pulmonary hypertension in mice

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Background: Chronic hypoxia is a key trigger of pulmonary vascular remodeling in pulmonary hypertension (PH). The mammalian target of rapamycin (mTOR) is involved in cell proliferation, which is negatively regulated by Tuberous sclerosis complex 1 (TSC1) in mice (Tek-cre(+)/TSC1fx/+) (provided by prof. Kai-feng Xu) were used. The mice were exposed to either hypoxia (10% O2) or normoxia (21% O2), then the right ventricular systolic pressure (RVSP) and index of right ventricular hypertrophy (RVHI) were measured. Histological examination was used to estimate the distal vascular remodeling. Western blot was used to detect the change of protein expression in vivo.

Results: Those two genotypic mice under normoxia showed no differences. After hypoxia, RVSP and RVHI of those two genotypic mice was gradually increased, but Tek-cre (+)/TSC1fx/+ mice were higher after 3 weeks (RVSP: 22.79±0.31 vs. 19.95±0.97mmHg, P<0.05; 0.32±0.01 vs. 0.25±0.02, P<0.05). The small pulmonary arteries of both Tek-cre (+)/TSC1fx/+ and Tek-cre (-)/TSC1fx/+ showed progressive medial thickening under hypoxia, but the former was more obvious. The expression of phosphorylation of S6 (biomarker of mTOR) gradually increased in progressive medial thickening under hypoxia, but the former was more obvious. The expression of phosphorylation of S6 (biomarker of mTOR) gradually increased in progressive medial thickening under hypoxia, but the former was more obvious.

Conclusion: This novel compound is able to achieve a more complete blockade of ET receptors and provides evidence for superior efficacy potential.

P3905
Feasibility of eccentric exercise training (ECCs) in monocrotaline (MT) rats: Effects on survival, echocardiographic and hemodynamic parameters

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ECCs may be of interest in patients with pulmonary hypertension (PH) because cardiac solicitation is much lower during ECC than during concentric exercise, performed at the same mechanical power.

Aims: We assessed the feasibility, hemodynamic and survival effects of ECCs in MT rats with PH.

Methods: ECCs on treadmill was initiated 2 weeks after MT injection (40mg/kg) (30 minutes at 50% of maximal speed, slope: -15°, 5 days/week for 4 weeks). Trained rats (MTsec, n=13, control ECC (Lccle), n=7) were compared with sedentary rats (M特斯ed, n=13, CSSed, n=7). Before and after 2 and 4 weeks training, maximal speed measurement and echocardiography were performed. At 4w, right ventricular (RV) catheterisation was performed.

Results: The RV systolic pressure was 40±2 mmHg in MT, and 22±1mmHg in CL rats (p<0.001). Exercise was generally well tolerated. In the MTcc and M特斯ed groups, 3 and 2 rats developed right heart failure and died. Maximal speed significantly increased in trained rats at 4w (p<0.01) (figure). Echocardiographic parameters were not significantly different in MTsed and MTcc (cardiac output (CO), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery flow acceleration time (PAAT)) (figure). RV systolic pressure was not different in MTcc (36±24mmHg) and in M特斯ed (42±3mmHg).

Conclusion: In this PH model, ECCs was well tolerated and not detrimental to the hemodynamic condition and survival. Whether ECCs could be an adjuvant therapy in PH deserve to be further investigated.

P3906
Superior in vivo efficacy of macitentan: Comparison to other endothelin receptor antagonists

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Endothelin (ET) receptor antagonists used for the treatment of pulmonary arterial hypertension present different pharmacological profiles depending on their selectivity and affinity for ET receptors. Macitentan (MACI) is a new dual ETA/ETB tissue targeting receptor antagonist designed to achieve a more complete ET receptor blockade. To investigate this property, we designed a study in which rats were given MACI on top of maximally effective doses of either ambriole (AMBRI, ETA selective) or bosentan (BOS, dual ETA/ETB).

First, we measured the effects of single doses of the compounds on mean arterial blood pressure (MAP) in conscious Dahl salt-sensitive rats equipped with telemetry, and constructed dose-response curves. Maximal effective doses were 30 mg/kg for MACI and AMBRI and 100 mg/kg for BOS.

Next, we tested the potential for an additive effect of MACI on top of the now defined maximal effective doses of AMBRI and BOS. MACI 30 mg/kg further decreased MAP by 17 mmHg when given on top of AMBRI 30 mg/kg (p<0.05 vs vehicle). In contrast, addition of AMBRI 30 mg/kg on top of MACI 30 mg/kg had no additional effect (5 mmHg vs vehicle, p=0.47), confirming use of the maximal effective dose of AMBRI. Conversely, AMBRI 30 mg/kg given on top of MACI 30 mg/kg failed to induce any additional MAP decrease.

In a similar experiment, MACI on top of maximal effective dose of BOS elicited a further MAP decrease of 21 mmHg (p<0.02 vs vehicle), whereas addition of BOS had no additional effect. The add-on effect of macitentan on top of ambriole or bosentan confirms that this novel compound is able to achieve a more complete blockade of ET receptors and provides evidence for superior efficacy potential.
Resveratrol attenuates hypoxic pulmonary vascular remodeling in simulated high altitude-exposed rats: potential role of HIF-1α/NOX4/ROS inhibition
Tao Wang1,2, Ling-Li Guo1,3, Guang-Ming He1,2, Peng Luo1,2, Fu-Qiang Wen1,2
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Objectives: Chronic high altitude hypoxia induces pulmonary vascular remodeling with marked hypertrophy and luminal narrowing leading to the development PAH. Pulmonary oxidative stress has been implicated in hypoxic PAH. This study aimed to investigate the effects of resveratrol, an anti-oxidant polyphenol, on hypoxic pulmonary vascular remodeling in rats.

Methods: Rats were exposed to simulated high altitude of 6000 m in a hypobaric chamber for 8 h/day, for up to 28 days. Resveratrol (10 mg/kg, ip) was daily administered 0.5 h before hypoxia exposure. Rat primary pulmonary arterial smooth muscle cells (PASMCs) were incubated under hypoxia (2% O2) in the presence of 10, 25, or 50 μM resveratrol. Pathophysiological changes and signal transduction were examined using histochimistry, fluorescence probing, Western blotting and RT-PCR.

Results: Resveratrol administration significantly reduced hypoxia-induced elevation in mPAP (23.6±2.4 mmHg vs. 30.3±1.9 mmHg; P<0.05) and medial wall thickness of pulmonary arteries (16.5±4.1% vs. 22.7±2.4%; P<0.05) in rats. Resveratrol also decreased pulmonary MDA and H2O2 levels as indicators of oxidative stress in hypoxic PAH rats. In vitro studies show that resveratrol dose-dependently inhibited hypoxia-induced rat PASMC proliferation and cellular ROS accumulation. Moreover, resveratrol reduced hypoxia-increased Hif-1α and NOX4 (a ROS contributor) expression both in vitro and in vivo.

Conclusions: Resveratrol attenuates hypoxic pulmonary vascular remodeling in rats exposed to high altitude exposure through its inhibition on Hif-1α/NOX4/ROS-generated oxidative stress under hypoxia.

Applying pharmacogenomics to pulmonary arterial hypertension (PAH): A target-based approach to therapy
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Introduction & aims: Pharmacogenomics, the study of how genetic variations influence the response to drugs, has the desirable objective of tailor-making drugs for each individual genetic makeup. The successful application of this concept in oncology provided the rationale for this study. Like most diseases in oncology, PAH is a heterogeneous disease. We aimed at identifying possible genetic variations in PAH patients. In this study, we used a target-based approach in order to perform a preliminary proof-of-concept study.

Methods: We examined 2 experimental models of PH: mice with deletion of the Vasooactive Intestinal Peptide gene (VIP-/-), and rats injected with monocrotaline (MCT), 2 models with comparable, though not identical, phenotypic features. We analyzed their particular gene alterations, with special reference to genes related to vascular remodeling and inflammation, and compared phenotypic and genotypic responses in each model to treatment with VIP.

Results: VIP+/- mice showed overexpression of genes promoting vascular proliferative and inflammation, with underexpression of anti-proliferative genes. VIP fully corrected all PH features and matching gene expression alterations. MCT rats, however, showed complex gene expression alterations: As in VIP-/- mice, those promoting vascular remodeling and inflammation, and others tending to modulate the PH. Further, VIP treatment failed to correct many of the phenotypic abnormalities, and only partially corrected the phenotype.

Conclusions: This preliminary proof-of-concept study demonstrates the importance of genomic information in determining the therapeutic response to a given drug. Full validation of the role of pharmacogenomics in PAH must await comparable studies in patients with different forms of the disease.

Resveratrol is a polyphenol that plays a major role in vascular biology, and is known to regulate the phenotype and activity of various vascular cell populations. Because most fibrotic diseases, such as Idiopathic Pulmonary Fibrosis (IPF), are associated with vascular remodeling and since endothelial progenitor cells may be involved in this process, we investigated the impact of TGF-β1 modulation of endothelial progenitor cell angiogenic properties.

Patients/methods: TGF-β1 plasma levels were determined in 64 patients with IFP and compared to controls. The effect of TGF-β1 on angiogenesis was studied in vivo in a Matrigel plug model and in vitro on Endothelial Colony Forming Cells (ECFCs). We studied the effects of inhibiting the expression of the three main receptors of TGF-β1 in ECFCs using siRNA.

Results: Total TGF-β1 plasma levels were significantly increased in patients with IFP compared to controls (P < 0.0001). TGF-β1 had proangiogenic effects in vivo by increasing hemoglobin content and blood vessels formation in Matrigel-plugs implanted in C57/B6 mice and in vitro by enhancing ECFC viability and migration. The effects were abolished by silencing the three main receptors of TGF-β1 in ECFCs.
P3912

Unique receptor dissociation kinetics of the novel endothelin receptor antagonist macitentan
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Association and dissociation rates of G protein-coupled receptor antagonists can influence their in vivo pharmacological activity, such as duration of action, activity in situ, and receptor cross sensitivities and ultimately clinical efficacy.

Using signaling assays in human pulmonary arterial smooth muscle cells (PASMDC), we investigated the endothelin (ET) receptor inhibition kinetics of macitentan, a novel ET receptor antagonist currently in phase 3 clinical trials in pulmonary arterial hypertension, and compared them with the kinetics of bosentan and ambrisentan.

Calcium flux assays showed that macitentan, but not ambrisentan or bosentan, increased in potency (10-fold) upon prolongation of antagonist pre-incubation time from 10 min to 120 min, indicating slow apparent association of macitentan with ET receptors. Macitentan furthermore displayed a slow receptor dissociation rate so that inhibition of ET1-induced calcium influx and lung fibroblasts for more than 60 min after macitentan wash-out. Conversely, bosentan and ambrisentan did not maintain receptor blockade after washout and displayed a ~15-fold shorter receptor occupancy half-life than macitentan. The slow dissociation kinetics represented macitentan's an efficient antagonist of ET1-induced IP3 synthesis and ET1-induced sustained calcium flux across the whole range of ET1 concentrations tested. In contrast, bosentan and ambrisentan did not display antagonism against high ET1 concentrations in these assays.

In pulmonary arterial smooth muscle cells, macitentan is a slow-offset competitive antagonist and, unlike bosentan and ambrisentan, capable of efficient receptor blockade in functional assays irrespective of the ET1-concentration.

P3913

Pulmonary gene expression of tenasin-C and fibronectin in chronic obstructive pulmonary disease (COPD)
Marina Manco-Enriqueke,1 Susanna Estany 1, Marta Lopez 2, Maria Molina Molina 1, Inesco Escobar 1, Rosa M. Penas 1, Victor Peinado 1, Joan A. Barbera 1, Jordi Dorca 1, Salad Santos 1. 1Respiratory Medicine. Pulmonary Research Group-IDBBELL, Hospital Universitari de Bellvitge, Hospitalat de Llobregat, Barcelona, Spain; 2Pathology Department, Hospital Universitari de Bellvitge, Hospitalat de Llobregat, Barcelona, Spain; 3Respiratory Medicine. IDIBAPS, Hospital Clinic de Barcelona, Barcelona, Spain

Background: COPD is characterized by pulmonary vascular remodeling and is associated with high prevalence of cardiovascular events regardless of other risk factors. Tenasin-C (TNC) and fibronectin (EDA-FN) are extracellular matrix proteins involved in the structural and functional organization of the lung. Our previous studies showed that TNC and EDA-FN are upregulated in lung fibroblasts from patients with COPD.

Objectives: To assess the expression of TNC and EDA-FN in lung tissue of COPD patients compared to smokers without COPD.

Methods: Expression of TNC and EDA-FN was assessed in tissue samples of 20 patients, 10 with COPD and 10 without COPD. In addition, expression of TNC was assessed in cell cultures of lung fibroblasts. The expression of TNC and EDA-FN was determined by quantitative real-time PCR and Western Blotting.

Results: The expression of TNC and EDA-FN was significantly higher in COPD patients compared to smokers without COPD. The expression of TNC and EDA-FN was also significantly higher in lung fibroblasts from patients with COPD compared to smokers without COPD.

Conclusion: Our findings suggest that TNC and EDA-FN play a role in the pathogenesis of COPD, and that their expression may be a potential biomarker for the diagnosis of COPD.

P3914

Effects of a soluble guanylate cyclase stimulator, BAY 41-8543, upon right ventricular function in experimental pulmonary embolism
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Background: Pulmonary embolism (PE) increases pulmonary vascular resistance (PVR) and may cause right ventricular (RV) dysfunction, leading to poor clinical outcome.

Methods: We studied the effect of soluble guanylate cyclase stimulator (BAY 41-8543) on RV function in experimental PE. PE was induced by injecting 2.6 million/100 gm body wt, 5 hrs or moderate PE (2.0 million/100 gm body wt, 5 hrs). PVR was measured before and after APhT. According to RHC data mean SPAP was 76.8±11.5 mmHg, pulmonary vascular resistance: 539±250 dynes/sec/cm5 and a10 healthy controls were included. Plasma levels of TNC were measured by enzyme-linked immunosorbent assay (ELISA).

Results: BAY 41-8543 significantly improved all three indices of RV function: (Control 10.6±0.4 mmHg/mil/min). Moderate PE caused a significant decrease in RV peak systolic pressure (PSP) (39±11 mmHg vs. 19±3.3 PE, -dP/dt [1192±433 mmHg/sec vs. 444±64] and -dP/dt [576±60 mmHg/sec vs. 278±80]). BAY 41-8543 significantly improved all three indices of RV function (PSP 35±3, -dP/dt 1128±100, -dP/dt -568±87). Severe PE caused significant RV dysfunction (PSP 256±2, -dP/dt 369±29) and BAY 41-8543 protected RV function (PSP 34±2, -dP/dt -535±4).

Conclusions: BAY 41-8543 protects RV function in experimental PE. RV dysfunction is a poor prognostic marker in PE patients. Further studies are necessary to determine if BAY 41-8543 can improve RV function in clinical PE patients.

P3915

Fluorescence activated cell sorting for simultaneous assessment of nine surface markers of circulating endothelial progenitor cells in pulmonary hypertension
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Background: The role of circulating endothelial progenitor cells (EPCs) in pulmonary hypertension (PH) is unknown. In this pilot study we established a nine-colour staining assay for the Fluorescent Activated Cell Sorting (FACS) to characterize the circulating EPCs in PH patients as compared to healthy controls.

Methods: Peripheral and central venous blood was taken from PH patients from the left innominate vein. The patients were classified as PH patients with idiopathic PH (iPH), CTEPH, or PH due to connective tissue disease. FACS analysis was performed on 20 PH patients and 20 healthy controls.

Results: N=10 PH patients (n=1 iPH, n=3 chronic thromboembolic, n=3 left heart disease, n=3 idiopathic) and mean pulmonary artery pressure: 42±14 mmHg, pulmonary vascular resistance: 539±250 dynes/sec/cm5 and a10 healthy controls were included. Plasma levels of TNC were measured by enzyme-linked immunosorbent assay (ELISA).

Conclusion: These preliminary results suggest that multi-colour FACS is suitable for EPC quantification and characterization. Further studies are necessary to define distinct circulating EPCs as markers of PH.

P3916

Assessment of tissue velocity imaging of both ventricles in vasoreactive patients
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The purpose: To estimate dynamics of right and left ventricular systolic and diastolic function by estimation Sa, of the lateral tricuspid and mitral valve annulus during acute pharmacological testing (APIT) with inhaled nitric oxide (iNO) in patients with idiopathic pulmonary arterial hypertension (iPAH).

Materials and methods: In the study we included 11 pts (11 females) with iPAH aged 31-51 (mean 39,8±7,4 years). All pts were performed right heart catheterization (RHC) with APIT and noninvasive vasodilator testing with iNO (20ppm for 10 min) before two hours to RHC. The estimation of SPAP was performed initially at rest and then at 10 min of nitric oxide Inhalation. All pts were responders. Echo included routine parameters and TVI was used for the estimation of systolic and diastolic function of RV/LV before and after APIT.

Results: In pts with iPAH (functional class II-III, WHO) the mean value of tricuspid regurgitation (TR) gradient was 64.8±11.5mmHg. In all pts included in the study the degree of TR was at least III. Taking into account right atrial pressure levels mean SPAP was 75±11.6mmHg by Transthoracic Doppler Echocardiography (TDEcho.) before APIT. Mean SPAP was 47.5±6.2mmHg, by echo APIT. According to RHC data mean SPAP was 76,8±16,6mmHg before test and 46,6±7,9mmHg after iNO. We found no significant dynamic of routine echo parameters. To 10’ of iNO there was significant improvement Sa. Eo of RV during APIT with iNO. There was improvement Sa, Eo of LV but not significant.

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Conclusion: TDEcho may be used for an accurate assessment of vasodilator response as compared to RHC data. During APht with INO only Sa, Eo of RV may be used for detecting vasoreactive patients.

P3917

Subtle assessment of quality of life in PH patients on inhaled iloprost treatment

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Background: Pulmonary hypertension (PH) is a disease characterized by vasoconstriction, remodeling of the small pulmonary vessels, and a lack of endogenous prostacyclin. Prostacyclin and its analogues are potent vasodilators and widely used in PH treatment. Information on the quality of life of PH patients is limited.

Methods: 24 patients who suffer from different forms of PH and receive inhaled iloprost, either as first line or as add-on therapy, are followed. Patients received questionnaires concerning multiple aspects of their quality of life. NYHA function, Borg dyspnea score (BDS) and heart rate increase during the test (6MWD), results of the right-heart catheterization, and biomarker levels were recorded at the moment of baseline and follow-up (Nov. 2007 - Feb. 2009).

Results: 76% of patients described an improved state of health compared with the situation before start of inhalation. Furthermore significant correlations between qualities of life and other important measures of PH could be shown. Improvements of NYHA-class, 6MWD, laboratory values (uric acid, BNP) and also of hemodynamic measurements (i.e. mPAP, PVR, CO, CI) during inhalative therapy with iloprost were detected. 6MWD improved significantly from 314.2±128.8 m to 354.4±131.0 m (p<0.001). 11 patients (23%) could improve their NYHA-class, 32 (66.6%) stayed unchanged and 5 (10.4%) deteriorated. These differences between baseline and follow up are significant (p<0.001).

Conclusion: Quality of life is an important measure for PH patients. Improvement in quality of life correlated very well with other important measures of PH.

P3918

The clinical relevance of heart rate increase in the interpretation of six-minute walk test in pulmonary hypertension

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Background: Six-minute walk test (6MWT) is an important prognostic marker in pulmonary hypertension (PH). We hypothesized that clinical improvement might not only be characterized by an increased walk distance but also by changes in Borg dyspnea score (BDS) and heart rate.

Patients and methods: Patients with PH and subjects without PH but with an abnormal exercise-induced pulmonary arterial pressure (PAP) increase were included. Each patient performed a 6MWT with "normal", "less than normal" and "more than normal" effort.

Results: 23 patients with PH (n=11 pulmonary arterial hypertension, n=10 chronic thromboembolic PH, n=2 other; mean PAP: 40±12mmHg) and 6 subjects with abnormal exercise-induced PAP increase (resting mean PAP: 16±5mmHg) participated. 6MWT were 482±89, 447±60 and 402±82m in the walks with "more than normal", "normal" and "less than normal" effort respectively. The respective BDS and heart rate increase was 3.2±1.5, 2.0±1.2 and 0.7±0.9, and 38±16, 31±14 and 23±14 min1 (3.0±1.4, 2.0±1.3 and 0.8±0.9, and 40±16 vs 34±13 vs 23±15 min1 in PH patients). The difference in walk distance between "less than normal" and "more than normal" tests was 342±84 m (p<0.001). The respective BDS and heart rate increase was 3.2±1.5, 2.0±1.2 and 0.7±0.9, and 38±16, 31±14 and 23±14 min1 (3.0±1.4, 2.0±1.3 and 0.8±0.9, and 40±16 vs 34±13 vs 23±15 min1 in PH patients). The difference in walk distance between "less than normal" and "more than normal" tests was 342±84 m (p<0.001). "Less than normal" BDS and heart rate increase was associated with the difference in heart rate increase during the test (p=0.001, r=0.61 in all subjects; p=0.001, r=0.76 in PH patients). On average, an 80m increase in 6MWT was associated with an additional 15 mm Hg heart rate increase. Between the BDS and 6MWT there was no significant correlation.

Conclusion: Based on our pilot study, heart rate may be suitable to assess the effort level of subjects and may be incorporated to refine 6MWT in the follow-up of PH patients.

P3919

Wrist actigraphy predicts outcome in patients with pulmonary hypertension

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Rationale: Pulmonary hypertension (PH) impair quality of life, exercise and survival. Simple measures to monitor the disease are needed. We tested whether actigraphy by a wrist-worn device in the patients home reflects disease severity in PH patients.

Methods: We studied 23 outpatients with precapillary PH (15 females) in WHO functional classes II-IV. Evaluations comprised clinical examination and actigraphy during 2 weeks while patients pursued their usual life at home. Actigraphies were correlated with clinical data and mean pulmonary arterial pressure (mPAP). Death, lung transplantations and pulmonary endarterectomy were recorded during 4 years.

Results: Actigraphies revealed a mean±SD day-time with activity of 14.5±7.1±14 hours, activity counts were 146±125±4. Very severely impaired patients (mPAP 501±79±59 mHz) rested more time immobile during nights (8.2±5±1±18h) and were less active during days (544±44±counts/mm) compared to modestly impaired patients (mPAP 33±7±7±mmHg; night-time immobile 6:58±0:39h; day-time activity 229±1±48±counts/mm, P<0.05 all instances). Of 19 patients followed for 4 years, 5 died, 1 underwent lung transplantation. Kaplan-Meier analysis revealed a shorter survival without lung transplantation in patients being active for less than 15h per day compared to patients with more than 15h of activity per day (log-rank 131.0 m (p<0.001). 11 patients (23%) could improve their NYHA-class, 32 (66.6%) stayed unchanged and 5 (10.4%) deteriorated. These differences between baseline and follow-up are significant (p<0.001).

Conclusion: A long nocturnal rest and reduced day-time activity recorded by actigraphy are associated with severe hemodynamic impairment and reduced survival in patients with PH. Therefore, wrist actigraphy performed during everyday life in the patient’s home holds promise as a simple tool for assessment of disease severity and prognosis in patients with PH.

P3920

Central venous-to-arterial carbon dioxide difference (CO2 GAP) in patients with arterial pulmonary hypertension: A pilot study

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Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance that can lead to right failure and death. Right ventricular (RV) function is a major determinant of functional capacity and prognosis in PAH, with a reduced survival in patients with decreased cardiac index. Several studies have already shown that venous-to-arterial CO2 difference (CO2 GAP = PaCO2 minus PACO2) is inversely correlated to cardiac index (CI) in septic and non-septic circulatory failure.

Objectives: To analyze the value of the CO2 GAP in PAH patients and its relationship with the cardiac index.

Methods: The right heart catheterization was performed using the Seldinger technique with a 2Fr sheath inserted via the basilica vein. Cardiac output was measured using the thermodilution technique.

Results: We analyzed 26 patients with PAH (80% women and 20% men). 86% were classified as WHO group 1 (34% had idiopathic PAH) and 7% were WHO group 4 (chronic thromboembolic pulmonary hypertension). Most patients were in NYHA functional class II (50%) and the mean 6-min walk distance was 451 meters. At the time of enrollment, 78% were treated with pulmonary vasodilators (39% sildenafil alone and 39% sildenafil + bosentan). CI, CO2 GAP and central venous oxygen saturation (ScvO2) were compared by Pearson correlation. We found a negative correlation between CI and CO2 GAP (R square 0.15 and p: 0.04) and a positive correlation between CI and venous oxygen saturation (R square 0.81 and p: 0.0002).

Conclusion: In PAH patients, the CO2 GAP may be a useful tool to analyze right ventricular function. Future research should analyze its value in the prognosis of PAH patients.

P3921

Psychometric validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients

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Background: The Living with Pulmonary Hypertension questionnaire (LPH) was adapted from the Minnesota Living with Heart Failure Questionnaire for use in patients with pulmonary arterial hypertension (PAH). Objectives: To confirm the structure, assess the psychometric properties and provide guidance for the interpretation of the LPH. Methods: LPH was given at baseline and last visit (week 12) to patients with PAH as part of a double blind, Phase III, clinical trial; this data was used to perform the LPH validation analyses: description of items, scores and quality of completion, construct validity, reliability, clinical validity and responsiveness. Analyses to provide an estimation of the Minimal Important Difference (MID) for the LPH scores were performed.

Results: The LPH Emotional and Physical scores met the criteria for convergent and discriminant validity; for the total score all but two items met the test for item convergent validity. Internal consistency reliability of the LPH scores was demonstrated by Cronbach’s alpha values of >0.70 for all LPH scores. The LPH Physical and Total scores discriminated between World Health Organisation (WHO) Functional classes and 6 Minute walking tests, indicating clinical validity and were also responsive to change in clinical severity, as measured by change in WHO functional class and Borg CR 10 Scale. Further investigation is required to confirm the responsiveness of the Emotional score. Estimation of MID using distribution-based methods indicated a change of 3 points for the sub-scales and 7 for the total score to be clinically meaningful.

Conclusion: The LPH is a valid and reliable instrument.
hypertension – The most relevant differences between survivors and non-survivors in three-years observation study

Introduction: The impact of modern treatments of pulmonary arterial hypertension (PAH) on pulmonary vascular pathology remains unknown. The last series reporting the pathology of severe pulmonary hypertension date back two decades, well before usage of current therapies (e.g. sildenafil).

Methods: Analysis of pulmonary vascular remodelling and inflammation in 62 PAH and 28 control explanted lungs systematically sampled, with matched clinical pathological data. The tissue was obtained by the Pulmonary Hypertension Breakthrough Initiative.

Results: Total wall, intima, and media fractional thicknesses of pulmonary arteries were increased in the PAH group versus the controls, and correlated with pulmonary hemodynamics. Despite a high variability of morphological measurements within a given PAH lung and among all PAH lungs, pathological subphenotypes were detected in cohorts of PAH lungs. This included a subset of lungs lacking intima or media remodeling, which had similar numbers of profiles of plexiform lesions, as seen in lungs with more pronounced remodeling. Perivascular inflammation was present in a high number of PAH lungs and correlated with mean pulmonary arterial pressure (mPAP) as well as intima and total wall thickness. The number of profiles of plexiform lesions was significantly lower in lungs of patients who were never treated with prostacyclin or its analogues.

Conclusions: Our results indicate that multiple features of pulmonary vascular remodeling exist in patients treated with modern PAH regimens. Perivascular inflammation may have an important role in the processes of vascular remodeling, all of which may ultimately lead to increased pulmonary artery pressure.

P3923 The proANP increase during exercise may predict the PAP increase in connective tissue disease patients at risk of PAH

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The proANP increase during exercise may predict the PAP increase in connective tissue disease patients at risk of PAH.

Patients and methods: We investigated plasma levels of proANP and NTproBNP stage of pulmonary vascular disease and may be clinically relevant.

Conclusions: Three-year survivors comparing to non-survivors had significantly higher DICO% pred. and less disturbances of gas distribution expressed as TLC-VA. Nevertheless only DICO% pred. was an independent prognostic variable.

P3925 Acquistion of echo-Doppler parameters of pulmonary hypertension in COPD

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Background: Pulmonary hypertension in COPD is of key prognostic significance. Doppler echo in the presence of TR can estimate RVSP/PAP. Acquisition rates and TR jet quality are reduced in COPD and hyperinflation. TR jet quality influences pressure estimation accuracy. An alternative assessment for PH is the time to peak pulmonary flow velocity, pulmonary acceleration time(ACT). An ACT <105 ms suggests PH. We examined the availability/quality of TR jet vs. pulmonary flow waves (FW) in COPD.

Methods: COPD patients were invited for echo and PFTs. Availability/quality of TR jet and FWs were assessed. RVSP was calculated from the max. TR velocity. RVSP=10 mmHg. ACT was a 3 measurement avg. using pulse wave Doppler placed in the right ventricular outflow tract.

Results: A total of 63 patients were screened, 63% male. Mean age 67.8 years (SD 11.5), FEV1 (%pred.) 64.7 vs 48.4 (p=0.01), FEV1/VC – 0.77 vs 0.69 (p=0.03), VC (%pred.) 84.7 vs 62.7 (p<0.05), TLC-VA (ml) – 660 vs 1470 (p=0.001), TLC-V/A. 58.5 vs 82.0 (p=0.01). TR was detected in 43 patients(68%) where TR jet was sufficient for RVSP measurement in 28(44% of total cohort). TR jet quality was poor, fair, good and excellent in 17,10,12, and 4 subjects respectively. Mean RVSP 43 mmHg, 95% CI[39-47]. ACT was measurable in 61 patients(97%) with good or excellent quality FWs in 58 (95%). Mean ACT 113 ms, 95% CI[108-118]; mean mAP 25 mmHg, 95% CI[23-28]. Subcostal vs. parasternal acquisition of ACT resulted in superior availability and quality in 80% of patients.

Conclusion: Contrasting RVSP, ACT is available in almost all COPD patients. TR jet quality is commonly poor whereas that of FWs is frequently excellent due to the ease of subcostal acquisition. These findings suggest that in addition to RVSP, ACT should be measured routinely when assessing COPD patients for PH.

P3926 Telemetric right ventricular pressure measurements and serial echocardiography in experimental pulmonary arterial hypertension

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This study characterized hemodynamic changes in the Sugen-Hypoxia (SuHx) model by telemetric acquisition and echocardiography. The SuHx rat model is based on the combined exposure to the VILEG-receptor inhibitor SU5416 and hypoxia and is used in Pulmonary Arterial Hypertension (PAH) research due its histological features resembling the plexogenic pulmonary vascular remodeling seen in human PAH.

SU5416 (25 mg/kg s.c.) was administered and animals were housed at 10% oxygen for 4 weeks, followed by re-exposure to normoxic conditions. Telemetric right ventricular pressure acquisition was continuous from surgery onwards. Serial echocardiography was performed weekly under anesthetic conditions. Speckle tracking and speckle strain correlations were calculated between echocardiographic parameters and telemetric RVSP.

Telemetric RVSP increased immediately after administration of SU5416 and exposure to hypoxia. In the consecutive re-exposure to normoxic conditions, a considerable interindividual variability was observed. Echocardiographic parameters were similar to those in the first exposure to hypoxia. The correlation between echocardiographic parameters and telemetric RVSP was higher in the second exposure to hypoxia. The model might be useful for the study of PAH and the evaluation of new treatment strategies.
differences were less pronounced. RVEDD, but not PAAAT/c and TAPSE was significantly correlated to RVSP.

Telemetry and echocardiography both show a progressive response in the hypoxic period. Individual variability among animals resulted in different RVSP responses upon re-exposure to normoxic conditions. RVEDD correlated significantly with RVSP, whereas TAPSE and PAAAT/c seemed not suitable as surrogate markers for RVSP.

P3927 Correlation of computed tomography measurement of small pulmonary vessels with hemodynamic factors in pulmonary arterial hypertension

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Background: Previous studies have shown that the percentage of total cross-sectional area of small pulmonary vessels (CSA) for the lung area assessed on computed tomography (CT) is significantly correlated to pulmonary arterial hypertension (PAH).

Purpose: We aimed to study correlation of the percentage of CSA less than 5 mm² (%CSA<5) with hemodynamic factors in patients with pulmonary arterial hypertension (PAH).

Materials and methods: 14 subjects (5 male, 53±12 yrs) with PAH underwent noncontrast CT scan and right heart catheterization (RHC). Three CT slices were selected from noncontrast CT images. The upper cranial slice was taken approximately 1 cm above the upper margin of the aortic arch, the middle slice was taken approximately 1 cm below the baria, and the lower cranial slice was taken approximately 3 cm below the right inferior pulmonary vein. We measured CSA less than 5 mm² and lung area from each images, and calculated the percentage of total CSA for the lung area (%CSA<5). The correlation of %CSA<5 and hemodynamic data obtained by RHC were evaluated.

Results: %CSA<5 was 11.2±6.26%. mean pulmonary arterial pressure (mPAP), systolic pulmonary arterial pressure (sPAP), and pulmonary vascular resistance (PVR) were 41.0±15 mmHg, 65.27 mmHg and 53.6±332 dyn cm⁻², respectively. The correlation coefficient of %CSA<5 with sPAP, mPAP and PVR were -0.60 (P=0.02), -0.59 (P=0.03) and -0.60 (P=0.02), respectively.

Conclusions: %CSA<5 measured on CT images significantly correlate with sPAP, mPAP and PVR in subject with PAH.

P3928 Does lung function predict response to therapy in PAH associated with connective tissue disease?

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Introduction: PAH specific therapies have been trialed in several lung diseases without success. It has also been shown that a low FVC is associated with a poor prognosis in CTD-PAH.

Methods: From the Royal Free Hospital pulmonary hypertension associated with connective tissue disease database we identified patients with lung function tests within 6 months of right heart catheterisation performed to confirm pulmonary hypertension. Patients who had repeat haemodynamic studies within a year of diagnosis on first line therapy (bosentan) were included.

Results: There were no significant haemodynamic differences between groups at baseline (ANOVA). Follow up catheter studies demonstrated a good haemodynamic response with improvements in mean PA pressure (FVC < 45%) and pulmonary vascular resistance (FVC > 70%).

P3930 Histopathology of idiopathic pulmonary arterial hypertension in patients with low or normal diffusion capacity

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Introduction: In patients with Idiopathic Pulmonary Arterial Hypertension (IPAH) a wide range of diffusion capacity for carbon monoxide (DLCO) values can be observed. Low DLCO in IPAH is associated with worse prognosis when compared to normal DLCO.

Hypothesis: Histopathological pattern(s) of pulmonary vasculopathy in IPAH differ between patients with low and normal DLCO.

Methods: We retrospectively analyzed the histopathological (combinations of) patterns of vasculopathy in IPAH patients with low and normal DLCO. Low DLCO was defined as lowest tertile of the bimodal distribution of DLCO-value in a series of 170 IPAH patients* (<45% pred.). DLCO in the upper 2 tertiles (>45% pred.) was defined as normal DLCO.

Results: Out of 170 IPAH patients, complete data sets were obtained in 20 patients: low DLCO N=10; normal DLCO N=10. Results are shown in table 1 (study is ongoing).

Table 1. Histopathology

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Low DLCO (N=10)</th>
<th>Normal DLCO (N=10)</th>
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<tbody>
<tr>
<td>Lung biopsies</td>
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<td>7</td>
</tr>
<tr>
<td>MCT</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Autopsy</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Pulmonary vasculopathy</td>
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<td>2</td>
</tr>
<tr>
<td>Hypoxic arteriopathy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PVOD*/PCH** pattern</td>
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<td>1</td>
</tr>
<tr>
<td>Congenital vasculopathy</td>
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<td>1</td>
</tr>
<tr>
<td>No specific pattern</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Pulmonary Veno-Occulsive Disease, **Pulmonary Capillary Haemangiomatosis.

Conclusion: A PVOD*/PCH-like pattern is more common in IPAH with low DLCO, while plexogenic arteriopathy prevails in IPAH with normal DLCO.

Reference: [1] Trpp et al. abstract this meeting.
Conclusions:
Iron deficiency is more prevalent in SSc-PAH than in SSc patients (ID vs SSc-PAH without ID, p<0.001) while circulating iron, ferritin and transferrin were higher than in SSc (p<0.001), hepcidin in both groups.

Methods:
One year changes in cardiopulmonary exercise test variables and six minute walking distance (6MWD) were related to survival using Univariate Cox regression and Kaplan-Meier analysis in 40 PAH patients (mean age 44±2 yrs).

Results:
After a mean follow up time of 81 (±5) months, two patients were scheduled for lung transplantation and 10 had died. Survival analysis showed that from all exercise variables only one-year changes in maximal oxygen uptake (VO2), VO2/heart rate (O2pulse) and 6MWD were significant predictors of survival. Kaplan-Meier analysis (with ideal cut-off points estimated by receiver operating analysis) showed that patients with > 5% increase in VO2 or O2pulse had a significantly better cumulative survival (78±12% and 78±10%, respectively) compared to patients with < 5% increase in VO2 or O2pulse (cumulative survival 40±13% and 27±20%, respectively). Patients with < 6% decrease in 6MWD had a significantly better cumulative survival (84±7%) compared to patients with > 6% decrease in 6MWD (cumulative survival 25±15%).

Conclusion:
Changes in VO2, O2pulse and 6MWD from baseline to one year of follow up predict survival in PAH. Consequently, these variables could be considered to guide treatment in PAH patients.

Iron deficiency in patients with systemic sclerosis-associated pulmonary arterial hypertension

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Background:
Systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) has a poor clinical outcome compared to other types of PAH. Recent data has shown that iron deficiency (ID) is associated with poor survival in idiopathic PAH. Inflammatory cytokines and increased hepcidin levels play a role. We hypothesise that a high prevalence of ID in SSc-PAH is linked to poor clinical outcome.

Methods:
Measures of iron status were performed retrospectively in serum from SSc-PAH patients (n=49) and systemic sclerotic patients without PAH (SSc, n=131). Six minute walking distance (6MWD) was also compared between the groups.

Results:
Circulating soluble transferrin receptor (sTfR) levels in SSc-PAH patients were higher than in SSc (p<0.001) while circulating iron, ferritin and transferrin saturation were reduced. The prevalence of ID, defined by sTfR >28.1 nmol/L, was 47% in SSc-PAH compared to 20% in SSc (p<0.001). Although hepcidin levels were lower in SSc-PAH than in SSc patients (p<0.001), hepcidin in both groups were high compared to reference values. There was no significant correlation with interleukin-6 (IL-6) levels (p=0.82), since IL-6 was higher in SSc-PAH compared to SSc patients (p<0.01). 6MWD was lower in SSc-PAH compared to SSc patients (p<0.001) and was even more reduced in case of ID (SSc-PAH with ID vs SSc-PAH without ID, p<0.05).

Conclusions:
Iron deficiency is more prevalent in SSc-PAH than in SSc patients and is associated with lower exercise capacity. The role of hepcidin in this process remains to be elucidated.
404. Epidemiology of asthma

P3936 Asthma and asthma-like symptoms in Greece. The Greece asthma national prevalence survey Eleftherios Zervas1, Stelios Loukides2, Konstantinos Kositskas2, Petros Bakkaoun3, Efthimis Tziratzakis1, Mina Gagua4, on behalf of Asthma Working Group of Hellenic Thoracic Society. 17th Respiratory Medicine Dept and Asthma Center, Athens Chest Hospital, Athens, Greece; 22nd Respiratory Medicine Dept, University of Athens Medical School, Attikon Hospital, Athens, Greece; 3Respiratory Medicine Dept, University of Athens Medical School, Athens Chest Hospital, Athens, Greece; 4Respiratory Medicine Dept, University of Crete Medical School, University Hospital, Heraklion, Greece

Background: Asthma is a major health problem world-wide. Prevalence surveys of asthma provide valid information and help design national programs of health care services. Recent were data missing from Greece.

Objectives: To study the prevalence of asthma and associated symptoms in the adult population of Greece.

Methods: A nation-wide, cross-sectional, community-based survey of asthma and asthma-like symptoms was conducted, using a pre-tested structured questionnaire based on the ECRHS Questionnaire for adults. A stratified random sampling method was used to select 2,191 participants, aged > 18 years old. Data was collected with face-to-face interviews.

Results: The self-reported current prevalence of physician-diagnosed asthma and asthma-like symptoms were as follows: physician-diagnosed asthma 9%, asthma attack 2.3%, use of asthma medication 3.7%, awakening from shortness of breath 22.3%, awakening from cough 24.1%, wheezing 19% and nasal allergies 23.3%. The incidence of asthma was calculated as 16 new cases per thousand people. Smoking prevalence was high both in the general population and in asthmatics (39.2% and 36.4%, respectively). Asthma prevalence was higher in Athens (10.9%), while there was no difference between rural and urban areas (8.5% and 7.8%, respectively).

Conclusions: The prevalence of asthma and associated symptoms in Greece is high, presenting a substantial increase from the last survey conducted 20 years ago. The results of this survey highlight the increasing social burden and impact of asthma in Greece and may aid policy makers and healthcare providers to plan effective health strategies for the proper diagnosis and management of this disease.

P3937 Assessment of the prevalence of bronchial asthma among the population in Yaroslavl from 1999 to 2010 and analysis of financial resources for the free-drugs from the funds of municipal budget in 2000-2010 Shamil Palvurtin1, Ilya Zilber2, Alexander Petrochenko1. 1Department of Clinical Pharmacology, Yaroslavl State Medical Academy, Yaroslavl, Russian Federation; 2Department of Pulmonology, Clinical Hospital n.a. N.V.Solovyev, Yaroslavl, Russian Federation

Objective: To evaluate the prevalence of bronchial asthma (BA) in Yaroslavl from 1999 to 2010 and analysis of financial resources for the free-drugs from the funds of municipal budget in 2000-2010.

Methods: A prospective cohort study; the data of the healthcare department.

Results: In 1999, patients with BA in Yaroslavl was 4053 man. In 2010 number of spirometry, unification of approaches to diagnosing of BA and education for doctors. Recent were data missing from Yaroslavl.

Implementation of standards and increased diagnostic capacity of healthcare made it possible to reveal a large number of patients with BA in the late 90-ies and in the beginning of 2000-ies. Due to great social significance of BA there was a steady tendency to increase the expenses on of free-drugs during the ten-year period.

P3938 Prevalence of asthma and asthma symptoms in a nationally-representative sample of adults in England Matt Kearney1, Jenny Mindell2, Rachel Craig3, Julia Hall4, Joanne Clarke1, Bronwen Thompson1, Anne Moger1, Kevin Holton1, Robert Winter4, Sue Hill1. 1Department of Health, Medical Directorate, London, United Kingdom; 2Department of Epidemiology & Public Health, University College London, United Kingdom; 3NatCen Social Research, NatCen Social Research, London, United Kingdom; 4Cambridge University Health Partners, Addenbrooke’s Hospital, Cambridge, United Kingdom

Introduction: Asthma imposes a major burden on the NHS and individuals, with high numbers of emergency department attendance, hospital admission and days lost from work. Although the goal of asthma treatment is for patients to be symptom-free and able to lead a normal active life, evidence suggests that there is a wide variation in quality of care and outcomes.

Aims: To estimate the prevalence of asthma and level of symptom control in the population of England.

Methods: The annual Health Survey of England is a cross-sectional study of a random, nationally representative sample of 8,000 adults. It includes detailed interviews and objective measures by nurses. The 2010 survey examined lung health awareness, earlier diagnosis and proactive disease management.

Results: The prevalence of lifetime doctor-diagnosed asthma was 16% in men and 17% in women: of these 30% of men and 39% of women had experienced an asthma attack in the last year. 9% of men and 10% of women had current asthma (i.e. symptoms or medication in the last 12 months): in the last week around half of these reported daytime symptoms, a quarter symptoms that interfered with usual activities, and a quarter difficulties with sleep. Over half those with current asthma used beta-agonist inhalers every day, suggesting inadequate management and poor symptom control.

Conclusion: This large population survey confirms that current symptomatic asthma is common and that many people with asthma have poor disease control with frequent symptoms that interfere with normal life. To tackle this, a national Outcomes Strategy for COPD and Asthma in England has been launched to promote lung health awareness, earlier diagnosis and proactive disease management.
Subjects with both the diagnoses of asthma and COPD represent a relevant clinical population with more severe and frequent exacerbations.

P3940
The prevalence of asthma symptoms in middle aged Australian adults
Michael Armstrong1, Michael Valente1, Minh Thi Hong Le1, Su Wei Khung1, Erik P. Rönmark2, Anders Bjerg3, Anders Bjerg4, Lucio Casali2, Maria Grazia Panico1, Pietro Pirritano1, Maria Grazia Panico5, Pietro Pirritano6, Caterina Bucca7, Giuseppe Verlato1, Marcella Ferrari1, Roberto de Marco1, Eva Rommark2, Kjell Toren3, Bo Lundback4, Jayanthi Natarajan9, Giselle Björkman6, Michael Valente3, Ming Zhe Liu1, Michael Valente1, Min Tho Hong Le1, Su Wei Khung1, Geza Benke1, Shi Yamali Dharmage1, Bruce Thompson1, 1School of Public Health & Preventive Medicine, Monash University, Melbourne, VIC, Australia; 2Centre of Molecular Environmental & Genetic Analysis, University of Melbourne, Parkville, VIC, Australia; 3Allergy, Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, VIC, Australia

Introduction: ISAAC and the European Community Respiratory Health Survey (ECRHS) have shown that the prevalence of asthma in children and young adults is higher in Australia than many other Western countries.

Aim: To describe changes in respiratory symptom prevalence in adults as they age.

Methods: We followed up a cohort of young adults from South Eastern Melbourne initially recruited for ECRHS in 1992. A validated postal questionnaire was sent to 726 surviving participants. After 1 month, non-respondents were sent a second survey. The survey is still on going.

Results: Of the first 166 questionnaires received to date, 73 (44%) were from males and the mean (SD) age was 55 (5.7) years. The prevalences (95%CI) of respiratory symptoms and diseases are:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing in the last 12 months</td>
<td>25.5</td>
</tr>
<tr>
<td>Breathlessness with wheezing</td>
<td>12.0</td>
</tr>
<tr>
<td>Wheezing without a cold</td>
<td>13.9</td>
</tr>
<tr>
<td>Woken with chest tightness in the last 12 months</td>
<td>15.7</td>
</tr>
<tr>
<td>Woken with shortness of breath (SOB) in the last 12 months</td>
<td>9.6</td>
</tr>
<tr>
<td>Woken with cough in the last 12 months</td>
<td>35.5</td>
</tr>
<tr>
<td>Asthma attack in the last 12 months</td>
<td>10.8</td>
</tr>
<tr>
<td>Medication for asthma</td>
<td>13.3</td>
</tr>
<tr>
<td>Nasal allergies including hayfever</td>
<td>43.4</td>
</tr>
<tr>
<td>SOB at rest in the last 12 months</td>
<td>10.8</td>
</tr>
<tr>
<td>SOB after strenuous activity in the last 12 months</td>
<td>22.9</td>
</tr>
<tr>
<td>Ever had asthma</td>
<td>29.5</td>
</tr>
<tr>
<td>Cough on most days for 3 months a year</td>
<td>11.4</td>
</tr>
<tr>
<td>Pneumonia for 3 months a year (chronic bronchitis)</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Conclusions: The prevalences of respiratory symptoms and asthma are broadly consistent with previous surveys of this age group. The prevalence of symptoms and diseases is significantly higher in females than in males. The prevalence of asthma increases with age. The results of this study are similar to those of the International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS). The results of this study are similar to those of the International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS).

Funding: NHMRC of Australia.

P3941
Association between upper airway diseases and bronchial asthma
Leonardo Antonio1, Pierpaolo Marchetti1, Massimiliano Bugiani1, Lucio Casali1, Maria Grazia Panico1, Pietro Pirritano1, Virginia Ferrerio1, Caterina Bucca2, Giuseppe Verlato1, Marcella Ferrari1, Roberto de Marco1, Eva Rommark2, Kjell Toren3, Bo Lundback4, Jayanthi Natarajan9, Giselle Björkman6, Michael Valente3, Ming Zhe Liu1, Michael Valente1, Min Tho Hong Le1, Su Wei Khung1, Geza Benke1, Shi Yamali Dharmage1, Bruce Thompson1, 1School of Public Health & Preventive Medicine, Monash University, Melbourne, VIC, Australia; 2Centre of Molecular Environmental & Genetic Analysis, University of Melbourne, Parkville, VIC, Australia; 3Allergy, Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, VIC, Australia

Background: In contrast to studies of asthma and rhinitis, few studies among adults investigating the associations between asthma, rhinitis and eczema have been published. The objective of the study was to investigate these associations including the impact of chronic rhinosinusitis.

Methods: A large-scale postal questionnaire on asthma, rhinitis, respiratory symptoms and eczema, as well as possible risk factors was mailed to 30000 randomly selected subjects aged 16-75 years in Sweden. Current disease was defined as report disease in combination with current symptoms or medicine use.

Results: The prevalence of current asthma, current rhinitis and current eczema was 8.0, 20.7 and 11.5%, respectively. The prevalence of those having either current asthma, rhinitis or eczema was 31.3%. Either current asthma or rhinitis was reported by 24.5%, current asthma or eczema by 17.8%, and current eczema or rhinitis by 28.3%. All three conditions was reported by 1.7%. The overlap was greatest for current asthma and rhinitis, 4.4%, while it was 3.9% for current rhinitis and eczema and 1.7% for current asthma and eczema. Family histories of either asthma and/or allergy were the dominating risk factors for all three conditions. Generally all clinical and morbidity variables, including lung function, methacholine reactivity and positive skin prick tests, were most affected among those having all three conditions, particularly if they also had chronic rhinosinusitis.

Conclusion: About one third of the adult population of West Sweden have either current asthma, rhinitis or eczema, while only 1% had all three conditions. Thus, there is a considerable need for more severe and frequent exacerbations.

P3942
Greater risk of wheeze in young female compared to male smokers – Results from the Swedish GAZLEN survey
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Smoking has greater negative impacts on lung function and COPD risk in females. However, sex-related differences in smoking burden, body composition and exposure confound this association. We studied wheeze in relation to smoking and sex in a large well-characterised population.

In 2008 the GAZLEN questionnaire was mailed to 45000 Swedish adults (16-75 yrs), and 66% participated. Respiratory symptoms, smoking and other exposures were analysed by multivariate regression. Asthmatic wheeze: wheeze with breathlessness and without a cold.

Females reported more wheeze and asthma wheeze, 17.3% vs. 15.8% and 7.1% vs. 6.1%, all p<0.01. 39% of both sexes were ever-smokers, and more females were current smokers, 14.5% vs. 13.3%, p<0.01. Males had higher mean age, BMI and pack-years, all p<0.01. Twice as many males were exposed to gas, dust, fumes, and fewer had university education. Females had more traffic exposure and employment in healthcare and cleaning. Adjusted for all these factors, female current smokers aged 16-52 yrs had higher risk of wheeze and asthmatic wheeze, OR 1.28 vs. males (interaction p<0.04) and OR 1.52 (p<0.02). Each pack-year increased the risk of wheeze more in women, OR 1.01 (p<0.01). The interactions were independent of weight, height and age at smoking initiation, and less consistent in subjects aged >52 yrs.

The large, population-based study of female compared to male smokers had higher risk of wheeze after adjustment for important confounders. This increased susceptibility was greater in pre-menopausal ages, and was not explained by differences in body composition or smoking habits. This points toward biological, possibly hormonal, underlying mechanisms.
P3944 The association between metabolic factors and asthma in adolescents of southern Taiwan
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Background: The prevalence of asthma has increased distinctly over the last two decades. Amongst metabolic syndrome has also been observed. Few studies have discussed the relation between metabolic factors and asthma.

Objective: This study aimed to assess whether there is an association with asthma and metabolic factors.

Methods: The cross-sectional study randomly sampled 5783 subjects ≤ 18 years old from elementary, junior and senior high schools in southern Taiwan. There were 5754 eligible subjects in the ultimate analysis because they completed a questionnaire, anthropometric measurements and blood samples collection. Furthermore, we conducted a meta-analysis including 13 studies according to criteria to review the association with asthma, BMI, and total cholesterol (TC). We also found a significant association between asthma and abdominal fat (aOR=4.4, p=0.009) and high concentrations of cholesterol (aOR=1.9, p<0.001).

Conclusion: We did not measure high density cholesterol [HDLC] and low density cholesterol [LDLC]. Therefore, we cannot determine the relationship between disease and cholesterol was resulted from HDL or LDL. Asthma patients are more obese, have higher concentrations of cholesterol and more metabolic factors.

P3945 Incidence of asthma and wheeze among teenagers is associated with environmental risk factors
Linnea Hedman1, Martin Andersson1,2, Anders Bjerg1, Sigrid Sundberg1, Eva Ronmark1. 1The OLIN Studies, Norrbotten County Council, Luleå, Sweden; 2 Public Health and Clinical Medicine, Occupational and Environmental Health, Umeå University, Umeå, Sweden

Aim: To study the incidence of asthma and wheeze among teenagers in relation to environmental risk factors, including smoking.

Method: In a longitudinal study about asthma and allergic diseases within the Obstructive Lung Disease In Northern Sweden (OLIN) studies, a cohort of school children (n=3,430) was followed annually from age 7-8yrs by completion of an extended ISAAC questionnaire. Skin prick tests (SPT) were performed at age 12yrs. In the endpoint survey (age 18yrs) 2,861 (83% of original responders) participated. Risk factor analyses for the cumulative incidence of asthma and wheeze from age 12 to 18yrs were performed (mean follow-up time 6.5y).

Results: The cumulative incidence of physician-diagnosed asthma was 7.6%, current asthma 6.6%, and current wheeze 22.4%. Interestingly, increasing number of siblings was inversely related to the incidence of physician-diagnosed asthma, current asthma and current wheeze in multivariate analyses (OR 0.8-0.9). Current smoking was related to the incidence of asthma (OR 1.6) and current wheeze (OR 2.8). Ex-smoking (OR 2.5), living close to a road with heavy traffic (OR 1.3) and house dampness (OR 1.3), respectively, was significantly associated with the incidence of current wheeze. As expected, female sex, positive SPT, and parental history of asthma were also significant risk factors.

Conclusion: Beside the risk factors sex, positive SPT, and heredity of asthma, several environmental risk factors were found, including smoking, traffic exposure, and house dampness. Thus, the incidence of asthma and wheeze among teenagers could partly be reduced by smoking prevention and improvement of their living environment.

P3946 A longitudinal study of airway symptoms among local residents after a Norwegian air polluting oil tank explosion
Jens Tore Granslo1, Bjørn Eli Hollund1, Lygre Stein1, Magne Bråtveit2, Bente Elisabeth Meen1. 1The OLIN Studies, Northseth County Council, Luleå, Sweden; 2 Department of Public Health and Primary Health Care, University of Bergen, Norway

Background: In 2005 oil tanks containing mixtures of sulphuric hydrocarbons exploded and caught fire in a Norwegian industrial harbour. This study assesses airway symptoms in the nearby population approximately 1.5 and 3.5 years after the explosion.

Methods: The population was examined twice, 1.5 and 3.5 years after the explosion, including persons above 17 years. Persons living ≤5 km from the accident site were examined. The questionnaire comprised 200 persons living ≥20 km away. 317 persons answered a questionnaire including four questions with symptoms related to upper airways and eight related to lower airways.

Results: In the follow-up period “Cough with phlegm” among exposed males was significantly reduced from 43% to 28% (McNemar test p=0.015). In the control group 28% and 24% had cough with phlegm at these time points. Adjusted odds ratios between exposed and controls in the first and second examination were 2.1 (95% confidence interval 1.0, 4.5) and 1.7 (0.7, 2.9), respectively. “Daily cough” among exposed males were 46% and 35% in the first and second examination (McNemar test p=0.057), and 31% and 28% in the control group. Adjusted odds ratios were 2.7 (1.3, 5.8) and 1.5 (0.5, 3.6) when comparing exposed and controls in the first and second examination. There were no changes in prevalence of airway symptoms among females between 1.5 and 3.5 years after the accident.

Conclusion: The prevalence of some symptoms from the lower airways was reduced among exposed males in the follow up period after an oil tank explosion.

P3947 Weather variables and emergency hospital visits for adult asthma exacerbations in Malta
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Background: Asthma exacerbation requiring hospital treatment has been shown to exhibit seasonality in several studies

Objective: To analyse the relationship between weather conditions and hospital visits with asthma in Malta.

Methods: All Adults treated for asthma exacerbation in our accident & emergency department (ED) in 2010 were included retrospectively. Information on demographic variables was collected. Daily weather data including: temperature, barometric pressure, maximum % relative humidity, mean wind speed and precipitation; was obtained from the Meteorological office at Malta International Airport.

Results: 328 adults received treatment for asthma exacerbation at the ED in 2010; 53% required admission. 70.4% were females. A high incidence of ED visits was observed during November, December and January, with the lowest incidence recorded in June and July. A significant association was found between age and number of ED visits (p<0.005); with the most common being the 20-40 age group.

Conclusions: ED visits for asthma in Malta exhibit seasonality. These are associated with high mean wind speeds and high precipitation 1 and 2 days before presentation. These findings have important implications for developing an effective preventive strategy with increased vigilance during periods of increased risk.

P3948 Worrying smoking habits in young Swedish women
Goran Wennergren1, Linda Ekerljung2, Bernt Alm1, Jan Lottvall1. 1 Department of Paediatrics and Refferting Research Centre, University of Gothenburg, Sweden; 2 Krefting Research Centre, University of Gothenburg, Sweden

Background: Following 10 years of decreased smoking among young people in Sweden, we now have indications of a drastically increased smoking prevalence. The aim was to provide up-to-date information on the prevalence of smoking and smoke-associated respiratory symptoms in young adults in Sweden, with special focus on possible gender differences.

Methods: A large-scale, detailed postal questionnaire focusing on asthma and respiratory symptoms, as well as possible risk factors (the West Sweden Asthma study). The questionnaire was mailed to 30000 randomly selected subjects aged 16-75 years in Gothenburg and the surrounding region in western Sweden, response rate 62%. The analyses are based on responses from 2702 subjects aged 16-25 years (1154 men, 1548 women).

Results: Significantly more young women than men were active smokers (23.5% vs 15.9%; p<0.001). In addition, women started smoking earlier and smoked more cigarettes per day. Longstanding cough, sputum production, recurrent wheeze, any wheeze last year, dyspnoea, wheezing with breathlessness or without cold, waking with tight chest, nasal obstruction and rhinorrhoea were significantly more common in smokers compared with non-smokers.

Conclusion: The smokers to a great extent had smoking parents, while subjects with non-smoking parents in 75% were non-smokers. In the multivariate analysis, smoking increased the risk of symptoms, such as recurrent wheeze, OR 2.0 (95% CI 1.4-3.0) and sputum production, OR 2.4 (1.9-3.1).

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P3949 Worrying smoking habits in young Swedish women
Goran Wennergren1, Linda Ekerljung2, Bernt Alm1, Jan Lottvall1.
P3949
Social determinants of asthma: Results from UK household longitudinal study
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Background: Asthma is a prevalent respiratory disease, but its social determinants are not well investigated in detail.

Aims: It is aimed to explore social determinants of asthma in recent years.

Methods: Data were extracted from UK Household Longitudinal Study (2009-2010). Demographics, family background, migration history, and self-rated health were taken as aspects of social determinants. Deprivation at the regional level was included as well. Asthma was defined according to physician diagnosis by self-reporting. Regression models were performed and 95% confidence intervals were calculated.

Results: Associations among family background, migration history, self-rated health, and asthma were observed (p < 0.001). Higher asthma episodes were also found in the deprived areas (p < 0.001). These are consistent with demonstration of a positive association between lower SES and risk of wheezing in children and adolescents, both in high- and low/middle-income countries from previous studies. These are also related to other medical chronic problems such as high blood pressure and heart disease.

Conclusions: The association between social inequality and asthma prevalence is critised not being fully understood until the 21st century and called on for further investigation. This study has tried to answer this with a large national representative sample with complete household conditions. Some shared contributing factors will absolutely need further care to be eliminated across common non-communicable diseases when then next step is to communicate with policy makers to generate proper strategies on preventing asthma from childhood to adulthood with a lifetime approach.

P3950
Difficult to control asthma in the EGEA2 study
Sébastien Candelise, Christiane Piri, Christophe Pison1,2, Frédéric Gomord1, Jocelyne Jun1, Nicole Le Moual1,2, Raphaelle Varraso1,2, Jean Bouquet1,2, Francine Kauffmann1,2, Valérie Siroux,1 1Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health. National Institute of Health and Medical Research, U823, Albert Bonniot Institute, Joseph Fourier University, La Tronche, France; 2Pediatry, Grenoble University Hospital, La Tronche, France; 3Team of Respiratory and Environmental Epidemiology, Centre for Research in Epidemiology and Population Health (CESP), National Institute of Health and Medical Research, U1018, La Tronche, France; 4Team of Fundamental and Applied Bioenergetics, National Institute of Health and Medical Research, U1055, La Tronche, France; 5Pneumology, Grenoble University Hospital, La Tronche, France; 6Pneumology, Lyon University Hospital, Lyon, France; 7Pneumology, Trousseau Hospital, Paris, France; 8IFR69, Paris-Sud University, Villejuif, France; 9Pneumology, Montpellier University Hospital, Montpellier, France

Introduction: Many French asthmatics still have uncontrolled asthma which may result from inadequate or lack of compliance to treatment, or difficult to control asthma. The aim of this study was to compare phenotypic characteristics of the difficult asthma patients and well controlled patients.

Methods: The study was conducted in 406 asthmatics recruited in the EGEA study (Epidemiological study on the Genetics and Environment of Asthma) and was performed as a cross-sectional study in 2010. Demographics, family background, migration history, and self-rated health were collected. Regression models were performed and 95% confidence intervals were calculated.

Results: Among the 227 (56%) uncontrolled asthmatics (120 partly-controlled), 71 (31%) had a high level of treatment. Compared to uncontrolled asthmatics with low treatment, those with high treatment did not differ by sex and smoking, but were 10 years older (p < 0.001), had more often adult-onset asthma (46.5% vs 28.2%, p < 0.001), had lower FEV1/Spredicted (75.4±21.3 vs 87.7±19.3, p < 0.001) and reported more often regular medical visits in the last 12 months (72.9% vs 21.8%, p < 0.001), among whom 80.4% vs 64.7% with a respiratory specialist, p(0.03).

Conclusion: In the EGEA study, a majority of asthmatics was uncontrolled despite adequate treatment in one third of the subjects. In this cross-sectional analysis, uncontrolled asthmatics with high treatment had significantly lower FEV1 compared to those with low treatment. Further longitudinal analyses will be conducted to assess the long term effect of asthma treatment.

P3951
Prevalence of severe asthma in the hospital of Montes Claros - MG
Rodrigue Caldeira, Maíra Rodrigues, Medicine and Pneumology, Fanorte, Montes Claros, MG, Brazil Medicine, Fanorte, Montes Claros, MG, Brazil

Introduction: Asthma attacks can be triggered by respiratory infections, environmental pollutants, sudden temperature changes, among other factors, being directly related to an increased likelihood of hospitalization. Every year occurs 370,000 hospitalizations for asthma in Brazil and this is the fourth leading cause of hospitalization in the public health system.

Aims: To investigate the prevalence of severe asthma in hospitalized patients in the University Hospital in the city of Montes Claros - MG.

Methods: Descriptive and retrospective study. We have analyzed 111 medical records of patients admitted in the University Hospital from January 2008 to June 2011, due to the exacerbation of asthma. Through the use of a form, information have been collected from the medical records of 50 patients with severe asthma.

Results: The prevalence of severe asthma was 45%. Of the 50 patients with severe asthma, the average was 15 years, 60% were females, 52% had other hospitalizations due to asthma. 82% of the cases had asthma diagnosed before the admission. Of these, 44% of subjects were doing regular treatment and 31% used inhaled corticosteroids associated with bronchodilator. Regarding the hospitalization, the average of admission time was 4.6 days. Related to the climate was observed that most of the patients were admitted in the fall (40%) or in the winter (26%).

Conclusions: The study showed high prevalence of severe asthma and that there is an increase in primary care patients because of the frequency of asthma exacerbations hospitalizations. Moreover, few patients do regular treatment, which causes low life quality, absenteeism from school and work and risk of death.

P3952
Characteristics of the uncontrolled asthmatic patients on GINA step 4 treatment in Korea
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Although the majority of asthma patients can obtain the targeted level of control, some patients will not do so even with the best therapy. The aim of this study was to explore the clinical characteristics of the bronchial asthma patients who do not achieve the well-controlled status despite the step 4 treatment of the GINA guideline in Korea.

This study was a part of the clinical phenotype of asthma investigation in Korea which was performed using structure questionnaire during February 2011 - June 2011. Of the overall study subjects, we enrolled 112 patients from 5 teaching hospitals in Korea who were on GINA step 4 treatment at least 1 year. We defined the difficult-to-treat asthma as uncontrolled asthma status or at least 1 unscheduled visit during the prior year related to the treatment of the difficult asthma. We compared the demographic, clinical, and laboratory data between difficult-to-treat asthma patients and well controlled patients.

The difficult-to-asthma patients had lower the ratio of FEV1/FVC than well controlled asthma patients (66.8% vs 69.0%, p=0.008). The proportion of patients with experiencing the symptom aggravation in work/place was higher in difficult-to-treat group than well controlled group (33.3% vs 14.5%, p=0.03). However, the age, FEV1, smoking status and body-mass index were not different between the groups. The presence of co-morbidities such as COPD, reflux esophagitis and cardiovascular was not also different. In conclusion, a total 24.1% of asthma patients are not in well controlled status despite GINA step 4 treatment. Occupational history should be considered in these patients an addition to the known risk factors.

P3953
The number of asthma attacks reported by subjects with physician-diagnosed asthma in Italy has increased from 1998-2000 to 2007-2010. Preliminary results
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In Italy, the prevalence of current asthma increased during the last 10 years, but few information are available on the temporal change of asthma severity in the same period.

The present study is aimed at quantifying the temporal change in the number of asthma attacks as a proxy of asthma severity in the last 10 years in the Italian adult population with diagnosed current asthma.

The same screening questionnaire was administered to random samples of 20-44 year-old subjects from the general population in 4 Italian centres (Pavia, Sassari, Turin and Verona) in 1998-2000 (in the frame of the Italian Study on Asthma in Young Adults, ISAYA; response rate 76%) and in 2007-2010 (in the frame of the Gene Environment Interaction in Respiratory Diseases, GEIRD, study; response rate 53%). The number of asthma attacks was modelled by means of a negative binomial model, adjusting for centre, sex, age, drug use and design confounders.
Asthma in the Young Adults (ISAYA)

Asthma remission and longitudinal changes in control in the Italian Study on physician adherence to the prescribing guidelines. It needs to be clarified whether this increase in the mean number of asthma attacks in GEIRD with respect to ISAYA subjects with diagnosed current asthma had a 62% higher mean number of attacks (s.d. 10.1) in ISAYA and 4.4 (s.d. 13.2) in GEIRD. The adjusted relative change (95%CI:3.6;4.7%). The mean number of asthma attacks in the last year was 3.1 asthma attack in the last year increased from 2.8% (95%CI:2.5;3.2%) to 4.1% (95%CI:3.4;4.8) in 5 years.

Methods:
Aims and objectives: To evaluate and compare a comprehensive set of existing and novel regression-based estimators of parameters from the two-compartment model of exhaled nitric oxide. Since CaNO estimation is a key result of multiple flow FeNO estimates were highly correlated. We used simulated multiple flow datasets to assess the statistical properties of the estimators and multiple flow datasets from 1507 schoolchildren from the National Institute for Cancer Research (IST), Genova, Italy; 2Dept of Epidemiology, University of Verona, Italy; 3Dept of Public Health and Community Medicine, University of Verona, Italy; 405. Methodology in epidemiologic research

P3954
Asthma remission and longitudinal changes in control in the Italian Study on Asthma in the Young Adults (ISAYA)

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There is little information on asthma remission and longitudinal changes in control in the last decade. In the frame of the ISAYA, a random sample of 354 asthmatics identified between 1998 and 2000 in 6 Italian centres (Pavia, Torino, Verona, Pisa, Sassari, Sassuolo) was followed-up 10 years apart (response rate 60%). At follow-up, asthma was considered in remission if a subject did not report any asthma-like symptom or drug use in the last year. A modified version of the GINA classification of asthma control, based on the frequency of diurnal and nocturnal symptoms, daily life activity limitations, and rescue medication use, was used. One of the 210 subjects who participated in the follow-up, asthma had remitted in 61 (29%) subjects and was still present in 149 (71%). The likelihood of remission for subjects reporting asthma-like symptoms, attacks and asthma drug use at baseline was 70% for the same IDA in subjects who did not report them, as evaluated by means of a logistic model. Among non remitted subjects, 41 (28%) had controlled, 60 (41%) partially controlled and 46 (31%) uncontrolled asthma at baseline. Among 138 subjects with information at follow-up, 38 (28%) had controlled, 69 (50%) partially controlled and 31 (22%) uncontrolled asthma. At a multicomponent logistic model, women were more likely to have partially or uncontrolled asthma than men; increasing age, chronic cough and phlegm and total or partial lack of control at baseline increased the risk of uncontrolled asthma at follow-up. More than 1 out of 4 subjects with asthma recover from their illness; however, less than 30% of the remaining subjects had controlled asthma a decade after.

P3955
Seasonality of primary care utilization for asthma, COPD and pneumonia in Karachi (Pakistan)

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Background: The increase in the health care burden from respiratory diseases is noticeable in the developing countries and its seasonal variation has epidemiological significance. Aims and objectives: This study aimed to assess the seasonality of primary care utilization for acute exacerbations of respiratory diseases with respect to the age and gender of the patients and to examine the mortality rates of the patients hospitalized.

Methods: We conducted a retrospective study to assess the seasonal patterns in hospital admissions due to acute exacerbations of respiratory diseases (asthma, COPD and pneumonia) in Jinnah Postgraduate Medical Centre, Liaquat National Hospital, and Aga Khan University Hospital, Karachi for a two year period from January 1, 2009 to December 31, 2010. Data were collected from Hospital Records Department through patients discharge files of those who had a primary physician diagnosed for asthma; COPD or pneumonia. Climatic data for average rainfall and humidity were obtained from Pakistan Meteorological Department and was analyzed with respect to the seasonal distribution of the diseases.

Results: There were total 3,205 patients analyzed, from them 53.77% had asthma, 26.35% had COPD and 19.87% had pneumonia. Highest number of hospital admissions for COPD, pneumonia and asthma were observed from mid of Dec to Feb (Winter), with a peak occurring in the month of March (early Spring), whereas significantly less cases occurred in May(Summer) and November (Autumn).

Conclusion: The results demonstrated a clear seasonal pattern indicating the highest number of patients admitted in the month of winter and a peak occurring in the spring season for asthma, COPD and pneumonia.

P3956
Estimating parameters in the two-compartment model of exhaled nitric oxide

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Introduction: The fractional concentration of exhaled nitric oxide (FeNO) is a biomarker of airway inflammation. FeNO decreases with increasing flow, which has led to the development of mathematical models whose parameters quantify proximal and distal sources. FeNO measured at the conventional 50 ml/s flow rate is primarily from proximal sources, so the parameters may provide additional insight. Parameters are estimated from FeNO data measured at multiple flow rates, but there is no standard estimation method.

Aims and objectives: To provide recent screening data from the German central laboratory for AATD in Marburg, Germany.

To provide recent screening data from the German central laboratory for AATD in Marburg, Germany.

Methods: From dried blood spot (DBS) samples we performed AAT measurements (for internal use only) and genotyping for S and Z alleles. When either of both tests was suggestive for AATD we went on to perform phenotyping by IEF. When phenotyping resulted in bands suggestive for rare deficiency alleles we conducted complete sequencing of the AAT gene.

Results: In the period from August 2003 to February 2012 more than 50,000 test kits had been requested of which 13,010 kits have been returned. Of these, 75 were not evaluable, and 185 samples had already been submitted before. Our results are based on 12,750 analyzed samples.

In descending order of frequency, we have diagnosed the following phenotypes: PMM (8577, 67.27%), PMZ (2383, 18.69%), PI (846, 6.69%), PIZ (441, 3.50%), PIZ (192, 1.51%), PSS (38, 0.29%). 140 samples were submitted to gene sequencing. Here we found 75 rare (R) genotypes (PZSR 59; PMR 10; PSR 2; PIR 2).

Conclusion: Almost a third (32.73%) of the submitted samples was found to represent at least a carrier status, and over 8% carried a genotype that is associated with a severe AATD. We conclude that screening is useful to detect AATD and should be expanded in Germany.

P3958
Normality ranges of urine oxidative stress markers (8-OHdG and isoprostane) in Italian people free from respiratory diseases – Preliminary results

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Background: The study of oxidative stress (OxS) is becoming increasingly im-
portant in respiratory disease research. To our knowledge, the reference ranges of urinary 8-hyroxy-deoxy-guanosine (8-OhD) and 8-isoprostane (isoprostane), a DNA and a lipid oxidation product respectively, have not yet been determined in subjects without respiratory diseases.

Aim: To assess the reference range of 8-OHd and markers in Italian people aged 20-64 free from respiratory diseases (controls).

Methods: 8-OhD and isoprostane were measured in spot-urine samples collected in the frame of Gene-Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. The biomarkers levels were corrected on creatinine concentration. Only controls (n=227) were considered for this aim of the work. The possible effects of potential determinants on 8-OHd-biomarkers were studied before determining the normality range in selected subgroups of controls. Multiple linear regression was fitted to data using the logarithm of 8-OHd or isoprostane as dependent variables and sex, age, season, smoke, body mass index, as covariates. The appropriate percentiles were calculated.

Results: Both 8OHd and isoprostane concentrations were significantly higher in smokers than in non smokers (p<0.05 and 0.047 respectively), while the other covariates did not influence 8-OHd. The 95% 8-OHd normality range in non smokers varied from 0.26 to 25.94 ng/ml. The 95% isoprostane reference interval was 0.03 - 5.42 ng/ml in non smokers.

Conclusion: Provisional 95% normality range for urinary 8-OHd and isoprostane were determined in subjects free from respiratory diseases.

P3959 Levels of cat, grass and mite specific IgE and symptoms on specific exposure

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Objective: To investigate the association between specific IgE levels to different allergens and symptoms on specific exposure.

Methods: In the frame of the European Community Respiratory Health Survey II specific IgE to cat, Timothy grass and house dust mite were assessed in 8409 subjects. Participants were asked whether they presented cough, wheeze, chest tightness, breath shortness, runny or stuffy nose, itchy or watering eyes on exposure to: cats, trees, grass, flowers, or pollen; a dusty part of the house, or near pillows or duvets.

Results: A clear dose-effect relationship was found between IgE levels to cat, grass and mite, respectively, and symptoms on exposure to animals, pollen and dust (Table 1). The relation between mite sensitization and symptoms on dust exposure was less steep. A similar pattern was observed when evaluating the number of symptoms on exposure: the Spearman’s ρ was, respectively, 0.45, 0.45 and 0.19 when considering the relation between sensitization to cat, grass and mite and number of symptoms on specific exposures.

Table 1. Percent prevalence of symptoms on exposure to animals, pollen and dust, respectively, as a function of IgE levels to cat, Timothy grass and house dust mite

<table>
<thead>
<tr>
<th>Specific IgE levels (kU/L)</th>
<th>Symptoms on exposure to animals</th>
<th>Symptoms on exposure to pollen</th>
<th>Symptoms on exposure to dust</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.35</td>
<td>&lt; 24 (162/6624)</td>
<td>&lt; 28 (1758/6352)</td>
<td>&lt; 21 (259/1209)</td>
</tr>
<tr>
<td>0.35 - 0.69</td>
<td>0.35 ≤ 11 (76/6818)</td>
<td>0.35 ≤ 24 (162/6624)</td>
<td>0.35 ≤ 28 (1758/6352)</td>
</tr>
<tr>
<td>0.70 - 3.49</td>
<td>0.70 ≤ 41 (76/196)</td>
<td>0.70 ≤ 54 (106/198)</td>
<td>0.70 ≤ 39 (115/296)</td>
</tr>
<tr>
<td>3.50 - 17.4</td>
<td>3.50 ≤ 82 (147/227)</td>
<td>3.50 ≤ 87 (455/5326)</td>
<td>3.50 ≤ 58 (190/328)</td>
</tr>
<tr>
<td>&gt; 17.5</td>
<td>&gt; 17.5 ≤ 82 (147/227)</td>
<td>&gt; 17.5 ≤ 87 (455/5326)</td>
<td>&gt; 17.5 ≤ 58 (190/328)</td>
</tr>
</tbody>
</table>

Conclusion: Both the prevalence and the number of allergic symptoms on specific exposure increase with increasing specific IgE levels.

P3960 Candidate gene association study of chronic obstructive pulmonary disorder using a targeted high throughput sequencing approach

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Aims: Assessment of objective and subjective impairment of the upper airways in chronic obstructive pulmonary disease (COPD).

Background: Pathologic correlates of the upper airways have been rarely evaluated in chronic obstructive pulmonary disease (COPD).

Methods: Chronic obstructive pulmonary disease (COPD), a progressive and disabling disease, is characterized by airflow limitation accompanied by symptoms including breathlessness, chronic cough, and sputum production. It is the third leading cause of death worldwide, and it is responsible for a significant burden of disease, including hospitalizations, emergency department visits, and workdays lost. The prevalence of COPD is estimated to be 15% of the adult population, and the prevalence is expected to increase as a result of the aging population and increased smoking rates. The pathogenesis of COPD is complex and involves both genetic and environmental factors. Genetic studies in humans and in animal models suggest that developmental genes are important determinants of adult lung function that may ultimately contribute to COPD.

Results: Patients carrying mutations in FGF10 show a significant decrease in lung function parameters consistent with COPD. Based on these results, we are currently investigating in total 200 kb enriched sequence, including 22 genes implicated in lung development and 71 genes or regions previously associated to COPD.

Conclusion: These findings support the idea that genetic variants affecting lung developmental genes are important determinants of adult lung function that may ultimately contribute to COPD.

P3961 Efficacy of COPD detection by using a community-based annual screening program for lung cancer

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Aims: Assessment of the effectiveness of COPD detection by using a community-based annual screening program for lung cancer.

Background: In Japan, community-based lung cancer screening by chest X-ray has been established. Japanese residents who are 40 years old or higher can freely receive chest X-ray every year. We utilized this screening system in Chiba City in order to detect COPD. From April 2010 to March 2011, 83,924 participants received regular lung cancer screening by chest X-ray at the first examination centers, which was approximately 30% of objective residents. We set the criteria of suspicious of COPD indicating 60 years or older, positive smoking history and having any chronic respiratory symptoms. 1,170 (1.3%) were recognized as suspicious of COPD and 351 of them (36.2%) received further examination including pulmonary function test (PFT) and/or chest computed tomography (CT) as the second close examination at 39 second examination centers.

Results: 138 participants (25.0%) were reported as COPD from the second examination centers and 42.2% of them were necessary for COPD treatment. Only eight participants (5.8%) were already diagnosed COPD before screening. PFT and/or chest computed tomography (CT) could be collected from 173 participants, and 43 (24.9%) were diagnosed as COPD (FEV1 less than 70%). Emphysema grades according to Goddard classification on CT revealed that 21.1% was radiological emphysema. One patient with normal chest X-ray was detected lung cancer by CT and could receive curative surgery.

Conclusion: COPD screening by using a community-based lung cancer screening program may be effective for detection of COPD. These patients can be treated COPD as early as possible.

P3962 Computed tomography of the paranasal sinuses in chronic obstructive pulmonary disease

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Aims: To investigate candidate genes, with emphasis on genes important for lung development, for genetic variants predisposing to the development of chronic obstructive pulmonary disease (COPD) using targeted enrichment in a cohort of COPD patients.

Methods: Twelve patients with heterozygous loss of function mutations in a lung developmental gene, the fibroblast growth factor 10 (FGF10), was investigated for pulmonary function and COPD was classified according to the ATS/EURS 2005 standard. To identify novel variants associated with COPD, we are currently conducting a candidate gene association approach using targeted enrichment (Haloplex; Halo Genomics) and a high throughput sequencing (Illumina) using patients and controls retrieved from the Swedish Obstructive Lung Disease in Norrbotten (OLIN) sample set. This strategy allows for the detection of all genetic variants in the enriched sequence, without the limitations when investigating known variants using SNP arrays.

Results: Patients carrying mutations in FGF10 show a significant decrease in lung function parameters consistent with COPD. Based on these results, we are currently investigating in total 200 kb enriched sequence, including 22 genes implicated in lung development and 71 genes or regions previously associated to COPD.

Conclusion: These findings support the idea that genetic variants affecting lung developmental genes are important determinants of adult lung function that may ultimately contribute to COPD.
We found a positive correlation between the CT score and the SNOT-PNS (r = 0.22, p < 0.05). The endoscopic score correlated positively with the SNOT-PNS (r = 0.29, p < 0.05) as well as with the SNOT-20 (r = 0.42, p < 0.01). Subjects in higher risk groups presented higher scores in endoscopy (p < 0.05), SNOT-PNS (p < 0.05) and SNOT-20 (p < 0.01).

Conclusion: Pathologic correlates of the upper airways were found in more than half of the patients with COPD.

P3963 Waist circumference and lung function among adolescents: The Pelotas 1993 birth cohort

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Background: BMI is frequently used to evaluate obesity, but it is unable to assess fat distribution. Much attention has been given to abdominal fat measured by waist circumference (WC). Abdominal fat is a known risk factor for chronic diseases, but the impact of lung function among adolescents remains uncertain.

Objective: To evaluate the association between WC and lung function parameters among adolescents.

Methods: The original cohort comprised 5,249 hospital born children during the calendar year of 1993 in Pelotas, Brazil. In 2008-9, when participants were 15 years old, all cohort members were evaluated. WC was measured by trained interviewers and lung function tests were performed to obtain FVC and FEV1. Multiple linear regression models were performed and all analyses were stratified by sex.

Results: 1,969 boys and 2,032 girls had data for spirometry and for WC. In the crude analyses we found a positive relationship between WC and FVC (liters) for both boys and girls. After adjusting for height, BMI, physical activity and wheezing in the past year, we found an inverse relationship between WC and FEV1 (β = -0.015 [95%CI -0.023; -0.008]), and FVC (β = -0.010 [95%CI -0.018; -0.001]) only for boys. For girls, the association was not significant. When we analyzed the predicted values, there was a significant association with WC, (%FEV1, β = 0.413 [95%CI -0.619; -0.206]; %FVC β = -0.242 [95%CI -0.464; -0.205]) only for boys.

Conclusions: Increases in WC were associated with worse lung function parameters in Brazilian boys aged 15 years old. Improvement of lung health in adolescent can prevent lung diseases in adult life.

P3964 Lung function and respiratory symptoms as predictors of mortality: The HUNT study

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Background: Impaired lung function is associated with increased mortality. However, whether respiratory symptoms, independent of lung function, are associated with all-cause or cardiovascular (CV) mortality is not clear.

Objective: To prospectively study associations of lung function and respiratory symptoms with all-cause or CV mortality is not clear. How- ever, whether respiratory symptoms, independent of lung function, are associated with all-cause or CV mortality is not clear. Therefore, we conducted a cross-sectional study to investigate this relationship.

Methods: The study included 5319 women and 4972 men who participated in the Lung study of the Norwegian HUNT study in 1995-97. Cox regression was used to calculate adjusted hazard ratios (HRs) for all-cause and CV death associated with pre-bronchodilator percent of predicted FEV1 (ppFEV1), grades of COPD, and respiratory symptoms (chronic bronchitis, wheeze, and dyspnoea).

Results: Lung function was inversely associated with all-cause mortality. A 10% reduction in ppFEV1, gave a HR of 1.17 (95% confidence interval [CI] 1.09-1.25) in women and 1.23 (95% CI 1.16-1.30) in men. Compared to ppFEV1 < 70%, ppFEV1 < 50% was associated with a HR of 6.85 (95% CI 4.46-10.52) in women and 3.88 (95% CI 2.60-5.79) in men. Results for COPD grades corresponded to those found for ppFEV1. Levels of the respiratory symptoms, only dyspnoea remained associated with all-cause mortality after adjusting for lung function (HR 1.68 [95% CI 1.11-2.53] in women and 1.63 [95% CI 1.11-2.11] in men), and within levels of lung function. Overall, associations between lung function and CV mortality were weaker, and no clear relation was found for respiratory symptoms.

Conclusions: Our results suggest that pre-bronchodilator lung function is a strong predictor of all-cause mortality, and that dyspnoea is associated with all-cause mortality independent of lung function.

P3965 The effect of menopause on the lung function among Korean women; the fourth Korean National Health and Nutrition Examination Survey (KHANES IV)

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Background: Sex hormones appear to play an important role in women’s lung health. But the literature on menopause and lung health is scarce, especially lung function. Some studies showed improvement or no change in forced expiratory volume in the first second (FEV1), forced volume capacity (FVC) in association with hormone therapy. And a few studies showed that postmenopausal women had significantly lower FEV1 and FVC, especially among lean women. This study examined whether menopausal status was related to the lung function.

Design & methods: Data were obtained from the 4th Korean National Health and Nutrition Examination Survey of 2007-9. A total of 1382 Women aged 44 to 61 years not receiving hormone replacement (712 premenopausal women and 670 postmenopausal women) were included in this analysis. Women who were current pregnancy, lactation, amenorrhea induced by hysterectomy were excluded. In our study, a postmenopausal woman was defined as a woman whose current age was 1 year after her age of menopause.Age, height, BMI, smoking status were adjusted by multiple linear regression analysis.

Results: Postmenopausal status is not significantly associated with lower FVC (-33mL, p-value = 0.353), but associated with lower FEV1 (-77mL, p-value = 0.032).

Conclusion: Postmenopausal status can be related with lower lung function in this study.

P3966 Effect of hospitalization on exercise capacity in patients with chronic obstructive pulmonary disease (COPD)

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Introduction: Exercise capacity has become an important measure to assess COPD functional status, response to medical interventions and prognosis. However, the determinants of exercise capacity change over time in COPD patients are poorly known.

Aim: To estimate the effect of hospital admissions on exercise capacity decline in COPD patients.

Measurements: 226 patients with moderate-to-severe COPD from our original PAC-COPD Study had their exercise capacity measured when clinically stable using the six minute walking distance (6MWD) both at baseline and 1.7 years after. Sociodemographic variables, lifestyle, co-morbidities, and clinical and functional status were also assessed. Hospital admissions (timelines and causes) during the follow-up were gathered from centralized government datasets. Linear regression was used to model changes in exercise capacity.

Results: At baseline, patients were mostly male (92%), aged mean (SD) 67(8) years, postbronchodilator FEV1 54(17)% and 6MWD 448(83) m. During the follow-up period, patients decreased their exercise capacity (mean -20m/y). More- over, 87 (39%) had at least one hospitalization (more than a half due to COPD). After adjusting for dyspnea, lung hyperinflation (RV/TLC), and baseline 6MWD, COPD admissions rate increased the 6MWD decline: -15m/y and -30m/y in ≤1 admission/year and > 1 admission/year, respectively, compared to patients with no admissions (p<0.001). Remaining variables were not related to the 6MWD decline, after adjusting for hospital admission.

Conclusions: These findings show that hospital admissions due to COPD exacerbation have a great impact on exercise capacity deterioration in moderate-to-severe COPD patients.

P3967 Chronic obstructive pulmonary disease surveillance: Potential usefulness of the Texas behavioral risk factor survey surveillance system

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Background: Public health surveillance of COPD has traditionally focused on risk factors and measures of disease occurrence, but these measures are insufficient to monitor effectiveness of disease control strategies.

Objectives: The purpose of this analysis was to evaluate the potential usefulness of a population-based telephone surveillance system for monitoring patient-reported outcomes among patients with COPD.

Methods: The Behavioral Risk Factor Surveillance System (BRFSS) is a state- based system of telephone surveys. In 2009, the Texas BRFSS included a question about physician-diagnosed COPD and self-rated health status. We conducted a cross-sectional analysis of self-reported COPD, fair/poor health status, and the in- fluence of lifestyle factors, health care access and co-morbidity conditions. Adjusted prevalence ratios (PR) were calculated using multivariate logistic regression.
Results: Adults with COPD reported significantly worse health status compared to adults without COPD (fair/poor: 49.1% vs. 13.7%, p < 0.001). In multivariate analyses lifestyle and health care access factors significantly (p < 0.05) associated with fair/poor health status included: current smoker (PR=2.9), former smoker (PR=2.0), physical inactivity (PR=3.0), having a personal doctor (PR=4.8), inability to see a doctor due to costs (PR=3.6), and pneumonia shot (PR=6.1). Co-variables considered significantly (p < 0.05) associated with fair/poor health status were: obesity (PR=3.5), asthma (PR=1.7), cardiovascular disease (PR=3.2), and cancer (PR=1.7).

Conclusion: These results suggest that the BRFFS may be useful at the population level for surveillance of COPD.

P3968 Newly developed simple QoL questionnaire in early detection of COPD in a population of smokers at risk for COPD development
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Objective: Assessing the role of the newly developed QoL questionnaire (MARKOQ) in early detection of COPD in a population at risk for COPD.

Methods: The MARKOQ is a self-administered questionnaire with 18 questions. Subjects were smokers with ≥20 pack-years, both gender, 40-65 yrs of age, with no diagnosis of COPD. They were referred to a pulmologist (history, physical, lung function) for diagnosis of COPD and the staging. MARKOQ was administered twice at primary care clinic and 2-4 weeks later at a pulmonology clinic.

Results: Sample included 219 consecutive subjects (48.5% males), mean (SD) age 52.6 (6.9) yrs with 38.0 (17.4) pack-years. 25.3% were diagnosed as COPD (stage I, 18.1%, stage II 6.7%, stage III 0.6%). Spearman correlations showed very good internal consistency of MARKOQ (Cronbach’s alpha=0.89) and test-retest reliability (r=0.84). The correlation with CAT scores was r=0.54. MARKOQ significantly discriminated (F=20.2, p=0.003) patients with GOLD stage II or higher (mean=19.9, SD=8.7) from those in stage I (mean=12.9, SD=10.1) and “healthy” smokers (mean=12.9, SD=8.4) (CAT scores were not discriminative). Correlations of MARKOQ scores were only significant for FEV1 (r=0.22, p=0.003).

Conclusion: The MARKOQ developed for an early detection of COPD may be able to detect early changes in QoL complementary to lung function impairment. The exact validity of the MARKOQ will be known after the reevaluation based on the cohort follow-up.

Supported by an unrestricted grant by GlaxoSmithKline (GSK) E-Tracking number CTR114338.

P3969 External multicentric validation of a COPD detection questionnaire
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Introduction: Chronic obstructive pulmonary disease (COPD) is a preventable disease. The development of a simple questionnaire can help to improve the diagnosis.

Objective: External validation of the questionnaire to detect COPD in Argentina.

Material and Methods: We performed a questionnaire in subjects with over 40 years old and history of smoking ≥ 10 or more pack/year. Demographic data and pre and post bronchodilator spirometry were performed. Subjects with previous diagnosis of COPD or asthma were excluded.

Results: 468 subjects were evaluated. 100 (21.1%) had spirometric diagnosis of COPD. In univariate analysis patients with COPD had higher median age (58 years vs 54 years, p < 0.001), pack years (PR=50) versus 30 (p < 0.001), lower BMI (26 vs 28, P = 0.02), higher incidence of males (68.8% vs 43.9%, P < 0.001), cough for 3 months (55.2% vs 33.8%, P=0.001), chronic cough (47.9% vs 28.8%, P < 0.001), phlegm for 3 months (50% vs 37.2, P=0.02), chronic phlegm (40.6% vs 26.1%, P = 0.005), dyspnea (62.5% vs 51.9%, P = 0.06), wheezing (55.2% vs 47%, P = 0.15), wheezing without infection (38.5% vs 33.9%, P = 0.39), stave at home (10.4% vs 7.5%, P = 0.35) and risk profession (18.9% vs 18.5%, P = 0.78). The presence of at least 3 of these variables had a sensitivity of 95% and a specificity of 25.29%, positive predictive value (PPV) of 22.62% and negative predictive value (NPV) of 95.65%. The presence of at least 6 variables had a sensitivity of 90% and a specificity of 70.97%, a PPV of 50% and a NPV of 95.65%

Conclusion: This simple questionnaire for demographic and clinical data can be useful for detection of COPD.

P3970 Childhood asthma control test: Validation of the Arabic Tunisian dialect version in 51 patients
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Children Asthma Control Test or c-ACT was translated in different languages. We propose to validate the Arabic Tunisian version by checking if it’s understood by patients and their parents and the conformity with the control criteria of international recommendations. Cross-sectional study was conducted in 51 asthmatic children, aged from 4 to 11 years, followed for at least 6 months. c-ACT was administrated before consultation. The level of asthma control was compared to that estimated by the expert based on GINA criteria with an evaluation period of 4 weeks. Understanding of this Arabic version has been confirmed with the parents and their patients. This version showed a satisfactory internal consistency with Cronbach’s alpha equal to 0.853. The area under the ROC curve equal to 0.993 is highly significant (p < 0.001). The c-ACT showed a significant discriminative ability of patients with different level of control of their asthma (p < 0.001). The study of the performance of c-ACT 19 point threshold, to identify children uncontrolled, found a sensitivity of 73.7% and negative predictive value of 86.5%. Considering the 20 point threshold, sensitivity and negative predictive value reached respectively 94.7% and 96.9%. There is a highly significant correlation (p < 0.0001) between the level of control patients detected by the c-ACT and that estimated by the specialist with a kappa coefficient equal to 0.778. Most children have understood the Arabic version of the c-ACT. This study demonstrated a good correlation between the result of c-ACT in dialectal Arabic and clinical evaluation. The usefulness of this version will be evaluated after its release.

P3971 Shortness of breath associated with chronic conditions among those with and without asthma or COPD
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Background: Some chronic conditions may result from similar underlying mechanisms or may exacerbate lung disease suggesting the investigation of disease inter-relationships. We sought to determine if SOB was more common among adults with chronic conditions and to examine this association among those with asthma and COPD.

Methods: In 2010 we conducted a cross-sectional mail survey of rural households as part of the Saskatchewan Rural Health Study. One adult per home provided information about each adult living in the home. There were 8261 adults from 4624 households (42% participation) included. We examined the associations between reported diagnosed chronic conditions (diabetes, cardiovascular disease, and sleep apnea) and SOB after adjusting for potential confounders and stratifying by history of doctor-diagnosed asthma or COPD. High SOB was defined by a score of ≥ 3 on the MRC breathlessness scale.

Results: The respondents’ mean age was 56 years (SD=16 years) with 51% of the population being female. Approximately 14% had a MRC score ≥ 3. After adjustment, there was increased risk of high MRC score associated with the presence of diabetes (odds ratio (OR)=1.68, 95% confidence interval (CI)=1.32-2.14), cardiovascular disease (OR=2.18, 95%CI=1.80-2.65), and sleep apnea (OR=2.19, 95%CI=1.60-3.00). The associations with SOB were weaker among those with asthma or COPD with the exception of that for sleep apnea, which was stronger.

Conclusions: Some conditions were associated with high SOB among those with and without a history of lung disease. These relationships may result from common pathways, possibly inflammatory, and may precede more serious chronic lung disease.

P3972 Detection of quality of life with COPD assessment test in chronic obstructive pulmonary disease and effect of dyspnea on disease-specific quality of life in these patients
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Background: The measurements for level of dyspnea such as Medical Research Council (MRC) dyspnea scale or modified Borg dyspnea scale were used common in the trials. COPD assessment test (CAT) is a recently introduced to use to disease-specific quality of life and follow-up of the patients with COPD.

Objective: We aimed that assessed effect of the dyspnea in disease-specific quality of life detected by CAT score in the patients with COPD.

Methods: In this study, 90 stable patients with COPD as defined by the GOLD criteria were included. The level of dyspnea was assessed with two different scales, MRC dyspnea scale and modified Borg dyspnea scale, and disease-specific quality of life assessed with the CAT score.

Results: Patients’ mean ± SD age was 68.5±10.9 (range 41 – 97) years. A significant relationship was established among CAT score, MRC dyspnea scale, modified Borg dyspnea scale, the GOLD stage of the patients with COPD. There

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was a positive correlation between dyspnea scales and the GOLD stage of the patients (p<0.001), and also positive correlation between CAT score and dyspnea scales (p<0.001). The CAT score and dyspnea scales had a significant correlation with hospitalization and emergency room applications (p<0.05).

**Conclusion:** It is suggested that dyspnea is an important symptom that impacts the quality of life in patients with COPD. The CAT is simple, fast and an easy intelligible measurement for the disease-specific quality of life and it is correlated with levels of dyspnea of the patients with COPD.

### P3973 Validation of quality of life questionnaire St George’s for patients with respiratory diseases in Colombia, Latin America

**Authors:** Ana Carolina Vargas1, Vector Calvo2, Antioquia, Hospital San Vicente de Paúl, Medellín, Antioquia, Colombia; 2 Antioquia, Instituto de Alta Tecnología Médica, Medellín, Antioquia, Colombia

**Background:** The SGRQ a self-administered questionnaire specific for pulmonary diseases, validated in different cultures and countries. The objective of this study was to adapt one specific scale of quality of life in patients with acute and chronic pulmonary diseases in Colombia, Latin America.

**Materials and methods:** The Spanish version of the SGRQ was applied to 277 patients with COPD and asthma; the different components and overall scores of SGRQ were described; the forced expiratory volume in one second (FEV1), % predicted FEV1, 6-minute walk test (6MWT) and SF36 were used in the assessment battery.

**Results:** The SGRQ showed Chronbach’s alpha coefficient internal consistence was 0.94 for the overall total scale, 0.89 for symptoms, 0.93 for activity and 0.89 for impact. Correlations of coefficient inter-reliability were 0.82 and intra-reliability 0.065 for the overall scores. The contents validity of the three factor structure was established; in construct validity met a slight difference between acute and chronic patients in activity with statistically and clinically significant (p<0.05). On evaluation of the concurrent validity of the SGRQ and the score of physical function (α=0.67), vitality (α=0.51) and social function (α=0.46) of SF68, good correlations were found. The responsiveness showed statistical differences (p<0.05) with the scores being less in the second measurement (better quality of life).

**Conclusions:** SGRQ version for acute and chronic patients in Colombia is psychologically equivalent to the original version, reliable, valid and could be used in our country and Spanish speaking countries with similar ethnic, cultural and social conditions.

### P3974 How accurate are assessments of exacerbations through patient self-reports? A systematic review

**Authors:** Anna Frei1,2, Lara Siebeling1, Callista Wolters1,2, Patrick Maggengrumm1,3,4, Marco Zoller2, Gerben ter Riet3, Milo Puhan1,5

**Methods:** To evaluate the accuracy of different methods to ascertain exacerbations in longitudinal studies and to estimate the effect of misclassification in randomised trials.

**Aims and objectives:** To evaluate the accuracy of different methods to ascertain COPD exacerbations in longitudinal studies and to estimate the effect of misclassification in randomised trials.

**Methods:** We used event-based definition of exacerbations that required newly prescribed systemic corticosteroids and/or antibiotics. Methods to ascertain exacerbations in 411 primary care COPD patients from ICE COLD ERCI cohort over 3 years included (1) 6-months follow-ups and (2) review of patient charts by an experienced physician. These 2 methods were compared against reference standard of adjudication committee (AC) where 3-4 experienced physicians independently adjudicated exacerbations following AC meeting where consensus on final classifications was reached. We calculated sensitivity and specificity and estimated the effects of long-acting bronchodilators vs. placebo on exacerbations by correcting for misclassification.

**Results:** 59.6% of 411 patients had at least 1 exacerbation during the 3 years according to the AC. Patient self-reports had a sensitivity and specificity of 84% and 75%, adjudication by single physicians between 88-96% and 87-96%. The pooled relative risk reduction from meta-analysis changed from 11% (95% CI 1-20%) to 35% (4-56%) when corrected for misclassification.

**Conclusions:** Conventional methods to assess exacerbations without central adjudication are likely to underestimate treatment effects substantially. Use of central or expert adjudication could reduce sample size requirements by up to 5-fold.

**References:**

### P3976 Surveillance of antibiotic resistance in Streptococcus pneumoniae from 2000 to 2011 and serogroup distribution in Tunisia

**Authors:** Emma Mehiri, Asma Ghariani, Sabrina Bouchenna, Leila Slim-Saidi

**Methods:** Multicenter study performed in public hospitals of Tunisia. Surveillance of antibiotic resistance in Streptococcus pneumoniae is a major problem and has reached very high levels in certain countries. In this study, we report the level of resistance of Streptococcus pneumoniae over a 12-year period and the serogroup’s distribution in Tunisia. From January 2000 to december 2011, 1953 strains were collected, in Aberraham Mami Hospital of pneumology, Tunis, Ariana, Tunisia.

**Results:** The rate of penicillin G non susceptible pneumococci (PNSS) was 40.4% including 8.2% of high resistance level. The strains showed reduced susceptibility to amoxicillin and cefotaxim in 17.4% and 12.7% of cases respectively. An increase of resistance is showed from 2000 to 2011 to B-lactamin. In addition, high levels of resistance to other antibiotics were noted. Thus 60.7%, 40.9% and 14.2% of strains were resistant to erythromycin, tetracycline and chloramphenicol respectively. The most common serogroups were 16, 9, 14, 23 and 23 and were associated to penicillin G non susceptible pneumococci. Serogroup 1 was also found in severe pneumococcal infection.

**Conclusion:** In conclusion, the high rate of PNSS and the multidrug resistance of S.pneumoniae show the need of rational use of antibiotics.

### P3977 Clinical, spirometric and radiological characteristics of Brazilian rheumatoid arthritis patients

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**Results:** Rheumatoid Arthritis (RA) is a common inflammatory disease, and pulmonary in-
volvement is usual. An algorithm has been proposed for evaluation and management of RA patients with suspected interstitial lung disease, based on chest radiograph, physical examination and symptoms (Kim, E.J. et al. Chest 2009;136:1397-1405).

**Objective:** To describe clinical, spirometric and radiological characteristics of Brazilian RA patients using low-cost evaluation.

**Methods:** Patients with RA, irrespective of having pulmonary involvement, were evaluated, and data regarding pulse oximetry, spirometric measures and digital chest radiograph were obtained.

**Results:** 248 RA patients were analyzed. 85% were female, mean age was 56±10 years, median disease onset time was 16 years (IQR 7.75-24). The most common exposure was mold (22%). 50% had no smoking history, 17% were current smokers and 33% were former smokers. Pulse oximetry was normal (above 94%) in 87%. MRC dyspnea index 1 or 2 were observed in 50% and 32%, respectively. Most commonly used drugs were Methotrexate (92%), Prednisone (80%) and Chloroquine (78%). Spirometry was classified as normal (70%), obstructive (11%), restrictive (11%), mixed (5%) and unspecified (7%) patterns. At the moment, data for chest radiograph is available for 71 patients (29%), parenchymal abnormalities were observed in 56%, mainly linear (38%) and reticular opacities (18%).

**Conclusion:** This is the first study in Brazilian RA patients to analyze digital chest, pulsoximeters and to evaluate lung function. Spirometric alterations are common in RA patients. Abnormalities in digital chest radiographs were more frequent than previously described in conventional radiographs.

**P3978**

**Risk factors that determine time to first RSV hospitalization in CARESS:**

**The Canadian registry of palivizumab 2005-2011**

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**Objective:** Evaluate risk factors that determine time to first RSV hospitalization in children at high-risk of RSV infection who received prophylaxis.

**Design:** Method: Prospective, observational, registry of infants who received ≥ 1 dose of palivizumab during the 2005-2011 RSV seasons across 30 sites. Neonatal and demographic data were collected from the parent/caregiver at enrollment. Data related to respiratory infection events were collected monthly.

**Results:** 10,452 infants were enrolled; average age 5.5±6.0 months. Infants were typically male (56-4%), Caucasian (71%), average gestational age (GA) 32 ± 5.6 completed weeks. 700C (67%) infants received palivizumab for prematurity (35 weeks GA) only, 836 (8%) had chronic lung disease, 1048 (10%) had congenital heart disease and 1562 (15%) had underlying medical disorders (e.g. CNS disorders, airway anomalies and cystic fibrosis). Hospitalization rates for respiratory- and RSV-related hospitalization were 14% and 1%, respectively. Risk factors for RSV hospitalization included: having siblings (HR=2.16, df=1, p=0.001), more than 5 people in household (HR=2.02, df=1, p<0.0005) and smoking exposure (HR=1.80, df=1, p<0.0005). Time to first hospitalization increased with the number of risk factors from 1 (HR=3.42) to 3 risk factors (HR=10.40).

**Conclusions:** Time to first RSV hospitalization after the first palivizumab dose are similar to those reported in the literature, with a natural history of RSV. The effect of multiple risk factors pose a cumulative increased risk for RSV hospitalization, similar to the Canadian and European risk scoring models for 33-35 weeks’ GA infants.

**P3979**

**Genetic epidemiology of hereditary hemorrhagic telangiectasia associated with pulmonary arteriovenous malformation**

**Takanobu Shioya1, with pulmonary arteriovenous malformation**

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**Background:** Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by aberrant vascular development such as pulmonary arteriovenous malformation (PAMV). We report here a genetic epidemiologic study in PAMV associated with HHT in Japan.

**Method and subjects:** A total of 137 pedigree members were traced of which 81 were alive and 42 were affected by HHT in a county, A population 1.1 million located in northern Japan.

**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 identified by PCR-RFLP method in peripheral blood DNA samples. Genotypes were distributed in a Hardy-Weinberg equilibrium.

**Conclusion:** These data demonstrate that the NAT2 fast or slow acetylators genotype did not associated with the risk of developing lung cancer in North Indian population when compared with controls.

**P3980**

**Nat2 gene polymorphism in lung cancer: A study from north India**

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**Genetics, Sanjivi Gandhi Post Graduate Institute of Medical Sciences, Lucknow, U.P, India**

**Purpose:** This study was conducted to examine: 1) whether the NAT2 genotypes are risk factors for Lung cancer, 2) to study possible association of tobacco smoking with NAT2 genotype of these patients.

**Materials and methods:** This case control study was undertaken over a period of 19 months and included 100 Lung cancer patients and 145 controls. The NAT2 genotypes were identified by PCR-RFLP method in peripheral blood DNA samples. Genotypes frequencies and the association of the genotypes among patients and controls group were assessed by x2 test and Binary Logistic regression.

**Results:** The NAT2 fast acetylator genotype frequency of slow or fast acetylator genotypes was not significant in lung cancer patients alone (OR = 1.18, 95% CI: 0.69 - 2.03, p value = 0.583) in non-smoker (OR = 1.06, 95% CI: 0.43 - 2.64, p value = 0.899) and smoker (OR = 1.32, 95% CI: 0.59 - 2.93, p value = 0.494) vs. immunocompetent adults in Spain.

**Conclusion:** These data demonstrate that the NAT2 fast or slow acetylators genotype did not associated with the risk of developing lung cancer in North Indian population when compared with controls.

**P3981**

**Serotypes distribution and clinical features of IPD in immunocompromised vs. immunocompetent adults in Spain**

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**Background:** Immunocompromise is a main risk factor for Invasive Pneumococcal Disease (IPD).

**Objectives:** To analyse clinical presentations, comorbidities, and outcome of IPD by immunological status and serotypes (Ss) distribution to determine PCV13 coverage.

**Methods:** Prospective surveillance of culture-confirmed IPDs in adults (≥18 years) performed in 7 Spanish hospitals (August 2010-June 2011). Immunocompromise included presence of immunosuppression, HIV infection/AIDS, other immunodeficiencies, cancer or chronic renal disease.

<table>
<thead>
<tr>
<th>Serum type</th>
<th>Immunocompromised</th>
<th>Immunocompetent</th>
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<tbody>
<tr>
<td>PPV23</td>
<td>25</td>
<td>19.6</td>
</tr>
<tr>
<td>PCV13 Sts</td>
<td>38.1</td>
<td>64.4</td>
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<tr>
<td>6C</td>
<td>6</td>
<td>5.6</td>
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<tr>
<td>PPV23nonPCV13 Sts</td>
<td>26.1</td>
<td>12.8</td>
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<tr>
<td>Other Ss</td>
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**Summary and conclusion:** The population prevalence of HIBT in the county was 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 HIBT is rare among Asians. We recommend that families with HHT be screened for gene mutations in order that high-risk individuals complicated with PAVM receive early diagnosis and treatment initiation that will substantially alter their clinical course and prognosis.
Results: 191 cases were included (age 62.2±17.8 years, 58.1% males). Table 1 shows by immunological status, patient characteristics and vaccines coverage. Conclusions: Previous pneumonia is significantly more frequent among immuno-compromised patients. PCV13 coverage depends on immunological status, with the highest coverage for immunocompetent patients (64.4%). Facing limitations of the 23-valent polysaccharide (25% of immunocompromised patients had been vaccinated), receiving conjugate vaccines could be a better strategy for both immunocompetent and immunocompromised patients.

P3982 Prescription of antitussives in asthma: A cross-sectional study in primary care in France and in Italy

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Background: Pulmonary hypertension (PH) has negative impact in sarcoidosis prognosis. Prevalence of pulmonary hypertension (PH) among patients with sarcoidosis has not been investigated by screening studies confirmed by hemodynamic evaluation.

Objectives: (1) to determine the prevalence of PH among outpatients with sarcoidosis in a tertiary center and (2) compare the presence of systolic pulmonary artery pressure estimated by echocardiogram (SPAP) ≥ 40 mmHg to the diagnostic gold standard for PH (mean pulmonary artery pressure mPAP ≥ 25 mmHg) measured by pulmonary artery catheterization, in patients with tricuspid reflux velocity (TRV) ≥ 2.5 m/s.

Methods: Seventy-two consecutive patients of 163, from our outpatient sarcoidosis clinic (ATS/ERS criteria), underwent echocardiographic evaluation to assess TRV and to estimate SPAP. Patients with TRV ≥ 2.5 m/s (possible PH) underwent pulmonary artery catheterization. Lung function testing and high-resolution CT (HRCT) also were performed in all patients in Italy.

Results: Nineteen patients had TRV ≥ 2.5 m/s; 18 underwent hemodynamic evaluation (one patient died before the procedure). PH (mPAP ≥ 25 mmHg) was diagnosed in 4 patients and its prevalence was 5.6% (95% CI 0.2-10.8%). Five patients (6.9%), had SPAP ≥ 40 mmHg, estimated by echocardiography, but only two of them had PH (mPAP ≥ 25 mmHg); on the other hand, two patients with SPAP < 40 mmHg, estimated by echocardiography, had PH in hemodynamic study.

Conclusion: PH prevalence in outpatients with sarcoidosis was 5.6%. SPAP > 40 mmHg estimated by echocardiogram was not accurate to diagnose PH (3 false positive and 2 false negative).

P3985 Study of pulmonary embolism prevalence depending on age and sex by autopsy data

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Background: Pulmonary embolism (PE) is the third most frequent cause of death after ischemic heart disease and stroke. Problems concerning statistic data as for PE and the dynamics of its prevalence are insufficient in Ukraine.

Aims and objectives: To study the dynamics of PE prevalence depending on age and sex, to determine factors leading to fatal outcome between 1993 and 2002 and to study the causes of fatal PE development.

Methods: To determine the dynamics of prevalence and causes of fatal PE development we undertook a retrospective analysis of 2260 case reports of patients who died during 1993-2002 years.

Results: The results of 2260 autopsies done during the period of 1993-2002 showed that PE in the structure of pathologic diagnosis occurred in 121 cases (5.3%). Deep vein thrombosis of lower extremities (23.1%) and ischemic heart disease (19.0%) were the major etiological factors causing the development of fatal symptoms of PE in patients during the last decade.

Conclusions: Individuals suffering from deep vein thrombosis, ischemic heart disease with atrial fibrillation and those undergoing operations for oncologic diseases are at great risk of PE development. If sudden dyspnea, chest pain and decrease of blood pressure appear in the patients of risk group additional methods of examination should be used to exclude PE.

P3986 Role of eczema as a risk factor for allergic rhinitis in adolescents

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Introduction: Allergic rhinitis (AR) is one of the most important chronic diseases affecting adolescents. AR often occurs together with eczema.

Aim: To investigate prevalence of eczema and/or positive family history of eczema in adolescents with AR and without AR.

Material and methods: A cross-sectional study conducted on a convenient sam-
ple of 300 adolescents with AR (180 boys and 120 girls), aged 14-17, and equal number of adolescents without AR matched by sex and age selected from three different provinces in Greece. Retrospective analysis of AR and eczema was based on anamnesis and data from medical archives.

**Results:** Eczema is presented in 34% of adolescents with AR (35% of the boys and 33% of the girls). The prevalence of eczema was significantly higher in adolescents with AR compared to adolescents without AR (34% vs 6%, p<0.01). Positive family history of eczema had 31% of adolescents with AR (33% of the boys and 29% of the girls) and its prevalence was significantly higher compared to adolescents without AR (31% vs 5%, p<0.05).

**Conclusion:** Results confirm the role of eczema (personal or family history) as a risk factor for AR in adolescents.

P3987 Effect of hospital volume on patient outcomes in pleural infection

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**Background:** We aimed to investigate the hospital view outcome relationship (HVOR) in patients with pleural infection, which is important because outcomes may be improved by volume-based selective referral if an inverse HVOR is present. **Methods:** We analyzed 24,876 patients with pleural infection in 2,188 hospital-years from Taiwan’s National Health Insurance Research Database between 1997-2008. Primary outcome was hospital mortality. Secondary outcomes were hospital length of stay and charges. Hospital volume was measured both as a categorical and a continuous variable (per one case increase per hospital-year); and the effect of volume was assessed using multivariate logistic regression models with generalized estimating equations accounting for hospital clustering effect. Adjusted covariates included patient and hospital characteristics (model 1), pleural surgery (model 2) and length of hospital stay (model 3).

**Results:** HVOR was significant only when volume was measured as a categorical variable. Patients treated in the highest volume quartile (≥14 cases per hospital-year) had a 23% lower risk of hospital mortality than those in the lowest volume quartile (1 case per hospital-year) after adjusting for patient and hospital characteristics (model 1: adjusted OR 0.73, 95% CI 0.55-0.96). However, after adjusting for treatment covariates (model 2 and 3), the volume effect on hospital mortality disappeared. Hospital volume only explained a small proportion of variation in hospital mortality (1.2 log likelihood/df=0.26%).

**Conclusions:** In patients with pleural infection, the effect of hospital volume on patient outcomes is small, depends on volume measures and can be explained by differences in treatment across hospitals.

P3988 Ethnic peculiarities of chlamydiosis in bronchial asthma

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**Aim:** To study ethnic peculiarities of chlamydiosis prevalence in bronchial asthma (BA) patients of Krasnoyarsk and Kyzyl.

**Materials and methods:** We have examined 239 subjects (from 17 to 78 years): the Europoids (n=159), the Mongoloids (n=80). Among them: BA (n=187), control (n=52). We have determined Chlamydia pneumoniae and Chlamydia psittaci (C pneumoniae et psittaci), Chlamydia trachomatis (C trachomatis) by direct immune fluorescence technique (DIF) for smears of oropharynx, their antibodies from blood serum by DIF – 3.9%, IgM – 3.1%, IgG – 25.6%; in the Mongoloids – 19.0%, 3.4%, 1.7%, respectively. In control groups C pneumoniae et psittaci had by DIF – 14.5%, IEA IgM – 3.9%, IgG – 41.9%; in the Mongoloids – 25.9%, 4.7%, 3.4%, respectively.

**Results:** The frequency of C pneumoniae et psittaci in the Europoids by DIF – 3.9%, IgA – 3.1%, IgM – 25.6%; in the Mongoloids – 19.0%, 3.4%, 1.7%, correspondingly. In control groups C trachomatis in the Europoids by DIF – 19.0%, IEA IgA – 0.0%, IgM – 0.0%, IgG – 6.7%; in the Mongoloids – 13.6%, 0.0%, 9.1%, 40.9%, correspondingly.

**Conclusion:** Were found ethnic peculiarities: in the Mongoloids more frequent than in the Europoids – IgG to C pneumoniae in BA; IgM to C pneumoniae, IgM to Chlamydia in control groups.

P3989 Clinical characteristics and outcomes of community acquired pneumonia (CAP) in adults ≥18 years of age in a well defined area of Badalona, Spain

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**Background:** It is known that CAP often requires hospital admission. However, the prevalence between hospitalizations and outpatient visits for CAP is not well established. **Objective:** To analyse differences between adults with CAP treated as inpatients or outpatients in a well-defined health care area. **Methods:** Retrospective review of medical records of patients ≥18 years old diagnosed with CAP from January 1st 2008 to December 31st 2009 belonging to Badalona (population ≥18 years: 90,015) and attended by 6 primary care centres and 2 hospitals. **Results:** 581 patients were included in the study (incidence rate: 6.0000 adults). 58% were diagnosed at hospital settings. Hospitalised patients (41.5%) were older (mean age: 66.6 years vs. outpatients: 51 years; p<0.001) and had more comorbidities. Inpatient admission was associated with liver disease (OR=5.9), stroke (OR=3.6), dementia (OR=3.5), COPD (OR=2.9), diabetes mellitus (OR=1.9) and age (ORs=1.1; p<0.002). Among cases with microbiological tests done (61.9%; 100% of inpatients vs. 35% of outpatients), 48.3% had negative result (52.7% in inpatients vs. 39.5% in outpatients). Strepococcus pneumoniae was the most prevalent pathogens (34.5% were older, 7.7% in inpatients vs. 46.3% in outpatients). For inpatients, readmission rate was 19.1% and mortality rate 2.5%. Length of hospital stay was 4.4 days. **Conclusions:** Despite current therapeutic measures, CAP continues to be a major health issue with almost 1 out of 2 CAP patients requiring hospitalization. The increase in the future of elderly people and thus of comorbidities stress the need to implement better strategies for CAP prevention.

P3990 Hospitalizations from pandemic influenza (pH1N1) infections among patients with asthma in Spain

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**Objectives:** We describe and analyze the clinical characteristics and outcomes for all persons suffering asthma who were hospitalized with laboratory confirmed pH1N1 infection in Spain in 2009.

**Methods:** This is an observational retrospective study using hospitalization data collected by the Spanish National Hospital Discharge Database. We selected all hospital admissions with diagnosis ICD-9-CM code 488.1 (pH1N1). Discharges were grouped according, according to the presence or not of asthma.

**Results:** The total number of persons hospitalized with pH1N1 was 11,499. Of those, 8,988 suffered asthma. The most common underlying medical condition among asthmatic subjects was obesity (10.97%). The IHM was much lower among asthmatic patients than among those without this disease (0.85% vs. 2.76%, p<0.05). Also, the mean LOS and the mean costs per patient were lower for asthmatic patients (5.38 days and 2,566 €), when compared to hospitalized patients without asthma (7.08 days and 3,186 €). Multivariate analysis, suffering asthma was a factor independently associated with a higher probability of surviving during the hospitalization with pH1N1, (OR=0.42, 95% CI 0.11-0.71). For asthma sufferers, those that died during the hospitalization with influenza pH1N1 were significantly older, suffered more concomitant chronic diseases and had a longer LOS and higher costs.

**Conclusions:** Among individuals hospitalized in 2009 with pH1N1 infection in Spain the prevalence of asthma was 8.98%. The most common underlying medical condition among asthma subjects was obesity. Suffering asthma was independently associated with lower risk of dying during the hospitalization with pH1N1.
The incidence of allergic diseases and respiratory infections in 5-6 years old children

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P3994

The incidence of allergic diseases and respiratory infections in 5-6 years old children

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Aim: To assess incidence of allergic disorders and respiratory infections in 5-6 years old children of Georgia.

Methods: The cross sectional study using specially developed parent questionnaire was conducted in Georgia. At all 1500 parent of 5-6 years children were interviewed. 1499 questionnaires were analyzed by SPSS program.

Results: From 1499 children 32% were 5 years old and 68% 6 years old. The 54% live in urban, 35% in rural area and 11% in high mountains. The study revealed that 23% of children have respiratory viral infections 7-8 times per year, 19.9 – 3.5 times, 53.4% – 1.2 times and 24.2% became ill very rarely. The study show statistically significant difference between the viral infection frequency in rural and urban area (Pearson Chi-Square = 33.895 df = 6 Asymp. Sig. (2-sided) = 0.000). There was not significant difference in morbidity according to family income, size and education. Morbidity is statistically significantly higher in boys and in children attending kindergarten and primary school in comparison with non-organized children (Pearson Chi-Square 14.985 Asymp. Sig. (2-sided) = 0.002). The frequency of chronic diseases reported by parents is 4.1%, from those 47% are allergic disorders (asthma, rhinitis, atopic dermatitis). The most parents associate the asthma exacerbation with viral infections. The 42% of children with asthma and rhinitis were vaccinated with seasonal influenza vaccine. Exacerbation of allergy was significantly less in vaccinated children.

Conclusion: Incidence of allergic disorders among children is raising. Viral infections are risk factors for asthma exacerbation. Vaccination against seasonal influenza should be encouraged.

P3995

PreventTB: Attitudes of decision makers and care providers towards tuberculosis prevention in Germany

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Background: Prevention of tuberculosis with chemotherapy is highly effective, if targeted at high risk populations. However, acceptance of preventive chemotherapy is very variable in Europe.

Methods: We developed and validated a standardized questionnaire to evaluate the attitudes related to tuberculosis prevention of decision makers and caretakers of patients in Germany.

Results: At a first stage we sent 500 questionnaires to health care professionals and received 130 answered forms back. During the second stage 3000 study inviations were sent for an online survey via e-mail. Among the 540 online survey participants were 250 pulmonologists, 189 health officers, 26 general practitioners and 45 other medical professions.

Out of all online participants 48.8% (n=249) would use QuantiFeron Gold in tuberculin-skin-test (n=126), 23.3% T-SpotTB® (n=119) and 3.2% (n=16) other testing devices in the future. In a first stage we sent 500 questionnaires to health care professionals and received 130 answered forms back. During the second stage 3000 study invitations were sent for an online survey via e-mail. Among the 510 online survey participants were 250 pulmonologists, 189 health officers, 26 general practitioners and 45 other medical professions.

In the last decade, ambient particles have decreased from 150µg/m³ to 40µg/m³ in Sao Paulo city (SP) because of public policies to control fuel emissions. Traffic professional are more exposed to air pollution. We tested if ambient air from SP is still deleterious to traffic professionals. Non or ex-smokers (≤1 year) car drivers (N=46) and traffic controllers (N=23) were evaluated 4 times. We checked clinical symptoms and blood inflammatory markers (HDL/LDL, total cholesterol, triglycerides, blood cell counting, clot tests, ultra sensitive c reactive protein- us CRP and erythrocyte sedimentation rate-ESR) on the day after workshift. Pollutants were collected during 24h exposure by individual samplers for fine particles (reflectance) and NO2/NOx (colorimetry). Clinical and blood data were tested against pollutants by linear regression model for repeated measures through generalized estimated equation (GEE). Alpha was 5%. PM2.5 was 40.33±20.83µg/m³ and NO2 197±43.47µg/m³.

407. COPD beyond tobacco
mation, hypercapnoleucytosis and lymphocytes and monocytes increment in traffic professional.

Troller fuel exhaust and respiratory impairments; cross sectional study in Indian fishermen
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Introduction: The fishermen of India are exposed regularly to the fuel exhausts of the trollers. No study has been reported on the respiratory health of the fishermen.

Aim: The study aimed to see whether there is a relationship between troller fuel exhaust and respiratory impairments among the fishermen in India.

Methods: A total of 259 male fishermen participated in the study among which 152 were regularly exposed to troller fuel exhaust (mean age 58±9.8 years) and 107 were never exposed to that (mean age 53±10.3 years). Evaluation of the examined subjects was done using the EIRS questionnaire for the assessment of respiratory symptoms and lung function test. Data were analysed using odds ratio with 95% confidence interval and independent ‘t’ test adjusting for age, smoking status, parental asthma and second hand smoke exposure at home or work.

Results: Fishermen exposed to troller fuel exhaust had higher prevalence of respiratory symptoms for chronic phlegm (OR = 3.4, 95% CI = 1.2-8.3), morning cough with sputum (OR = 2.3, 95% CI = 1.1-4.6), prolonged cough (OR = 2.5, 95% CI = 1.4-6.2), whistling in chest (OR = 2.8, 95% CI = 1.4-7.3) and breathing trouble (OR = 2.6, 95% CI = 1.2-6.2) compared to the those exposed to troller fuel exhaust. Spirometric parameters showed that the mean values of FVC, FEV1, FEV1/FVC, FEV25/75%, FEV50%, FEV75% and FEV25-75% were lower in the subjects exposed to fuel exhausts but statistically significant (p<0.01) was observed for FEV25%, FEV50%, FEV75% and FEV25-75%.

Conclusion: The study suggests that occupational exposure to troller fuel exhaust is associated with higher respiratory symptoms and lung function impairment among fishermen of India.

P3998
To study the effect of chronic inhalation of street dust on pulmonary function in street cleaners
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Purpose: Street cleaners who sweep streets manually are exposed to different types of substances which have deleterious effect on pulmonary functions. We conducted this study to find out this study to know the status of pulmonary functions in these occupationally exposed persons.

Methods: One hundred ten street cleaners, 30 non-smokers and 30 smokers, who were cleaning the streets for more than 5 years were included in this study. Sixty controls, 30 smokers and 30 non-smokers, were also included for comparison. Their lung functions FVC, FEV1, PEFR and FEV25-75 were assessed by spirometry. Statistical analysis of data was done according to unpaired ‘t’ test using SPSS version 16.0 software.

Results: The mean FVC, FEV1, PEFR and FEV25-75 were 85.87±15.16%, 63.82±14.79%, 65.65±16.22% and 53.31±20.29% respectively in nonsmoker cleaners, while in smoker cleaners these were 85.0±15.96%, 59.96±17.35%, 60.90±14.91% and 51.78±19.31% respectively. FVC was not found to be affected in these persons while other parameters were significantly decreased as compared to those in controls. In controls these were 88.66±12.92%, 88.50±18.80%, 90.16±14.30% and 84.00±18.20% respectively in nonsmokers and 84.25±11.2%, 78.42±16.80%, 60.62±18.22% and 62.36±16.50% respectively in smokers.

Conclusion: Obstructive pattern was observed in both smoker and non-smoker cleaners. Smoker cleaners had significantly higher obstruction than smoker controls. Thus street dust was found to act synergistically with smoking and further aggravated obstruction in airways so these persons should take proper preventive measures.

Clinical implications: Street dust acts synergistically with smoking and further aggravates obstruction in airways so these persons should take proper preventive measures.

P3999
COPD among non-smokers
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Aim: COPD among non-smokers from chronic obstructive pulmonary disease [COPD] and at investigating into its etiology.

Subjects & methods: The study comprised a total of 250 subjects, diagnosed with COPD in line with 2010 Global Initiative for chronic Obstructive Lung Disease [GOLD] criteria. The subjects were first divided into 3 GOLD criteria-based subgroups [GOLD I, GOLD II & GOLD III/V] and later on into the smoking and non-smoking arm. The non-smoking arm was also subdivided based on possible COPD risk factors. All study subjects underwent lung function and bronchodilator response testing.

Results: Age differences between the two study arms were proven statistically insignificant. Age differences between GOLD I and GOLD II subgroups proved statistically significant [p=0.0405]. The disease severity registered across younger smokers equaled to that of far older non-smokers.

As for COPD risk factors, occupational exposure and earlier pulmonary TB were far more common in men, while passive smoking and the exposure to bio-fuel combustion releases were more common in women. Frequent respiratory infections experienced during childhood and adolescence were also more common in women. Out of 66 non-smokers, 40 had only one, 17 two and the remaining 9 none of the COPD risk factors, but this failed to affect the disease severity.

Conclusion: The results of this study prove that tobacco smoke and its constituents are not the only culprits for COPD onset. The disease can also be developed by non-smokers due to a number of risk factors elaborated herein.

P4000
Respiratory symptoms and lung function parameters in workers exposed to wood smoke and cooking oil fumes in Nigeria
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Introduction: Exposures to wood smoke and oil fumes occurs in both home and industrial setting and is associated with occurrence of both respiratory and non respiratory diseases.

Mai suya is a common job in most northern Nigeria. Our aim is to study the prevalence and respiratory function parameters among this group.

Method: This is a community, and case controlled study involving mai suya and workers who are not exposed to wood smoke and oil fumes in an occupational setting.

Results: Both groups underwent an interviewer administered questionnaire followed by on spot spirometric test. Chi square was used to test association between respiratory symptoms and the job categories. Odd ratios were determined for the risk of respiratory symptoms and exposure to wood and oil fumes.

Conclusion: The mean FEV1, FEV1 (predicted), FVC, PEFR and FEV25-75% were significantly lower among the test group compared with the control group among all respondents.

Conclusion: Workers exposed to wood smoke and oil fumes have increased risk of respiratory and altered pulmonary functions.

P4001
Gene polymorphism could be a useful prognostic tool in patients with work-related chronic bronchitis
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Objective: Study aimed to assess gene polymorphism for the prognosis of the work-related chronic bronchitis.

Methods: 63 patients with work-related chronic bronchitis were enrolled to the study. Control group included 20 healthy comparable male volunteers without occupational hazards. Study participants were genotyped on tumor necrosis factor-a (TNF- a) gene - G308A and G238A, IL-8 gene (A=252T2), proteintyrosine-kinasephosphatase 22 (PTP 22) gene(R620W), microsomal epoxidhydrolase gene (T337C and A416G). Spirometry, CAT questionnaire data were analyzed.

Results: TNF- a gene polymorphism revealed that heterozygous type was most frequent. IL-8 gene heterozygotes A=252T2 carriers revealed higher IL-6 values vs the homozygote AA and TT (Kruskal-Wallis test: H=5,34, p=0,07). Respiratory failure was the rare complication in proteintyrosinephosphatase 22 gene(R620W) heterozygotes (Chi-Square=6,12, p<0.05). TritTpr carriers had higher pulse rate vs theArgArg carriers(Kruskal-Wallis test: H=9,23, p<0,01). Heterozygotes had higher CAT points and lower minute volume of respiration vs theArgArg carriers (Chi-Square = 10,28, p<0,005). PTP 22 heterozygotes revealed first work-related chronic bronchitis manifestation in younger age than those with theArgArg type (Chi-Square=3,96, p<0,05).
P4002 Indoor pollution and poor ventilation inside the houses synergize to cause airflow limitation in non smokers high altitude dwellers

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Indoor air pollution from biomass smoke fuel is linked to respiratory diseases. We performed spirometry in 3 villages of a nepalese valley where neither traffic nor industries are present, people use biomass fuels for heating and cooking, often without a chimney, and have a very low smoke habit (4%) so that only the effect of indoor pollution can be investigated. We measured the ventilation inside the houses (Ventilation Index [VI] = window surface/kitchen cubic meters) and the environmental (not reported) and exhaled carbon monoxide as a surrogate marker of indoor pollution. A total of 364 subjects performed an acceptable and reproducible spirometry. We calculated the % of subjects with non reversible bronchial obstruction (GOLD) and the % of subjects with FEF25-75 <70% of predicted. Note that in the last ten years indoor ventilation has been improved in the buildings of Pengboche, the village most frequented by trekkers.

Results

| Village-altitude, m | Subjects | Age (mean±SD) | FEV1/FVC | FEF25-75 | Exhaled CO | VI | P
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Thame</td>
<td>154</td>
<td>37 (14–84)</td>
<td>&lt;0.07</td>
<td>&lt;0.7</td>
<td>4.6±0.7</td>
<td>&gt;0.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Phakding</td>
<td>58</td>
<td>29 (16–73)</td>
<td>11.4%</td>
<td>4.4%</td>
<td>9.1±5.3</td>
<td>&gt;0.08</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>Pengboche</td>
<td>92</td>
<td>43 (32–74)</td>
<td>22%</td>
<td>21.7%</td>
<td>9.6±2.7</td>
<td>&gt;0.12</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

In cells 4, 5, the % of subjects with spirometric characteristics (i.e. FEV1/FVC <0.75) is reported.

Exhaled CO and VI are negatively correlated (p <0.002). We conclude that subjects living in poorly ventilated houses and only exposed to indoor pollution have a high incidence of COPD and of abnormalities of FEV1/FVC which could be interpreted as an early marker of bronchial obstruction (Pellengiaro R et al, 2005).

*p <0.05 vs Pengboche

Funded by Ev-K2-CNIR, Italy.

P4003 Investigation of lung involvement with DLCO in women exposed to biomass smoke

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Objective: The reason why the female gender has a significantly higher risk factor to respiratory illnesses compared to males is not known, although some researchers speculate that sex hormones may interfere in the proneness to these diseases. The physiologic hormonal fluctuation during the menstrual cycle is known to induce changes in nasal epithelium and lung inflammation. The aim of this study is to analyze how the hormonal cycling of female mice is affected by near-ambient levels of pollution. Particulate matter (PM) was concentrated by an ambient particulate matter concentrator (APC). 14 Male (M) Balb/C mice were divided into two groups: without exposure to PM (M/A/control group) and exposed to PM. 28 Female Balb/C mice were divided into four groups, according to the estrous cycle. Only female mice from proestrus (PE) and estrus (E) were enrolled. Those from PE were divided into two subgroups: with and without exposure to PM (PE/PM and PE/A). Mice from E were also divided into two subgroups: with and without exposure to PM (E/PM and E/A). Neutral and acidic mucus content was quantified in epithelium through morphometry. Inflammatory cells were analyzed by bronchoalveolar lavage (BAL). APM exposure in MPM increased both neutrophils in BAL (p<0.001) and neutral mucus content (p<0.016) from nasal epithelium, when compared to PE/PM. No statistical difference was observed to E/PM. In the M/A group, it was observed an increase in both total BAL (p=0.042) and macrophages (p=0.003) when compared to PE/PE. At high altitudes these levels of PM exposure promoted a higher neutrophil recruitment in male than in female mice in proestrus.

P4005 Tumor necrosis factor-α (TNF-α) gene polymorphism in work-related chronic bronchitis patients

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Objective: Cytokine gene polymorphism could contribute to different susceptibility of occupational dust exposure and work-related chronic bronchitis development and management.

Methods: 87 work-related bronchitis patients were enrolled in the study. Spirometry, pulse oximetry data, autonomic regulation, questionnaire SDNA were obtained on exacerbation and after treatment. Patients were genotyped on TNF-α gene G(-308)A and G(-238)A transitions.

Results: TNF-α gene polymorphism revealed that heterozygous type was most frequent. Homozygous GG- G(-308)A and G(-238)A were determined in 5.7% and 1.1% of patients respectively. GG 308 carriers had a higher bronchial obstruction (FEV1/FVC) in heterozygotes .70 kg vs 85 kg, p<0.04). Homozygotes revealed better pulmonary tests results after the treatment FEV1/FVC increase (1.00 vs -0.69, respectively, p<0.04), respiratory volume (0.18 vs 0.02 L/min,0.05), minute volume of respiration (6.20 vs 0.55, L=0.01) GG 238 homoygotes demonstrated lower vital capacity vs those in the heterozygous (63 vs 71.5% of the predicted, respectively, p<0.02) GG 238 had higher oxygen saturation at rest (p<0.02), at the breathing holding (p<0.01) and at the hyperventilation (p<0.005). Homozygotes had lower points increase in CAT test than those in heterozygotes after the treatment (-5 vs -1, p<0.04) better. Patients results (1.20 vs 0.35 points, p=0.04).

Conclusion: TNF-α gene polymorphism is reliable for the prognosis of the work-related chronic bronchitis. GG 308 and GG 238 carriers with work-related chronic bronchitis revealed better pulmonary tests results and better improvement after the treatment vs the heterozygotes with the comparable length of service.

P4006 Cytokines and immunoglobulins for the prognosis of the work-related chronic bronchitis

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Objective: Study aimed to assess cytokines and immunoglobulins for the prognosis of the work-related chronic bronchitis due to the occupational dust exposure.

Methods: 63 patients with work-related chronic bronchitis were enrolled to the study. Control group included 20 healthy comparable male volunteers without occupational hazards. Serum IL-6, IL-10, TNF-α, IgG, IgA, total IgM were measured. Spirometry and respiratory pressure measurements were analyzed. Results: TNF-α levels correlated with the body mass (r=0.39, p<0.05), age (r=-0.37, p<0.05) and spirometry data - minute volume of respiration (r=0.51, p<0.01) and respiratory volume (r=0.44, p<0.03). IL-10 levels were associated with the body mass (r=0.45, p<0.02) and total protein level (r=0.50, p<0.02). IL-6, Ig A and Ig M levels revealed statistically significant correlation with the WEC counts (r=0.07, p<0.01), eosinophils (r=0.39, p<0.03), total eosinophils (r=0.51, p<0.05). Ig A, E,G values correlated with the minute volume of respiration (r=0.42, p<0.05).

738s
TUESDAY, SEPTEMBER 4TH 2012
Effects of differences in exposure conditions on pulmonary functions

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Introduction: Air pollution due to industrial waste and tobacco smoke has a serious detrimental influence on pulmonary functions. However, few reports have been published regarding the effects of differences in exposure conditions on the pulmonary functions.

Aims and objectives: The objective of this study was to examine how the differences in exposure conditions affect the pulmonary functions.

Methods: The subjects consisted of 869 people presented with functional decline as a result of working or living in an area with air pollution, and 434 people participated in an epidemiological investigation in an area without air pollution. Reviews of pulmonary function tests were conducted by employing the medical examination data. Pulmonary functions were compared in smokers versus non-smokers in the area with pollution vs. non-smokers with pollution and were also compared to smokers in the non-polluted area (smokers without) and non-smokers in the non-polluted area (non-smokers without).

Results: In terms of the %VC, the values were 90.9%, 95.5%, 98.2%, and 97.4% in the smokers with pollution, non-smokers with pollution, smokers without and non-smokers without, respectively. For the FEV1%, the value for smokers with pollution was 65.2%, non-smokers with pollution was 70.1%, smokers without was 70.8%, and non-smokers without was 79.2%. The smokers with pollution had a lower FEV1% than the other groups (p<0.001).

Conclusions: Air pollution and tobacco smoke exposure are associated with reduced VC and FEV1%. In particular, exposure to both factors had a stronger effect on the FEV1 than did exposure to one factor. Therefore, active smoking cessation instruction is necessary for subject in the polluted area.

P4007

The effects of atorvastatin in mustard gas exposed patients with chronic obstructive pulmonary disease: A randomized controlled trial

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Background: Statins have anti-inflammatory effects in patients with chronic obstructive pulmonary disease. This study designed to evaluate the effects of atorvastatin on serum highly sensitive C-reactive protein (hs-CRP) and pulmonary function in sulfur mustard (SM) exposed patients with chronic obstructive pulmonary disease.

Methods: In a double blind clinical trial, 50 patients with chronic obstructive pulmonary disease due to sulfur mustard and high hs-CRP, randomly entered in this study. 45 patients completed the study (n=22, placebo and n=23, atorvastatin). Serum hs-CRP, pulseoximetry, spirometry and six-minute walk distance test (6MWDT) were measured. COPD assessment test (CAT) and St George's respiratory questionnaire (SGRQ) were completed by patients at the beginning of trial and after 9 weeks of prescription of 40 mg/day atorvastatin or placebo. At 4th week, pulseoximetry, spirometry and 6MWDT were measured.

Results: At 4th week, there was no improvement in the atorvastatin group compared to the placebo group in SP02, FEV1, and 6MWDT (p=0.79, p=0.12, p=0.12 respectively). At 9th week, there was no improvement in atorvastatin in serum hs-CRP, SP02, FEV1 and 6MWDT compared to the placebo (p=0.35, p=0.28, p=0.94, p=0.43 respectively) but there was an improvement in atorvastatin in quality of life with (CAT score, P<0.01 and SGRQ total score, P=0.004).

Conclusions: Atorvastatin does not alter serum hs-CRP and lung functions but may improve quality of life in SM-injured patients with chronic obstructive pulmonary disease.

Key Word: Sulfur mustard, Atorvastatin, hs-CRP. Chronic obstructive pulmonary disease.

P4010

Presence of hypertension (HT), ischemic heart diseases (IHD) and a family history of hypertension are independently associated with reduced peak expiratory flow (PEF) and lower Forced Vital Capacity (FVC) in Saudi population

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Background: Reduced lung function has been shown to be an independent predictor of cardiovascular mortality in patients of hypertension and IHD in earlier studies.

We aimed to study the association between HT, IHD and PEF values amongst road transport workers from Andhra Pradesh, India.

Methods: 7,154 bus drivers, conductors, garage workers and office-based workers of the Andhra Pradesh State Road Transport Corporation (APSRTC) were randomly selected from 24 bus depots and administered a health questionnaire, underwater blood pressure monitoring, spirometry, and PEF values with the EU scale peak flow meter (Breathmeter®). CIPLA Ltd., India). Current, past and family histories of cardiovascular and respiratory ailments were captured. Associations between PEF values and HT and IHD were studied using the chi square test and the values expressed as odds ratios.

Results: Presence of HT, IHD and a family history of HT were independently associated with low PEF values, defined as less than 80% predicted PEF value [OR 1.3, 95% CI 1.1 – 1.5, p=0.008; OR 1.9, 95% CI 1.2 – 2.0, p=0.004; OR 1.2, 95% CI 1.0 – 1.4, p=0.039 respectively]. No difference in odds ratios were observed between different occupations.

Conclusions: PEF values of at least 80% predicted are strongly associated with presence of HT, family history of HT and presence of IHD. Reduced peak flow values should stimulate the need for performing a cardiovascular assessment.

P4011

Study of daytime sleepiness among tunnel workers on rotating schedule

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Introduction: Working on shifts, and especially, on a night shift, influences the endogenous sleep regulation system leading to diminished sleep time and increased somnolence. This may be dangerous in some cases, especially in large scale constructions, such as tunnels.

Aims and objectives: The aim of our study was to examine whether sleep duration and daytime sleepiness differed between day and night shifts among tunnel workers.

Methods: In this study 42 male workers (during the last semester) in a tunnel construction were recruited and examined at workplace. They underwent spirometric control and they were asked to complete a questionnaire referring to demographic factors, status of health and the Epworth Sleepiness Scale.

Results: The workers present a mean age of 42 years old and a mean Body Mass Index (BMI) of 27.2 kg/m². 69% of them were active smokers, while 31% have never tried smoking. Interestingly, 93% of the tunnel workers were consuming two coffees per day at least, while the remaining 7% were not drinking coffee at all. Almost one third of them reported alcohol consumption on a daily basis. Severe cardiologic, respiratory or endocrine disease was not reported among the participants and neither were depression and anxiety disorders. Our results showed that almost all the workers had gathered a score less than 10 in the Epworth
Sleeping Time Scale (a score of 10 or more is considered sleep), except for two subjects in which statistical analysis did not reveal any statistically significant correlation between somnolence and the work schedule (p>0.88).

Conclusions: The rotating shift in a dark and demanding environment, as in the tunnel construction, does not play a significant role in daytime sleepiness.

P4012
Basic spirometric parameters of coke plant workers over the years
Emilija Kolarczyk, Wiesława Szot, Joanna Zajac, Department of Hygiene and Dietetics, Jagiellonian University Medical College, Kraków, Poland

The aim of this study was to examine respiratory system efficiency in workers employed as coke plant battery staff in Steel Mill in Kraków over the years.

Methods: The spirometric examinations were performed at 3 different times: 1st in 1974 -65 workers (age: 32.7±4.8 years, period of occupational exposure: 8.8±4.6 years), 2nd in 1990 - the same 65 workers (they worked all the time in the same workshop: 48.8±5.1 years; 24.6±4.7 years). 3rd in 2012 - 49 workers (age: 46.27±8.9, period of occupational exposure - 22.4±7.91). In 1974-1990 the levels of industrial pollution at workplace were similar. The concentration of SO2 was 15.4±6.6 mg/m3 and exceeded TLV, NOx -2.6±1.5 mg/m3, total dust-7.5-29.1 mg/m3 and free silicon dioxide-1.5-11.5%, geometric dimension of dust granule-3.9-4.5 um. In 2012 due to changes in both ownership of coke plants and increase in workers security, measured values were: SO2 -8.9±4.4 mg/m3, NOx -2.1±1.1 mg/m3, total dust-0.3-3.0 mg/m3 and free silicon dioxide -2.0-3.6%.

Results: The medians of basic parameters measured at 1st, 2nd and 3rd examination were as follows:

<table>
<thead>
<tr>
<th></th>
<th>VC</th>
<th>FEV1</th>
<th>FEV1/VC</th>
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<tbody>
<tr>
<td>1st</td>
<td>5.22</td>
<td>4.91</td>
<td>79%</td>
</tr>
<tr>
<td>2nd</td>
<td>4.46</td>
<td>3.37</td>
<td>79%</td>
</tr>
<tr>
<td>3rd</td>
<td>4.89</td>
<td>3.81</td>
<td>79%</td>
</tr>
</tbody>
</table>

Conclusions: After 16 years of occupational exposure to gaseous and dust pollutants (1st & 2nd) significant decline of basic respiratory parameters was noted but they were still in the normal range. After transformations in Poland the coke plant was modernized and environmental conditions significantly improved therefore it was agree with expectation that the new generation of workers also had the high efficiency of respiratory system.

P4014
Spriometric findings in asbestos-exposed subjects with pleural plaques missed by chest radiography but detected by HRCT
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Introduction: High-resolution computed tomography (HRCT) is recognizable more sensitive than chest X-ray (CXR) in detecting small-to-moderately large pleural plaques (PP) in asbestos-exposed subjects.

Objectives: We reasoned that if the PP missed on CXR is associated with decreased lung function, this would lend support to a wider use of HRCT in these subjects.

Methods: HRCT and spirometry were obtained in 1075 miners and millers who have been exposed to progressively lower airborne concentrations of asbestos over time (Groups I to III) and were free of PP or asbestosis on CXR.

Results: We found that 100/1075 (9.3%) of the subjects had PP only on HRCT (44/40 (48.8%) in Group I, 44/537 (8.2%) in Group II and 12/448 (2.7%) in Group III. As shown in the Table, subjects with PP on HRCT but not CXR had consistently lower spirometric values than those defined as normal by both methods (p<0.05). Similar results were obtained after adjusting for smoking status.

Conclusions: We conclude that the lack of sensitivity of CXR in detecting PP in asbestos-exposed subjects is a matter of concern, as subjects with these abnormalities only on HRCT had decreased lung function values. This seems of special relevance among more exposed subjects.
P4016
Exposure characteristics of patients with different pathological types of malignant mesothelioma
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Background: Malignant mesothelioma (MM) of the pleura and peritoneum has 3 main pathological sub-types: epithelioid, sarcomatoid and biphasic with different clinical behaviour and prognosis but all related to asbestos exposure.

Aim: To identify any distinguishing characteristics of patients with different subtypes of MM that may relate to their differing clinical manifestations.

Methods: All cases of MM that have been recorded in Western Australia since the first case in 1962 until 2010 were reviewed for the demographic characteristics, histological type, and asbestos exposure history.

Results: There have been 1867 (1612 male) confirmed cases of MM between 1960 and June 2011. Of those there are 23 sarcomatoid, 744 epithelioid and 367 biphasic subtypes with 519 cases not specified. Analyses were confined to cases with defined pathological sub-types. Results from univariable analyses are presented in Table 1. In a multinomial regression, age at diagnosis, exposure route and topography were significantly associated with subtype.

Characteristics of MM subtypes

<table>
<thead>
<tr>
<th>Epithelioid</th>
<th>Sarcomatoid</th>
<th>Biphasic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%male)</td>
<td>84.0</td>
<td>90.3</td>
<td>89.4</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>66.8 (11.9)</td>
<td>70.2 (9.9)</td>
<td>66.4 (11.4)</td>
</tr>
<tr>
<td>Time since 1st exposure (years)</td>
<td>43.2 (11.9)</td>
<td>45.4 (11.5)</td>
<td>41.7 (11.8)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>55.6</td>
<td>50.2</td>
<td>53.7</td>
</tr>
<tr>
<td>Exposure history (%Environmental)</td>
<td>24.7</td>
<td>14.7</td>
<td>26.9</td>
</tr>
<tr>
<td>Exposure route (%Environmental)</td>
<td>15.9</td>
<td>8.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Topography (%Pleural)</td>
<td>91.5</td>
<td>98.7</td>
<td>94.3</td>
</tr>
</tbody>
</table>

Mean (SD)

Conclusion: Compared to other subtypes sarcomatoid MM appears in older subjects and is less common with environmental exposure to asbestos. It is also less common in the peritoneum than pleura.

P4017
End of domestic asbestos exposure epidemic in Metsovo; N.W. Greece
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Introduction: Metsovo has been exposed to tremolite asbestos from a white-wash used by all until 1940. This exposure has resulted in frequent pleural calcifications (PCs) and a mesothelioma epidemic, fading due to abandonment of lito.

We have reported that most older Metsovites have PCs in chest CT and asbestos bodies (ABs) in BAL. These parameters are used now in younger Metsovites to evaluate if those not exposed are free from signs of exposure.

Materials & methods: 22 Metsovites age 30-49 had chest CTs and 8 of them BAL. Age was chosen because it takes 30 yrs for PCs to appear and because they were born between 1960-80 when lito use had declined considerably giving us unique opportunities to correlate clinical and pathological findings.

Results: Only 3/22 had used lito (35,47,48 yo). All 8 BAL studies were negative, in contrast to the exposed control group, where 6/7 (85.7%) BAL studies showed ABs. Only one chest CT was positive for PCs (49yo: lito until 13yo). From the 86 chest CTs, 5 belonged in the 30-39 and 9 in 40-49 yo group. None of the 30-39yo group had PCs and none had used lito. There was one CT positive in the 40-49yo group (11%). He had used lito in childhood as was the case with 2/6 others of this group in which lito history was obtained.

Conclusion: There is no evidence of asbestos exposure in younger Metsovites who have not used lito. The domestic use of this tremolite-whitewash has been the only source of asbestos in Metsovo. Its abandonment has resulted in the end of this epidemic.

P4018
Asbestos-related disease: Clinico-pathological correlation
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Introduction: The accurate diagnosis of asbestos-related diseases is important. For compensation asbestos is definately diagnosed without the aid of pathology while the diagnoses of lung cancer and mesothelioma require surgical lung biopsies. South African law makes provision for the autopsy examination of the cardiorespiratory organs of deceased miners for compensation purposes. This provides unique opportunities to correlate clinical and pathological findings.

Methods: Deceased cases assessed in-life for compensation using chest radiographs by the Asbestos Relief Trust and who had an autopsy at the National Institute for Occupational Health from May 2010 to May 2011 were studied. The in-life and autopsy diagnoses of asbestosis and its severity, mesothelioma and lung cancer were compared. Sensitivities, specificities and related values were calculated.

Results: 94 cases were studied. ARDs were diagnosed at autopsy in 78 (83%) of the cases: 47 (50%) had asbestosis, 20 (21%) mesothelioma and 15 (16%) lung cancer. Sensitivity, specificity and accuracy rates for the clinical diagnoses were 47%, 83% and 65% for asbestosis; 65%, 96% and 89% for mesothelioma and 49%, 100% and 90% for lung cancer respectively.

Discussion: Cases with slight asbestosis were more likely to be missed clinically (69%) than marked disease (42%). Many malignancies were undiagnosed in life. These findings underline the difficulty of diagnosing ARDs and the importance of autopsies in detecting disease missed in-life.

P4019
Relationship between endogenous NO and blood gas parameters in former asbestos workers
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Introduction: Background: Nitric oxide is a major endogenous regulator of the vascular tone. Inhaled nitric oxide gas has been used for treatment of pulmonary arterial pressure and hypoxaemia (especially in persistent pulmonary hypertension of the newborn).

It is not known whether there is a relationship between endogenous bronchial NO concentration and blood gas parameters.

Patients and methods: 48 former asbestos workers (all non-smokers) were examined within the framework of a surveillance program. Lung function tests, blood gas analyses, diffusion capacity for CO (DL,CO), and multiple FeNO measurements were obtained within the framework of a surveillance program. None of the patients exhibited high FeNO values (FeNO=16.9 ppb).

Results: Only 3/22 had used lito (35,47,48 yo). All 8 BAL studies were negative, in contrast to the exposed control group, where 6/7 (85.7%) BAL studies showed ABs. Only one chest CT was positive for PCs (49yo: lito until 13yo). From the 86 chest CTs, 5 belonged in the 30-39 and 9 in 40-49 yo group. None of the 30-39yo group had PCs and none had used lito. There was one CT positive in the 40-49yo group (11%). He had used lito in childhood as was the case with 2/6 others of this group in which lito history was obtained.

Conclusion: There is no evidence of asbestos exposure in younger Metsovites who have not used lito. The domestic use of this tremolite-whitewash has been the only source of asbestos in Metsovo. Its abandonment has resulted in the end of this epidemic.

Discussion and conclusions: The decreased values of DL,CO reflect the pulmonary fibrosis in asbestos exposed subjects. This is associated with reduced FeNO. The positive correlation between Cao2 and DL,CO may be due to its vasodilatative effects.

P4020
The evaluation of the relationship between malignant mesothelioma and environmental asbestos exposure in Sivas
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Objectives: Sivas province is located in the Central Anatolia where asbestos exposure is common. We aimed to study the relationship between environmental asbestos exposure and epidemiologic features of patients with MM.

Methods: In total, 219 patients with MM who were diagnosed in our hospital between 1993 and 2010 were retrospectively analyzed in terms of demographical and clinical features. Rock, soil and house plaster samples were taken from the habitats of those patients and were evaluated with optical microscopy and X-ray diffraction methods.

Results: The patients aged between 18 and 85 years (male/female=1:4.4). Most of the patients (86%) confirmed an asbestos exposure. The most frequent symptoms were chest pain (60%) and dyspnea (50%) and the duration of the symp-
Conclusions: MM is primarily related to environmental chrysotile exposure in Sivas. However, single or combined roles and/or interactions of other fibrous and non-fibrous minerals in the etiology of MM are not yet fully understood and remain to be investigated.

P4021
Prevalence of obstructive and restrictive functional patterns in a population of environmental asbestos exposed
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Background: Tremolite is one of the six recognized types of asbestos. This material is toxic and inhaling the fibers can lead to asbestosis, lung cancer and both pleural and peritoneal mesothelioma. Resident population in the area of Lagonegro (Basilicata, Italy) has been shown to be exposed to environmental tremolite pollution, deriving from superficial rocks and asbestos caves. A branch of the ongoing health surveillance program for residents is evaluating the prevalence of obstructive or restrictive pulmonary functional patterns.

Methods: A total number of 1353 individuals were included into this study. The study group was composed by 695 residents in the tremolite-exposed area of Lagonegro (age 49.3±16.68, current smokers 122, ex-smokers 134). The control group was composed by 658 individuals living in areas not tremolite-exposed (age 54.13±17.75, current smokers 121, ex-smokers 174). All the participants to the study performed a lung function test.

Results: Prevalence of obstructive disease was 0.58% in the exposed group and 0.236 (95% CI 0.079-0.708) in the non-exposed group (p=0.539). Prevalence of obstructive disease was 0.58% in the exposed group and 0.236 (95% CI 0.079-0.708) in the non-exposed group (p=0.539). Prevalence of obstructive disease was 0.58% in the exposed group and 0.236 (95% CI 0.079-0.708) in the non-exposed group (p=0.539). Prevalence of obstructive disease was 0.58% in the exposed group and 0.236 (95% CI 0.079-0.708) in the non-exposed group (p=0.539).

Conclusions: According to our data, tremolite exposure has apparently no influence on the prevalence of functional respiratory deficit. It is necessary to follow the exposed group in time by repeated measurements.

P4022
The prevalence of silicosis in dental prosthetic technicians working in Kahramanmaras City
Hasan Kahraman1, Muge Cinkara1, Nurhan Koksal2, Fuat Ozkan2, Hasan Ekerbicer1, 2Chert Disease, Kahramanmaras Sutcuimam University, Faculty of Medicine, Kahramanmaras, Turkey; 3Radiology, Kahramanmaras Sutcuimam University, Faculty of Medicine, Kahramanmaras, Turkey; 4Public Health, Kahramanmaras Sutcuimam University, Faculty of Medicine, Kahramanmaras, Turkey
Objective: The aim of our study is to determine, the presence and the frequency of occupational silicosis in dental prosthesis technicians in Kahramanmaras.

Materials and methods: The questionnaire was administered to participants prepared by the Turkish Thoracic Society for occupational and environmental lung diseases, physical examination was performed, PFT were measured, and HRCT was taken. The resulting images were evaluated independently by three readers. When at least two report as pathologic, cases were accepted as silicosis.

Results: Technicians involving the study were 82, 80 of them were male (97.5%). The mean age was 30.9±6.8, the mean pack-year of smoking was 12.4±13.8, the mean working period was 15.8±8.7 years. In 7 abnormal respiratory examination findings were detected. During working, 24 (29.3%) continuously, 21 (25.6%) never, 37 (45.1%) occasionally used the mask. No statistically significant difference was found between the mask usage and HRCT findings of silicosis (p>0.05) and between the symptoms in workplace and the duration of working period (p>0.05). PFT of employees were evaluated as normal. In evaluation of HRCT, 51 (62.2%) had normal and 19 (23.2%) had radiology compatible with silicosis. The localizations of the radiological involvement were determined; only upper lobes in 12 (63.2%), only the lower lobes in 1 (5.3%), upper and middle lobes in 3 (15.8%), upper and lower lobes in 2 (10.5%) and together with the upper, middle and lower lobes in 1 (5.3%) person.

Conclusions: This study showed that dental prostheses technicians have high risk for catching silicosis.

P4023
Silicosis caused by sandblasting in teflon coated pan manufacturing
Nurhan Koksal, Hasan Kahraman, Nurhan Atilla. Pulmonary Diseases, Faculty of Medicine, Kahramanmaras Sutcuimam University, Kahramanmaras, Turkey

Silicosis is an occupational disease of the lungs caused by inhalation of crystalline silica and is marked by fibrotic pulmonary reaction. Sandblasting has been commonly used during abrading of jeans, glass, and metal. We presented 17 silicosis cases occurring in teflon coated pan manufacturing. Symptoms questionnaire, pulmonary function tests, carbon monoxide diffusion test, and thorax HRCT were done. All of employees are male and mean age was 28.8±5.2 (18-41). The mean duration of working period for this job was 24.8±15.4 (9-60) months.

Table 1. Silicosiis demographics

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Smoking (pack-year)</th>
<th>Employment time (months)</th>
<th>Symptoms</th>
<th>Silicosis type</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>C-D</td>
<td>AS</td>
<td>NCS</td>
</tr>
<tr>
<td>2</td>
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<td>–</td>
<td>60</td>
<td>S</td>
<td>CS</td>
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</tr>
<tr>
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NS=No symptom, D= Dyspnea, C=Cough, S=Sputum, CP=Chest pain, AS=Acute silicosis, ACS=Accelerated silicosis, CS=Classical silicosis, ST=Silicotuberculosis, NCS=No clinical symptoms, RF=Respiratory failure.

Clinically total 17 cases was evaluated, 7 cases as classic silicosis, 6 cases as classical silicosis, 3 cases as accelerated silicosis (ACS) and one case as silicotuberculosis (ST). Four cases of AS and one ST case were died during follow-up. Acute respiratory failure was present in one AS case and one ACS case. Clinical follow-up of other patients has been continued. In view of this report, sandblasting of teflon pan manufacturing cause silicosis. These clinical type commonly acute form and mortaly was high.

P4024
Silica-induced inflammammasome activation in lung epithelial cells
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Introduction and objectives: In myeloid cells the inflammasome plays a crucial role in innate immune defenses against pathogen- and danger-associated patterns such as crystalline silica. Respirable mineral particles impinge upon the lung epithelium causing irreversible damage, sustained inflammation and silicosis. In this study we investigated lung epithelial cells as a target for silica-induced inflammasome activation.

Methods: Primary mouse tracheal epithelial cells, human bronchial epithelial cells (BEAS-2B) and primary normal human bronchial epithelial cells (NHBE) were exposed to toxic but nonlethal doses of crystalline silica over time to perform functional characterization of NLRP3, caspase-1, IL-1β, IL-18 and HMGB1. Gene expression microarray, quantitative RT-PCR, BioPlex analysis, caspase-1zymatic activity assay, western blot techniques and cytokine specific ELISA were performed.

Results: We were able to show particle uptake by lung epithelial cells, transcriptional and translational upregulation of the components of the NLRP3 inflammasome platform, as well as activation of caspase-1. This activation furthermore led to maturation of pro-IL-1β to secreted IL-1β, and a significant increase in the unconventional release of alarmins such as IL-33 and HMGB1. Small interfering
DNA experiments using sNLRP3 revealed the pivotal role of the inflammatory component in diminished release of pro-inflammatory cytokines, danger molecules and growth factors.

**Conclusion:** Our novel data indicate the presence and functional activation of the NLRP3 inflammasome by crystalline silica in human lung epithelial cells, which prolongs an inflammatory signal mediating a cadre of lung diseases.

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**P4025**

Screening healthcare workers for Mycobacterium TB: Is QFT-G now the test of choice?

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**Introduction:** Quantiferon-Gold (QFT-G) is FDA approved for the diagnosis of infection with Mycobacterium tuberculosis. CDC guidelines have supported the use of QFT-G in all cases where Tuberculin Skin Test (TST) is used, including screening of healthcare workers (HCWs). We sought to establish the benefits of QFT-G in HCW screening within our own hospital practice.

**Methods:** In June 2010, a QFT-G test was screened, by TST all newly employed HCWs. 41 patients over the period had full data for analysis. Country of origin and evidence of prior distant history of BCG vaccination on examination, were also documented. A TST of ≥10mm was considered a positive result and was followed by a QFT-G.

**Results:** 41 TST were performed, 35/41 (85.4%) had a BCG scar. TST was positive in 23/41 (56.1%). QFT-G was positive in 15/23 (65.2%). Significantly 8/23 (34.8%) TST proved to be false positives on the basis of a subsequent negative QFT-G. **Conclusion:** HCWs are identified as a cohort at risk of Mycobacterium TB infection. As a lab based assay QFT-G is not subject to biases or the errors of TST placement or reading. It also negates the need for a return visit in 48-72 hours for interpretation. 34.8% of our cohort had a false positive TST leading us to question the sensitivity of the test in this cohort. QFT-G has proved itself to approach 98% sensitivity and 89% specificity and is a suitable replacement for TST in HCW screening.

**References:**


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**P4026**

GTn heme oxygenase-1 polymorphism in beryllium-exposed dental technicians

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**Background:** Dental technicians (DTs) are exposed to Beryllium (Be) and other substances capable of inducing lung disease. Heme oxygenase-1 (HO-1) play a protective antioxidant role in the lung. The guanine-thymidine (GT) n repeats in the HO-1 promoter determine HO-1 induction level. Short (GT) n repeats (n < 25) and (S genotype) is considered as protective since HO-1 is induced more rapidly than in long (GT) n repeats (n ≥ 25; L genotype).

**Aims:** To evaluate the correlation of HO-1 polymorphisms to functional and exposure parameters in DTs and the protective role of HO-1 on Be Oxide (BeO) exposed A549 epithelial cells apoptosis.

**Methods:** 65 DTs were followed-up for 2 years by questionnaires, induced sputum (IS) particles size distribution laser analysis (Dapi 2000 Donner Tech and Pulmonary Function Tests). HO-1 genotyping was done by PCR DNA sequence (ABI prism 310). A549 epithelial cell line was cultured with BeO and pretreated with Hemin and ZnPP (for stimulation and inhibition of HO-1 respectively), HO-1 gene expression was evaluated in IS and A549 cells by quantitative PCR and apoptosis by TUNEL staining.

**Results:** Association was found between GTn and HO-1 gene expression in IS (p=0.35 p=0.017), the GTn>25 group had higher HO1 expression than the GTn≤25 group (0.18±0.16 Vt 0.70±0.06 p= 0.007 respectively). Decrease in DLCO (Diffusion Lung CO) was associate with GTn>25. Hemin increases the HO-1 gene expression and decreases the apoptosis levels in A549 epithelial cells while is increased by ZnPP.

**Conclusions:** DLCO decrease is associated with L genotype. Decrease apoptosis in BeO-exposed A549 epithelial cells by hemin may indicate a protective role of HO-1.

Supported by USA-Israel Bi National Science Foundation.

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**P4027**

Hypersensitivity pneumonitis related to Streptomyces mesophile and Penicillium chrysogenum: The usefulness of the Medical Indoor Environment Council (MIEC)

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**Introduction:** Hypersensitivity pneumonitis (HP), secondary to the inhalation of organic antigens at home are rare and the diagnosis is very often difficult without home visit. Observation: We report a case of a 55 years male patient, ex-smoker, with an allergic asthma since childhood, well controlled with inhaled cortico-steroids, who developed two respiratory distresses during asthma exacerbations. HPS was suspected because of the fever (39°C), the dry cough, rapidly progressive dyspnea, chest pain and crutches. Blood gas analysis found a hypoxemia of S2 immHg, and the CT-scan showed a few ground glass images in the upper lobes. 126 respiratory function tests showed a severe obstructive syndrom and a decrease of diffusion test. Allergological investigation: The diagnosis was suspected because the symptoms were linked to domestic environment, triggered by stays in a camper. The (MIEC) visited the house and the camper and performed air and dust samples. Moldy walnuts were found in the camper. The identification of microorganisms presents on the nuts, in the air and in the dust, were used for the search for precipitins in double diffusion (DD) and electroversion (IE). Of the 14 antigens tested, serological tests were considered significant for Streptomyces mesophile (5 bands DD, 6 bands Eisand Penicillium chrysogenum (1 band DD, 4 bands E)). The patient removed the nuts from his camper. Since then, he has not experienced any exacerbation.

**Conclusion:** This is a case of domestic HSP to Streptomyces mesophile and Penicillium chrysogenum. The MIECs intervention was useful for the diagnosis and the treatment.

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**P4028**

Geochemical factors and incidence of sarcoidosis in Tomsk region

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**Methods:** Sarcoidosis incidence has been studied according over a 20-year period (528 patients without unhealthy working conditions). The incidence rate has been defined per 100000 of population in the geochemical and environmental regions. 126 measurements of 23 chemical elements (Na, Ca, Sc, Cr, Fe, Co, Zn, Br, Ag, Sb, Au, La, Th, U, Hf, Se, Hg, Sm, Eu, Yb, and Lu) were made by the neutron activation analysis in the dust-aerosol, soil and drinking water in Tomsk and Tomsk region. Sarcoidosis highest incidence was found on the territories exposed to anthropogenic factors: in Seversk 67.3 (nuclear fuel industries), Octabryksky district of Tomsk 56.8, Tomsk rural district 68.14, Strezhevoy 47.2 (fuel and oil industries). In these districts the incidence rate was significantly higher compared to the mean findings in region - 42.6 (χ2 = 7.9411.6; p < 0.05). The incidence in the mainly agricultural districts was minimal 23.5. In Seversk recurrent forms were significantly higher - 20.56 versus 0.23 in Tomsk (χ2 = 7.941; p < 0.01). The correlations have been found between: the sarcoidosis incidence and the Na content in the dust aerosols (r = 0.9; p < 0.05), Ce in the soils of industrial territories (r = 0.9; p < 0.05), Ca in drinking water (r = 0.8; p < 0.01), recurrent forms of sarcoidosis and Lu in soils of the contaminated territories (r = 0.8; p < 0.05), Cr in soils of agrarian districts (r = 0.65; p < 0.05). Thus, the correlation between the ecological state of the territories and sarcoidosis incidence is sure to exist. Uncertainty of the obtained data does not allow understanding which factor plays the role. One cannot deny the influence of trace elements which have shown the correlations: Na, Ca, Lu, Ce, Cr.

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**P4029**

Exhaled airway and alveolar nitric acid in extrinsic allergic alveolitis

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**Background:** In extrinsic allergic alveolitis (EAA), alveolar nitric oxide (AlvNO) and the airway fraction of exhaled nitric oxide (FEno) have not been well studied.

**Methods:** EAA cases were derived from a referral center and an integrated health delivery organization (BHCDO); age- and gender-matched referrals were recruited from the BHCDO. Subjects were invited to participate in home visits including spirometry (EasyOne; ndd Medical Technologies, Andover, MA, USA) and FEno electrochemical quantification (NO Vario; FILT, Berlin, Germany) at 3 months (EasyOne; ndd Medical Technologies, Andover, MA, USA). Flow rates (50, 100, and 300 ml/sec) yielding the measured airway FEno and the calculated AlvNO. We tested differences by EAA status using the chi square, t-test, and Wilcoxon rank sum.

**Results:** We completed home visits in 18 EAA cases and 106 referents; 91 in each group (77% and 86%, respectively), yielded interpretable FEno and AlvNO
results. There were no statistical differences by case vs. referent status for age (60.6±13 v. 60.6±11 years), female sex (50% v. 65%), or height (167.9± vs. 167.9± cm). EAA cases compared to referents had lower forced vital capacity (FVC) (3.1±1.0 l.; v. 3.5±1.0 l.; p<0.01) and reduced FVC % predicted (81.1± v. 96.1±%: p<0.001). Airway Fluo was higher in cases than referents (22.5±14.1 ppb v. 17.4±8.4 ppb: p=0.03), as was Alveo (4.1±4.9 v. 2.7±4.9 ppb: p=0.003).

**Conclusion:** Both airway Fluo and Alvio are increased in EAA, supporting exploration of their associations with disease activity and health status.

**Clinical:** Assessing airway Fluo and Alvio in EAA may provide insights into exposure status and disease management.

Supported by NIH 1RC1ES018211.

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**409. Tobacco cessation**

**P4030**

**Smoking cessation clinic: One year experience**

Jose Andrés García Romero de Tejada, Cristina López Roedobos, Gonzalo Segrelles Calvo, Emma Vazquez Espinosa, Rosa Mar Gómez Punter, Julio Ancochea Bermúdez, Olga Raja Naranjo. Pulmonology, Hospital Universitario de La Princesa, Madrid, Spain

**Introduction:** Tobacco is the most important preventable cause of premature death worldwide. Only about 45% of people are able to quit smoking on any given attempt without medicines or other help. Smoking cessation clinics and others healthcare providers have been shown to improve smoking cessation rates.

**Aim:** To analyse the characteristics of the smokers in a Smoking Cessation Clinic in Madrid.

**Material and methods:** From November 2010 to October 2011, 200 consecutive smokers were included in this study. Demographic data, comorbidities, smoking history, nicotine dependence (Fagerstrom test scores), motivation to quit (Richmond test scores), treatment and success in quitting smoking were recorded. The statistical software SPSS was used for analysis of the results.

**Results:** Mean age of 51.7 years, with 56% of them being women. Body mass index was 25.35 kg/m². Mean age at smoking initiation was 17.33 years, and men were slightly younger (16.11 vs 17.3, p=0.002). Men also consumed more tobacco (pack-years index was 47.23 in men vs 34.47, p=0.001) and had higher nicotine dependence than women (p=0.019). Six-month continuous abstinence quit rate was 46.43% in women and 50.68% in men (p=0.024). Varenicline was the more effective treatment (success rate 46.9%). 70% of the smokers had tried to quit before, and just 10 patients success at their first attempt (all of them were women). 72 smokers (36%) left the program after the first visit.

**Conclusions:** 1. Men significantly started to smoke earlier, consumed more tobacco and had higher nicotine dependence than women. 2. Six-month continuous abstinence quit rate was significantly higher in women. 3. Varenicline was the more effective treatment for smoking cessation in our experience.

**P4031**

**Results in a tobacco consulting room in Albacete University Hospital in 2009**

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**Introduction:** Results in a Tobacco Consulting Room in 2009.

**Material and methods:** Retrospective descriptive analysis of the results obtained from patients who attended in a Tobacco Consulting Room from 1 January to 31 December 2009 and subsequent follow-up to complete a year.

**Results:** 291 of 428 patients (51.2% male), mean age 46 years and mean cigarettes/day 27.5. Moderate-severe nicotine dependence (Fagerstrom 6.8) and high motivation (Richmond 8.11). Respiratory comorbidity: 12.1% COPD, 7.6% asthma, 11% OSAS and 0.3% HOI; Cardiac: Ischemic Cardiopathy, 4.8% and Arrhythmia, 2.1%; CVRF: 30.9% dyslipidemia, 19.9% HT and 9.3% DM. 42.6% global asthmatic, 11% OSAHS and 0.3% HOT; Cardiac: Ischemic Cardiopathy, 4.8% and Ar-

**Conclusions:** 1. Men significantly started to smoke earlier, consumed more tobacco and had higher nicotine dependence than women. 2. Six-month continuous abstinence quit rate was significantly higher in women. 3. Varenicline was the more effective treatment for smoking cessation in our experience.

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**P4032**

**Smoking cessation success rate in smokers referred to Iranian clinics**

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**Background:** Quitting smoking at any age can be effective in reducing smoking-related health conditions. At present, smoking cessation is considered the cornerstone of tobacco control policies. This study aimed to evaluate the success rate of smokers presented to smoking cessation clinics during 2005-2010 and to determine the effective factors in this respect.

**Methods:** In this historical cohort study, all participants attended the smoking cessation clinics, affiliated to the Iranian Anti-Tobacco Association, between 2005 and 2010 were studied. Success rate was assessed two weeks after the quitting onset.

**Results:** Totally, 772 participants including 510 men and 262 women were studied. 50.9% of participants reported a history of quitting and a significant correlation was observed between history of quitting and success rate (p=0.04). The success rate also had a significant relationship with higher educational level and presence of restrictions on smoking. In addition, the success rate was inversely correlated with increased nicotine dependence. However, no significant relationship was found between sense of pleasure, increased concentration or personality boost and success rate of smoking cessation. By the end of the second week following abstinence, 544 participants (71%) had successfully quit smoking.

**Conclusion:** History of quit attempts and higher educational level had significant correlations with success rate of smoking cessation. Presence of restrictions on smoking is also effective in this regard. However, this study showed that increased rate of nicotine dependence reduced the success rate of smoking cessation.

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**P4033**

**Russian advisory telephone line of help for smoking cessation**

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Effective assistance in stop smoking must include behavioral and medical ther-

**Aim:** To describe the prevalence and intensity of different symptoms in relation to tobacco abstinence, personal’s abilities and demand of telephone psychological and medical counseling.

**Methods:** 3840 smokers (18-78 years) who rang the Russian advisory telephone line of help for smoking cessation (ATL) were interviewed about smoking (nico-

tine dependence, smoking behavior, motivation to quit smoking, earlier cessation experience), respiratory symptoms, personal’s traits and social status.

**Results:** There were men (69,4%) and women (30,9%) among the respondents (63,9% - people 18-34 years); 31,4% had high education.43% were married. The mode of respondents had high motivation to quit smoking (71%). In 85% of cases smokers had experience in smoking cessation (including 8% were treated with nicotine dependence) and in 48% of cases had high intensity of withdrawal symptoms (4 and more scores) of withdrawal symptoms (more two symptoms). Frequency of respiratory symptoms among smokers was 39%, chronic diseases - 41%. 63% respondents are needed in consultation only; 31,4% received the consultative psychological and medical support during 1 month, 5,6% were sent to the hospital doctor to quit smoking. After 1-3 sessions ATL 28,4% of smokers stopped tobacco consumption.

**Conclusion:** Consultative telephone line helps change behavioral patterns and contributes to effective smoking cessation.

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**P4034**

**Values of saccharin transit time test in smokers following a smoking cessation programme in Brazil**

Fernanda Maria Machado Rodrigues, Dionei Ramos, Alessandra Quchoeta Toledo, Rafaela Fagundes Xavier, Marceli Rocha Leite, Juliana Nicollino, Luiz Carlos Carvalho Junior, Juliana Tivaki Ino, Ercy Mara Cupido Ramos. Physiotherapy, State University of Sao Paulo, Presidente Prudente, SP, Brazil

**Introduction:** Exposure to cigarette smoke causes changes that undermine the mucociliary clearance and may be influenced by different exposure conditions. The aim of this study was to present nasal mucociliary clearance (MC) by means of the saccharin transit time (STT) test and to evaluate the effects of different exposure intensities on MC in smokers following a smoking cessation programme in Brazil.

**Methods:** 42 current smokers with normal lung function were divided into mild [under 20 packyears (PY); n=15] and heavy (from 21 PY; n=27) smokers and evaluated concerning exhaled carbon monoxide (CO) by CO analyser and MC by STT. A matched control group of 25 healthy non-smokers was assessed using
the same text. Tests were conducted between 8 and 9 AM with air temperature and relative humidity controlled. Statistical analyses were performed using Mann Whitney U test.

**Results:** Smokers showed higher eCO and STT (6.5±5.9 ppm and 12.2±18 ppm) compared to control group (21±33 ppm and 7.9±6.13 ppm) (p<0.0001 and p=0.0187), respectively. Also, STT in heavy smokers was higher than in mild smokers. Stanely et al. (1986) evaluated smokers’ STT and also found a higher STT when compared with nonsmokers, however, despite were younger smokers with lower PY these values have been higher than those found in both groups in Brazil.

**Conclusion:** Cigarette smoke impairs mucociliary clearance and, in Brazilian smokers, the damage intensity was directly related to the charge exposure. Even at worse exposure conditions, this sample showed better STT.

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**P4035 Smoking cessation: A problem for older adults?**
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**Introduction:** The prevalence of tobacco smoking is high in both men and women and touch all ages. Cigarette smoking poses substantial health risks at any age, but is particularly alarming for older smokers with all various illness.

**Objective:** To compare the efficacy of smoking cessation pharmacotherapy among older and younger smokers and to evaluate whether the age represent an obstacle to quit smoking.

**Method:** We evaluate 216 male persons interested to stop smoking in an national romanian program from 01.07.2008 to 31.12.2009. The volunteers were grouped: age < 40, 40-59 and > 60. Terms assessed were: number of cigarettes, Fagerstrom test, type of treatment, the level of CO expire. The therapies used include nicotine replacement, bupropion and varenicline for a maximum 12 weeks.

**Results:** For the group > 60 it was a highest number of packs of cigarettes per year 46.3±21.8 (95% CI 38.01 - 54.61). The nicotine dependence evaluated by the Fagerstrom test is not significantly different in the three groups (5.8±2.2, 5.2 SD for the group >60, 6.29±2.55 for the group for 40-60 and 6.17±2.01 for the last one). The results of CO expired levels sound alarming for all clusters: > 60 - CO > 13.03±4.58 SD, 40-60 age CO 13.98±5.72 SD and for the group < 40 we rest in the same coordinates: CO = 15.13±8.716 SD. Abstinence rates in the older group > 60 was 34.48% in report with group 40-59 (48%) and group > 39 (44.8%).

**Conclusion:** The treatment for smoking cessation guide to almost similar abstinence rates in older and younger smokers. Physicians have annually a lot of opportunities to sustain their older patients to improve their health status and quality of life by quitting smoking.

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**P4036 Effectiveness of varenicline as an aid to smoking cessation in primary care: An observational study**
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**Introduction:** The effectiveness and safety of varenicline have been well established in randomized controlled trials. In the primary care setting, in which varenicline is commonly prescribed, only limited information is available on its use in patients with smoking-related comorbidities.

**Objective:** To assess the efficacy and safety of varenicline in a large sample of patients seeking smoking cessation treatment through their general practitioners.

**Methods:** This was a 12-week, prospective, observational, non-comparative phase IV trial conducted in Germany. The primary endpoint was the 7-day point prevalence of abstinence rate at Week 11–12, evaluated by verbal report using the nicotine use inventory.

**Results:** Overall 1391 subjects were enrolled. 1177 received study medication and were evaluated for efficacy and safety. A total of 66.7% participants had at least one concurrent comorbidity, chronic obstructive pulmonary disease (35.5%), hypertention (29.6%), depression (10.4%), diabetes mellitus (8.2%), and asthma (7.9%) being the most commonly reported. In the 7-day period between Weeks 11 and 12, 837 of 1177 subjects (71.9%; 95% confidence interval: 68.5, 73.7) were abstinent. A total of 205 all-causality adverse events were reported in 130 subjects (11.0%), of which 189 (in 122 participants [10.4%]) were considered treatment-related, and 2.2% were classified as serious or severe. There were no fatal adverse events.

**Conclusion:** These real-world data indicate that even in a setting outside of the clinical trial environment and in patients with smoking-related comorbidities, varenicline is an effective smoking cessation aid with an acceptable safety profile.

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**P4037 Efficacy of nicotineless non-pharmacologic alternative tool for smoking cessation program using varenicline**
Ya Kasamatkas, K. Yoshimoya, M. Kadaya, Respiratory Medicine, Matsushita Memorial Hospital, Osaka, Japan

**Background:** Tobacco addiction is associated with not only nicotine dependence but also mental dependence based on the habitual smoking situation (e.g. drink alcohol, after meal). The efficacy of substitute nicotineless non-pharmacologic tool (e.g. nicotineless electronic cigarettes) in these situations for smoking cessation was unclear.

**Method:** This prospective observational study aimed to investigate the efficacy of non-pharmacologic alternative tool in patients who were treated with a 12-week outpatient smoking cessation program using varenicline. We screened 180 patients who were treated with the program from March 2010 to February 2012. Tobacco addiction in this study was defined as a condition with both at least five points of the Tobacco Dependence Screener (TDS; Kawakami, et al., 1999) and at least 10 pack year. At the first medical examination, we instructed all the patients to use the nicotineless alternative tool when they urge to smoke. We assessed the success rate of smoking cessation at 12 weeks.

**Result:** Of 136 patients were eligible (35 were lost, 9 dropped). The success rate was 77.8%. Eighty patients (58.9%) used alternative tool as we instructed. The success rate of the patients who used alternative tool was significantly higher than that of the patients who didn’t use the tool (p<0.001). In multivariable logistic regression analysis, the independent predictors of smoking cessation failure were unreatable side effect (p=0.05) and disuse of alternative tool (p=0.01).

**Conclusion:** In ourpatients smoking cessation program using varenicline, non-pharmacologic alternative tool was useful for patients who urge to smoke in the habitual smoking situations.

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**P4038 Evaluation of the correlation between pictorial health warning labels and decision to quit smoking**
Ali Abdallahs, Research Unit, Iranian Anti Tobacco Association, Tehran, Islamic Republic of Iran

**Background:** Applying health warning labels on tobacco products, as an efficient measure for reducing tobacco consumption rate, put an end on tobacco industry abuse through attractive and beautiful packaging. Iran is among the leading countries in legalizing the application of warning labels on tobacco products and has executed it since February, 2009. At present in Iran, 50% of the front and back of tobacco packages should be covered by warning labels. The present study aimed at investigating the relationship between health warning labels and smoking cessation intention in smokers.

**Methods:** This descriptive cross-sectional study was carried out in summer of 2011, two years after applying the first series of health warning labels on tobacco products in Iran. 2,020 smokers from all districts of Tehran were interviewed. Data were collected. Obtained data were analyzed by SPSS v.17.

**Results:** Among our understudy subjects, 1,273 (65.7%) consumed labeled cigarettes (66% of men and 41% of women). Regarding influence of warning labels on tobacco consumption by the smokers, 18.2% stated a decrease in their consumption rate, and 15.7% reported their intention for quitting. Also, 35.7% of these smokers believed that putting disgusting graphic labels on cigarette packaging would increase their motivation for quitting.

**Discussion:** Evidence reveals that graphic warning labels could produce a great motivation for quitting and avoid smoking initiation in non-smokers. We found that more than 58% of female smokers used non-labeled cigarettes that was twice the rate in men. It may be indicative of less motivation in women and greater impact of pictorial warning labels on them.

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**P4039 Smoking cessation process**
Ika Perse,1 Nada Lazovic2, Branimar Gvozdenovic3, 1 Department for Tobacco Prevention and Smoking Cessation, Clinic for Pulmonary Diseases and TB, Clinical Center of Serbia, Belgrade, Serbia, 2 Department for Smoking Cessation, Health Center Cacak, Serbia, 3 PPD Serbia, Belgrade, Serbia

**Introduction:** Serbia has ratified the Law on protection from exposure to tobacco smoke. The Law regulates all working and public places to be a smoke-free.

**Objective:** Consideration of the effects of smoking cessation by gender, education, and the employment status in 2010 when the Law is ratified.

**Methods:** The analysis of data was performed by means of t-test for independent samples and analysis of variance (ANOVA).

**Results:** A total of 2,030 smokers were interested for the smoking cessation program in the Serbian counselings. Of these, 1,489 smokers attended the program, and 1,134 (75.7%) finished it. The Law motivated 187 (16.5%) smokers to participate in the cessation program. There were 34.6% (M) and 65.4% (W) (p<0.01). The majority of subjects (59.9%) had the secondary school education 59.9%. There were 64.7% employed smokers in total. Regarding the gender, women (40.4%) were more successful than men (32.7%). Women with the secondary school and those not employed (60.7%, 30.7% respectively) were significantly more successful than men (43.7%, 21.9% respectively) (p<0.01). Men with higher education and male students (54.7%, 7.8% respectively) were significantly more successful than women (40.4%, 18.2% respectively) and those not employed (43.7%, 21.9% respectively) (p<0.01)
Results: include Nicotinic substitutes, the bupropion and varenicline.

Methods and material: 

Material and methods: Prospective study with the patients attending our smoking cessation practice in the last 6 months. We analyzed different variables and Cardiovascular events.

Agustín S. Valido Morales

Cardiovascular events related to the use of varenicline

Table 1. General features

<table>
<thead>
<tr>
<th>n=113</th>
<th>Varenicline (n=175)</th>
<th>Bupropion (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age CV*</td>
<td>50.2 (10.6)</td>
<td>48.7 (11.5)</td>
</tr>
<tr>
<td>Gender M/F %</td>
<td>101/129</td>
<td>71/67</td>
</tr>
<tr>
<td>HBP %</td>
<td>26.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>21.7</td>
<td>15.2</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>10.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Ischemic heart disease %</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>AMI %</td>
<td>1.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Perip Art Dis %</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>CVA %</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>COPD %</td>
<td>14.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Asthma %</td>
<td>6.5</td>
<td>7.2</td>
</tr>
<tr>
<td>SAHS %</td>
<td>16</td>
<td>12.3</td>
</tr>
<tr>
<td>Anx-Depress Synd %</td>
<td>1.7/10.9</td>
<td>2/27.2</td>
</tr>
<tr>
<td>Suicide ideas/Attempts %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMI CI</td>
<td>27.7 (5.8)</td>
<td>26.6 (5.5)</td>
</tr>
<tr>
<td>Smoke Hist CV*</td>
<td>41.9 (23.4)</td>
<td>37.7 (21.4)</td>
</tr>
<tr>
<td>Cessation CI</td>
<td>34.1 (15.4)</td>
<td>31.5 (18.4)</td>
</tr>
<tr>
<td>Fagerstrom CI*</td>
<td>2.4 (0.6)</td>
<td>2.2 (0.7)</td>
</tr>
<tr>
<td>Richmond CI</td>
<td>2.9 (0.3)</td>
<td>2.9 (0.2)</td>
</tr>
</tbody>
</table>

*p<0.05, CI confidence interval 95%.

Table 2. Frequency cardiovascular events (CV)

<table>
<thead>
<tr>
<th>CV</th>
<th>Varenicline (n=175)</th>
<th>Bupropion (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP Crisis</td>
<td>4/100</td>
<td>3/6100</td>
</tr>
<tr>
<td>Angina Classic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CVA</td>
<td>0/6100</td>
<td>0/7100</td>
</tr>
</tbody>
</table>

This evaluation was carried out 3 and 6 months after the treatment initiation which lasted up to 2 months. We carried out a descriptive analysis.

Results: From a total of 313 patients (175 varenicline; 138 bupropion). The treatment with varenicline was more frequent in men who were older, with a higher smoking history, diabetes, ischemic heart disease and higher scores in the Richmond test. We observed no significant differences regarding the cardiovascular events in both groups.

Conclusions: Both drugs have shown the same safety profile for cardiovascular events.

We observed a higher frequency regarding the blood pressure increase.

The role of gender within the “stop smoking” program

Manuela Stoica, Pulmonology, Hospital Bisericani, Alexandru Cel Bun, Neamt, Romania

Introduction: Understanding individual differences in smoking behavior and addiction to nicotine can increase knowledge in the development of therapy, influence the outcomes of treatment, and is a challenge for developers.

Objective: The purpose of our study was to evaluate the role of sex in the effectiveness of smoking cessation to the National Romanian Program.

Methods and material: It is a study of a sample of 306 smokers from 01/07/2008 to 31/12/2009 interested in stopping smoking. They were assessed on the age, sex, domicile, the level of CO expire, test Fagerstrom, the family situation, the type of tobacco and the amount for a maximum period of 12 weeks. First line treatments include Nicotinic substitutes, the bupropion and varenicline.

Results: We evaluated 216 (70.58%) male, the average age was 43.72 years SD 13.5 95% CI 41 92-45.53, smoking 30.9 mg/day compared with 41 women age 40.53 average SD 11.8 95% CI 38.06 43.01 who smoke 15.66 mg/day medium, SD Ni 11 95% CI = 14.87 - 19.64. Men also started smoking earlier and had high dependence on nicotine than women. There is not a clear difference in the Fagerstrom test: TF = 5.85 for women TF = 5.62 for men.

The costs were almost equally distributed between the two categories.

Conclusion: There are no significant differences in looking at marital status: 76.92% compared to married women with 77.77% men. In both categories, the therapeutic attitude is dominated by the Champs 65.95% men to 51.38% women. At the end of the treatment, were abstinent 40.65% men and 47.68% women.

Conclusion: Sex does not appear to be a predictive factor of cessation in treated individuals persons. Analyses of individual differences should focus on the identification of the processes that control the smoking behavior.

Correlation between the age of smoking initiation and maintaining continuous abstinence for 5 years after quitting

An Abdulahim1, Makan Sadri2, Valid Moosavi3, Mohammadreza Masjedi3, 1Research Unit, Iranian Anti Tobacco Association, Tehran, Islamic Republic of Iran; 2Truuck Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases, Tehran, Islamic Republic of Iran; 3Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases, Tehran, Islamic Republic of Iran

Background: Several factors are involved in increasing or decreasing the success rate of quitting smoking and continuous abstinence. This study aimed at evaluating the correlation between age of smoking initiation and continuous abstinence after quitting smoking.

Materials: This study was conducted on 398 smokers who presented themselves to the smoking cessation clinic in 2005. Participants were then followed continuously for 5 years and their success or failure in continuous abstinence was recorded in 2010.

Results: Three hundred and five participants (76.6%) including 172 males and 132 females were able to successfully quit smoking at the end of the course. Evaluation and follow up on these subjects at the end of 2010 revealed that 111 cases (27.8%) including 64 men and 47 women were still maintaining their continuous abstinence after 5 years. The mean age of initiation of smoking among participants was 21.01 ± 5.28 years. This rate was 21.94 ± 5.33 in cases 5 years after their smoking cessation and 20.71 ± 5.35 in unsuccessful quitters. Analysis showed a significant correlation between age of smoking initiation and daily cigarette consumption rate (P<0.001). By one year increase in age of smoking onset chance of daily cigarette consumption rate less than 30 cigarettes decreased by 6% (OR=0.94).

Conclusion: It seems that age of smoking initiation can to a great extent predict the success or failure of smoker in quitting and holding on to their abstinence in the future. The sooner the person starts smoking, the lower the chance of successful quitting and abstinence.
Conclusion: The family socioeconomic status, smoking habits, dependence degree, treatment adherence and the occurrence of lapses were predictors of relapse.

P4044

Couples of significant others (COSO) in a joint effort to quit smoking are more successful in achieving and maintaining abstinence
Aikaterini Tsoutsa, Ioanna Nikoloutou, Theodoros Vassilakopoulos, Spyridon Zakynthinos, Pararkevi Katsanos, Pulmonary & Critical Care Dpt, Evangelismos Hospital, Athens, Greece

Motivational support is crucial in the success of the smoking cessation. Significant others are a proven source of that support. As far as we know social support has been used to achieve smoking cessation higher rates, but only as support and not as a concurrent attempt of a couple to quit smoking. We investigated whether the inclusion of couples of significant others in a joint effort to quit smoking in smoking cessation groups formed by a population based sample of participants would increase their success rate compared to the participants that receive the same treatment alone. This was a randomized population-based intervention study at the smoking cessation clinic of Evangelismos hospital. We monitored for people that are related in the initial screening stage. Couples included life partners, family members or very close friends. Smokers were in all motivational stages. All participants underwent the same intervention with motivational and behavioural components in the smoking cessation groups and received medical consultation and pharmacotherapy (Varenicline). We compared so far the smoking cessation rates of 25 “couples” and 50 randomized smokers that followed our smoking cessation programme. We found that participants that joint the COSO quit smoking in a higher rate (58%) than of smokers (38%). Within the dyad the person more motivated to quit smoking was usually the first to quit. Among couples that quit smoking, men were more successful (65%) than women (49%). We conclude that higher smoking cessation rates were obtained in COSO joining our smoking cessation program.

P4045

Education level and relapse to smoking
Michelis Davy1, Giuseppe Madonia 2, Franca Impellizzeri 2, Vincenzo Bellia1, Maria Rosaria Bonigjorno1, 1Dipartimento di Medicina Interna e Specialististica. Sezione di Pneumologia, Università di Palermo, Sicily, Italy; 2U.O.C. di Pneumologia, A.R.N.A.S. Civico Palermo, Palermo, Sicily, Italy

Background: Cigarette smoking is the most common risk factor for COPD and lung cancer. Smoking cessation programs are very important for primary prevention of lung disease, but limited data are available on their effectiveness in the long term. Aim: To investigate the factors responsible for smoking relapse over 24 months after smoking cessation.

Methods: From January 2009 to December 2009, 148 smokers (72 men and 76 women, mean age ± SD 49.9±11.8 yr) undergoing a smoking cessation program were enrolled. The protocol included motivational counselling, drug therapy (Nicotine Therapy Replacement), Fagestrom Test, exhaled CO measurement and spirometry. We assessed cigarette smoking cessation at 12 months. The smoking-cessation rates were calculated. Cessation rates were compared between smokers and persistent quitters. We analyzed the baseline, week-4, week-8, week-12, week-24 and week-28 of smoking abstinence and number of cigarettes smoked, and exhaled carbon monoxide levels were measured at each visit. Smoking reduction and abstinence rates were calculated. Adverse events and product preferences were also reviewed.

Results: Sustained 50% reduction in the number of cig/day at week-52 was shown in 16% of participants. Sustained smoking abstinence at week-52 was observed in 9.75% of participants. Participants’ perception 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.

P4047

Physicians’ smoking habit, training and attitude toward cancer patient smoking cessation: The Istituto Nazionale dei Tumori experience
Micaela Lina 1,2, Paolo Pozzi1, Cinzia Brunelli1, Marco Alessandro Pierotti1, Roberto Botti1, 1Psychology Unit, 2Tobacco Control Unit, 3Scientific Direction, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Backgrounds and aim: Guidelines recommend all physicians to ask patients (Pts) about their smoking status and to offer cessation advice (SC). Aim of the study was to examine the smoking habit of medical doctors (MDs) at the Milan Istituto Nazionale dei Tumori (INT), to relate this to their level of training and to their attitudes in suggesting patients to quit smoking.

Materials and methods: All MDs of the INT (n=285) were mailed a web-based survey.

Results: Fourteen percent of MDs were current smokers; only 23% of all clinicians received a training proposal in SC; 6% attended a SC course, even if 43% declared their willingness to do it. 86% of them asked Pts about smoking status, but only 50% advised Pts to quit and 32% assessed their motivation to do it. Guidelines were disregarded because of lack of time, fear to increase patients’ stress or lack of skills in SC. Smoking habits didn’t influence training attendance,willingness to be trained in SC or Pts referral to Tobacco Control Unit.

Conclusion: Smoking prevalence among INT MDs was still too high for healthcare providers and a low proportion of them was ever involved in a SC training session; however, smoking status doesn’t appear to influence MDs’ choice of training rather than the eventual referral of cancer smoker Pts to the dedicated Unit. Surveys like this should encourage cancer centers to make SC as part of their core mission and to implement SC training in their institutional policies.

P4048

Differences between the recommended and real dose in a smoking cessation practice
Ana Gómez-Bastero, Virginia Almadana, Concepción Romero, Estefania Lugue, Andrés Vega, Soledad Montserrat, Teodoró Montemayor. Respiratory Medicine Unit, Hospital Universitario Virgen Macarena, Seville, Spain

Aims: To analyze the dose and time decided by the patient regarding what is recommended and its influence on the tobacco cessation rate.

Methods: We included patients who attended our practice during the last 6 months. We analyzed several variables: recommended dose (varenicline (V): 0.51 mg, 2 months; bupropion (B): 150 mgs/day, 2 months), real dose and duration of the treatment, tobacco cessation rates and causes of early abandonment of medication.

Results: n=312 patients: V (56%) and B (44%). By comparing both groups, we couldn’t find differences regarding cessation rate after 3 V (64.4%/B: 67.2%) or 6 months (V: 64.2%/B: 67.2%). We realized the patients followed the recommended dose (V: 82.3%/B: 94.2%, p<0.001). Cessation rates are shown in figure 1.

Figure 1. Patients who fulfilled the dose recommended versus patients who didn’t: N.S.: not statistically significant.

P4046

Modifications in the smoking habits of 200 regular smokers experimenting the electronic-cigarette focusing on smoking reduction and smoking abstinence
Pasquale Caponnetto, Biomedicine Clinica e Molecolare, University of Catania, Italy

Background: Cigarette smoking is a tough addiction to break. Therefore, im-proved approaches to smoking cessation are necessary. The electronic-cigarette, a battery-powered electronic nicotine delivery device resembling a cigarette, may help smokers to remain abstinent during their quit attempt or to reduce cigarette consumption. (1)

Aim and objectives: We designed a prospective study to monitor possible mod-ifications in the smoking habits of 200 regular smokers, not intending to quit, experimenting the most popular marketed e-Cigarette in Italy (‘Cigaretta’) focus-ing on smoking reduction and smoking abstinence.

Methods: Study participants were invited to attend a total of six study visits: at baseline, week-4, week-8, week-12, week-24, and week-52. At each visit, number of cigarettes smoked, and exhaled carbon monoxide levels were measured at each visit. Smoking reduction and abstinence rates were calculated. Adverse events and product preferences were also reviewed.

Results: Sustained 50% reduction in the number of cig/day at week-52 was shown in 16% of participants. Sustained smoking abstinence at week-52 was observed in 9.75% of participants. Participants’ perception 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.

Data table:

<table>
<thead>
<tr>
<th>Education level</th>
<th>Relapsing subjects</th>
<th>Persistent quitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary school</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Middle school</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Secondary school</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Graduate education</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

p<0.0001 by x²

Conclusion: About a fourth of the quitters at 12 months restart smoking at 24 months. The level of education seems to be an important factor in late, but not early, relapse to smoking. Both subjective and environmental effects may play a role.
Regarding the duration of treatment: V: 6.6±1.6/B: 7.9±0.7, p<0.001. Cessation rates after 6 months: V: 96% vs 51.2%/B: 95.7% vs 6.8%; p<0.001. Causes of medication abandonment are shown in table 1.

Table 1: Causes of abandonment of medication

<table>
<thead>
<tr>
<th>Abandonment causes</th>
<th>Varenicline (%)</th>
<th>Bupropion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic reasons (%)</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Psychological dependence (%)</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>False self-control on abstinence symptoms (%)</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>Side effects (%)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Oversight (%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Others (%)</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

p<0.134

Conclusions: Using 2 month treatments and half the recommended dose of B, cessation rates are good >64%. Below 5 week treatments are clearly insufficient with B as well as V. Causes of early abandonment of medication were mainly due to economic and psychological reasons.

P4049 Can we really relieve the withdrawal syndrome with pharmacotherapy in smoking cessation?

Zeynep Pınar Önen, Elif Sen, Banu Eris Gulpay, Pınar Akın Kahalak, Ozmut Akkoç Yıldız, Turan Acıcan, Sevgi Saryal, Gürbüzer Karabiyikolu.

Chest Disease, Ankara University School of Medicine, Ankara, Turkey

Primary goal of the smoking cessation treatment protocols are to relieve the withdrawal symptoms. However the exact effectiveness at the high tobacco dependence patients considering the smoking cessation treatment is still an unknown problem.

Aim: To evaluate the prevalence of withdrawal symptoms during smoking cessation treatment and compare the effectiveness between the different treatment modalities in high tobacco dependence patients.

Methods: From a total number of 435 active smokers (mean age of 44±11) with high tobacco dependence rates were prospectively evaluated between 2004 and 2010. Each patient answers the same questionnaire including smoking status and medical background. Nicotine dependence and CO levels were evaluated. Smoking cessation program was administered individually according to the guidelines and all of the patients were followed at least 1 year.

Results: The continuous abstinence following therapy at the end of first year was 50.5%. Withdrawal syndrome during smoking cessation treatment developed at 89% of behavioral treatment without pharmacotherapy, 80% of nicotine replacement 88% of bupropion and 94% of varenicline in all treatment protocols (more than 50% in each group) and somnolence is the distinctive symptom for the bupropion treatment (p<0.001). Hunger was not the predominant withdrawal symptom in the varenicline treatment.

Conclusion: According to our results, even one year smoking cessation success is high in our cohort the main goal of the smoking cessation protocols is not achieved. Pharmacotherapy is not superior to pure behavioral treatment to relieve the withdrawal syndromes.

410. Tobacco and shisha exposure in children and adolescents

P4050 Acute impact of a single e-cigarette smoking on symptoms, vital signs and airway inflammatory response

Sofia Viskidi1, Stamatis Tiskirka2, Sofia-Antiopi Gemmimata1.

George Kasalas1, Anaustasios Palaimidas1, Nikolaos Kouvalis1, Christina Gratziou1, 1 1Athens University Respiratory Medicine Clinic, Sotiria Chest Diseases Hospital, Athens, Greece; 2 3rd Respiratory Medicine Clinic, General Hospital Sismanoglion, Athens, Greece

E-cigarette is a battery powered electronic nicotine delivery device. Many smokers use it, because it is marketed as a safer alternative to smoking. The aim of our study was to evaluate the acute effect including smoking a single e-cigarette for 10 minutes on symptoms, vital signs, exhaled CO, exhaled NO and airways temperature in never smokers and in smokers with and without chronic airway obstruction.

We studied 37 consecutive subjects (17 male), aged:42±1.4year (mean±SD). Nine were never smokers, 15 were smokers with normal spirometry and 13 smokers with chronic airway obstruction (7 asthmatics, 6 with COPD). All subjects answered a questionnaire about symptoms (cough, sore throat, eye irritation, dizziness and feeling of satisfaction) immediately after smoking a single e-cigarette for 10 minutes. We also measured oxygen saturation (SpO2), heart rate (HR), exhaled CO, exhaled NO and airways temperature pre and post smoking.

After smoking a single e-cigarette for 10 minutes, our group reported cough (65%), sore throat (68%), irritation in eyes (24%), difference in taste (78%), dizziness (24%) and feeling of satisfaction (51%). In addition, there was a statistically significant: a) increase in HR (from 75±10 to 92±17, p<0.001), b) increase in eCO (from 15±12 to 15±9, p=0.03), and c) a decrease in SpO2 (from 97±6±1 to 96.76±1, p=0.012) after smoking.

We conclude that after smoking a single e-cigarette for 10 minutes there was a change in symptoms, vital signs and indices of airway inflammation in a statistically significant manner. Further studies are needed to establish the immediate and long-term effects of e-cigarette smoking.

P4051 Occurrence, health impact and motivation to quit smoking among young people and effectiveness of tobacco control programs

Natalia Astalavery, 1 O. Naumova, 2 D. Kobzev, 1 I. Gamova, 1 L. Perfilova, 1

E. Udovichenko. 2 Allergy and Immunology, Saratov State Medical University, Saratov; Russian Federation; 1 Business & Management, Leeds Trinity University College, Leeds, United Kingdom

Introduction: Global Adult Tobacco Survey identified high levels of smoking in Russia and was followed by the young people smoking study in Saratov region in 2011 to improve Tobacco Control effectiveness.

Aim: The assessment of smoking, its health impacts and motivation to quit was conducted among college (FE) and university (HE) students.

Methods: Anonymous standardized Respiratory Health Assessment and COPD Differential Diagnoses Questionnaires were used in 3 groups: FE: 15-18 years (126 respondents) and HE: 19-24 years, studying medicine (120) and management (168); 54%-male, 46%-female. CO testing of breath (1ppm resolution) was used (10% respondents did not reveal their smoking). Respiratory disease risk assessment was based on respiratory symptom scores, spirometry was performed in line with ERS/ATS standards.

Results: The prevalence of smoking among students: FE:31%, medics-5.1%, managers-35.2%. With the same starting age (12.6-male and 13.9-female) in all students the respiratory problems symptoms: cough, sputum, dyspnea, etc occurred in: FE-18%, medics-27%, managers-39%, and FEV1 decreased 10.2%, 26%, and 45% correspondingly. Unlike HE students, FE does not realise health risks and will not seek a support to quit. There was a difference in major motivations to quit: female-fertility impact, appearance; male-erectile & sperm impact, sport; medics-pulmonary health, impact on intellect; managers-cost of cigarettes and waste of working time.

Conclusion: Tobacco Control among young people can be more effectively promoted through personalized messages to a particular target group, g. e. addressing specific motivations via Social Media.

P4052 Knowledge about smoking and its harm among high school students

Mariana Martins Ambroz, Liana Sousa Coelho, Suzana Erica Tanni, Lívia F.S. Baldini, Laura M.O. Caram, André Luiz Bertani, Caroline Knaut, Iilda de Godoy, Irmã de Godoy. Disciplina de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, UNESP, Botucatu, SP, Brazil

Introduction: Harmful effects of tobacco for human health are widely known, nevertheless, the prevalence of smoking is still increasing among adolescents.

Objectives: To evaluate the behavior as well as the knowledge of high school students in Botucatu, São Paulo, Brazil.

Methods: This work was developed with authorization of the Board of Education of the city Botucatu, in public secondary school. The students of the high school were invited to answer a questionnaire about smoking and its harms. Descriptive analysis of the data was done.

Results: We obtained 292 (41.7%) valid questionnaires (age: 15.9±1 years, 54.8% female). About smoking habits, 33.2% tried cigarettes at least once and 64.9% were female, 5% smoke more than 15 days/month, and 89.0% reported don’t smoke. Most students (68.5%) do not have parents or relatives who smoke indoor. 91.1% know that cigarettes cause health problems and 81.8% said that nicotine is the substance responsible for addiction. Besides of that, 62.7% are not sure about the amount of toxic substances present in the cigarette. About the use of nicotine in young people, 7.9% believe that it acts more lenient, while 19.5% believe that it acts in a powerful way, making the addiction more difficult to overcome, 24.3% say the nicotine activity is the same as in adults, and 43.2% are unsure (5.1% did not answer). About the possibility of smoking, 79.5% said that they will not smoke in the next five years and 73.3% would refuse a cigarette if their best friend offered one. 51% confirmed that they received information about the harm of smoking from teachers.

Conclusion: This study noticed that, despite of all media information, young people show little knowledge about smoking and its harms.
Dijana Mayer1, Ivana Pavic Simetin1, Divo Ljubicic1

Introduction: Important changes have occurred in the prevalence and patterns of cigarette smoking by young people. Given the known consequences of smoking for morbidity and mortality and the nature of smoking habits established during adolescence, changes in smoking behaviors carry extraordinary implications for the health of these youngsters throughout their lives.

Aims and objectives: To investigate the prevalence and pattern of cigarette smoking among Croatian pupils.

Methods: The Croatian GYTS (Global Youth Tobacco Survey) was a school-based survey of pupils in 7th and 8th grade primary, and 1st grade secondary school conducted in year 2011. A two-stage cluster sample design was used to produce representative data for all of Croatia. A total of 3,551 students aged 13-15 participated in study.

Results: The overall response rate was 90.1%. Any form of tobacco is currently used by 28.6% pupils (boys = 28.6%, girls = 27.9%); 66.5% of pupils had ever smoked cigarettes (boys = 66.6%, girls = 65.9%). More than one-quarter (27.2%) currently smoke cigarettes (boys = 26.7%, girls = 27.6%). 12.0% smoke daily manufactured cigarettes (boys = 12.1%, girls = 11.2%). 14.9% currently smoke cigarettes (boys = 15.2%, girls = 14.1%). Almost one quarter of ever smokers initiated smoking before age ten (boys = 30.4%, girls = 16.3%). Of never smokers, even 22.1% are likely to initiate smoking next year.

Conclusion: The results of Croatian GYTS 2011 indicate significant tobacco use and exposure to tobacco among pupils in Croatia. There is an urgent need to prevent tobacco smoking prevalence among these individuals and reduce morbidity and mortality throughout their lives.

P4054

Influence of family’s smoking on their children in high school
Hiroshi Okiyama, Yuaki Amimoto, Youko Murakami. Pediatrics, Fukuoka National Hospital, Fukuoka City, Japan

Background: Smoking is important as one of the aggravation factors of respiratory diseases, including bronchial asthma. The smoking rate in Japan is maintaining the still high value. Although it is presumed that the start of smoking is before 20 years old, the actual condition is not necessarily clear. To grasp the actual condition of smoking in high school students is important for this age is the points to be the time for remission or adult asthma.

Aim: The aim of this study is to clarify the reality of the smoking in high school students from the viewpoint of the influence of family smoking.

Subjects and methods: In 2009, four high schools in Japan were asked to complete a questionnaire to students. Questionnaire is anonymous and, as information about individuals, was asked to fill in only in the age and gender. 1815(827 male, 988 female) were obtained from a valid answerer.

Results: 1. Who currently has asthma symptoms, history of asthma was decreased in the order of the person who has smoking mother, father, others.

2. Children had a higher prevalence of smoking and from younger age when father and mother is smoker, especially father had been smoking.

3. Children of smoking parents are more likely to initiate smoking at a younger age than non-smoking parents.

Conclusion: Parental smoking is likely to influence adoption of smoking among young children. Preventing smoking habits and at least reducing smoking habits among children makes a protective factor against tobacco use in people.

P4056

Tobacco false attributions in smokers and not smokers teenagers
Khall Abu Shams1, Maria Hernandez1, Mercedes De Carlos1, Amaia Irure2, Susana Clemens2, Amaya Villanueva2. 1Pneumology, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain; 2Psichiatric, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain; 3Internal Medicine, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain

Introduction: The tobacco is now a widespread habit among the teenagers where they begin early to smoke. The false attribution have an important role to push the adolescents to take the decision to begin early to smoke i.e. to think that they are more attractive, modern, adult and more independent.

Methods: A representative sample of teenagers of our community offering a questionnaire. The results of Croatian attributions with two answers: true or not true. The sample was of 350 students, 180 girls and 170 boys between 12-18 years. The values of the correct answers is between 0 and 10 points analyzing the results with Kruskal Wallis test.

Results: 193 students (55.14%) smoke and 157 (44.86%) not smoke. We found significant differences of false attributions between smokers and not smokers. The smokers have most of false attributions about smoke habit having less scoring in the questionnaire (HI: 6.45, gl: 1, p: 0.011).

Table 1

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Smokers(n=193)</th>
<th>Not smokers(n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>4.67</td>
<td>4.46</td>
</tr>
<tr>
<td>5–7</td>
<td>46.63</td>
<td>35.67</td>
</tr>
<tr>
<td>8–10</td>
<td>47.7</td>
<td>59.87</td>
</tr>
</tbody>
</table>

Conclusions: The smoke teenagers have more false attributions than not smokers.

P4057

Does parental smoking influence the adoption of this habit among their children?
Maria Malik, Umar Misbah. Chest Medicine, Jinnah Post Graduate Medical Centre, Karachi. Pakistan Research Department, Institute of Business Administration, Karachi, Pakistan

Hypothesis/Background: Parental smoking is likely to influence adoption of the habit by their children. There is a positive correlation between parents smoking and their children developing this habit.

Objective: To find out if there is a correlation between parental smoking and their children adopting this habit.

Methods: Primary and secondary researches were undertaken. Primary research comprised of a questionnaire, filled by 256 participants aged between 16 to 25 years from different private schools and colleges all over Pakistan. Interviews of 30 people were also conducted for further collection of information as a part of secondary research.

Results: Literature review supported our hypothesis. Children were 5 percent less likely to smoke if parents did not smoke; children both whose parents smoked were 2.69 times more likely to smoke than 12thgrade compared to those whose parents did not smoke. Primary research showed that indigenous data also corresponds to the hypothesis. The chi-squared test of association, Χ2 = X2 (0.05, 1, 1), shows there is association between parental smoking and children smoking.

Conclusions: The effect of parental smoking cannot be ignored, however since smoking habit is caused by a variety of factors, only a correlation can be developed. Prevention from and negative attitudes of parents are the most effective way of preventing or at least reducing smoking habits among children.
P4058
Prospective inquiry studying of tobacco smoking among high-school students in Plovdiv, Bulgaria (2004-2010)
Fili Staneva1, Rosita Vakancheva1, Zlatka Ivanova2, Stanislav Kavet2, Georgi Belev1, Nonka Mateva1, Ivan Novakov1, 1Pulmonology, University Hospital "St. George", Plovdiv, Bulgaria; 2Haelt Management and General Medicine, Medical University, Plovdiv, Bulgaria; 3Thoracic Surgery, University Hospital “St. George”, Plovdiv, Bulgaria

Introduction: Tobacco smoking is world major cause for premature death and serious health problems. The efforts should be directed towards prevention of smoking, which most often is even in childhood.

Aims: To investigate in dynamics certain aspects of smoking among adolescents.

Methods: It was organized a study in sections method, using a direct anonymous interview in Plovdiv schools. There were interviewed 800 students in 2004 and 460 in 2010. The questionnaire is from translated and adapted version by GYTS, WHO’s program form. The statistical processing of data is completed by descriptive statistics and Student’s t-test. It was used the program pack SPSS v.18.0.

Results: For the six year period, we reported a statistically significant decrease in the number of students who have tried to smoke cigarettes and of those who smoke regularly. In 2004, 84.875% of the adolescents have tried a cigarette, as well as in 2010 72.39% (t=5.12; p<0.001). At the age of 14-15 those who have started to smoke were 28.375% in 2004 and 23.04% in 2010 (t=2.11; p<0.05). The percentage of the students who smoke every day reduces from 25.375% to 19.565% (t=2.42; p<0.05). There is a statistically significant increase in the percentage of students who disagree with the smoking in common places from 57.75% to 68.48% (t=3.86; p<0.001). The ability to easily buy cigarettes from young people remains alarming- 46.625% in 2004 and 68.48% in 2010 (t=6.79; p<0.001).

Conclusions: There is a significant decrease in the number of adolescents who smoke and in the same time there is more to be done in preventing tobacco smoking by children.

P4059
Estimation of prevalence and features of smoking status in young people
Natalia Mokina, Galina Sakharkova, Nikolay Antonov. occupational Diseases and Clinical Pharmacology, Samara State Medical University, Samara, Samara Region, Russian Federation

The purpose: To study the prevalence and features of tobacco smoking in young people (students of Samara region, for revealing the most informative, sensitive and effective question from the given category.

Methods: 158 young people aged of 17-27 years (20±21,1), 66 male and 82 female were surveyed by means of BMI, PEF, FEV1, FVC, FEV1/FVC, the experience and non-smoking, smoking index.

Results: 59% men were smokers and 41% non-smokers. 15% women were smokers and 85% non-smokers. The greatest number smoking was at the age of 22 years of both sexes.

The most informative parameters by standard canonical coefficient (SCC) were: PEF (SCC=4,7), the factor of smoking (SKK=1,4), the intensity of smoking (AUROC=0,7), the age (SCC=0,7). The ROC-analysis has shown the greatest sensitivity and specificity, at a confidence interval of 95%, for: PEF (AUROC=0,9), smoking index (AUROC=0,7), smoking duration (AUROC=0,7), smoking intensity (AUROC=0,7).

Conclusions: Thus, the group of high risk was young people aged 22 years of both sexes. The most informative, sensitive and specific tests at the given category of patients were PEF, [P]ICB, smoking index, duration and intensity.

P4060
The attitude of the teachers working in Manisa City Center toward the practice of the law on prevention of hazards of tobacco products numbered 5727 and the rate of smoking cessation among teachers
Tugba Goktalay1, Yavuz Havlucu1, Saliha Altiparmak2, Gul Gerceklioglu 3, Selhan Ozbey4, Pinar Guzel4, 1Department of Biostatistics, Ege University, Izmir, Turkey; 2School of Health Services, Celal Bayar University, Manisa, Turkey; 3Vocational School of Health Services, Celal Bayar University, Manisa, Turkey; 4School of Public Health, Dokuz Eylul University, Izmir, Turkey; 5Department of Biostatistics and Medical Informatics, Celal Bayar University, Manisa, Turkey

This study is aimed to investigate the attitude of the teachers in Manisa toward the law numbered 5727 came into force on 19 July 2009 and the smoking cessation rate before and after of application of this law.

The study was conducted in 727 teachers working in primary and secondary schools in Manisa between May2011 and June2011.588 teachers(80,8%)participated to the study filled out the questionnaire.

47.8% of them had positive rate of ex-smokers and current smokers were 30% and 36.1% in male and 16.7%and 26.4% in female respectively.97.3% of nonsmokers, 94.5% of ex-smokers,100% of occasionally smokers,and 75.5%of current smokers supported the law(p<0.001). In current smokers,annual smoking cessation rates between 2001-2002,2006-2007 were between 1.1% and 3.4%.

Smoking cessation rates in 2007-2008,2008-2009, and 2009-2010 were 3.61%,6.16%, and 6.50%respectively. Between August2010 when the law came into force and June2011, It was 10,69%. With joinpoint trend analysis, there was no statistically significant change in annual smoking cessation rate between 2001-2001 and 2006-2007 years(p=0,5); but it was found statistically significant between 2007-2008 and 2010-2011 years(p=0,02).

Teachers have a positive attitude about the law. Smoking cessation rate in current smoker teachers was significantly increased after July 2007.

P4061
What do the adolescents think about smoking and ban strategies in Turkey? Bakir Umut Tugay1, Burcu Ihan1, Tubat Cakat1, Tugba Kabakci2, Hatice Koç2, Nazan Tugay3, 1Physiotherapy and Rehabilitation, Mugla University, Mugla, Turkey

Preventing youth from initiating tobacco use is a key aspect of all tobacco prevention efforts. Most smokers become tobacco dependent before age 18 years. The purpose of the present study was to investigate thoughts of high school children about smoking behaviours and antismoking policies in Turkey. 731 students volunteered (336 male, 395 female, mean age 16.20±1.15) to participate in the study from 7 different high schools. After taking written consent from their parents all the students filled the 16 item questionnaire developed by the researchers. 72.7% of the students thought that their teachers were not good models for not smoking. 10.9% believed that smoking is a sign of growing up and 45.7% the students believed that they can quit whenever they wanted if smoked. 85% of the students totally or partially agreed with the prohibition of cigarette advertising and 95.4% of the students agreed with the prohibition of smoking in public places but 42.8% of the students believed that smoking on the streets is not a stimulating behavior. 30.6% did not think that increasing the cigarette prices would not have positive effect on decreasing smoking rates. 10% and 12% of the students thought that water pipe and light cigarettes are less harmful than the normal cigarettes respectively. A clear opportunity for intervening with youth lies in the school setting, so besides the ban policies, comprehensive tobacco control and education programs including the parents should be initiated.

P4062
Prospective analysis among medical school of University of Sao Paulo: GHPPS (2008/2011)
Renato Pascoli, Stella Martins, Gustavo Prado, Ana Mortas, Elisa Lombardi, Frederico Fernandez, Mario Terra-Filho, Ubiratan Santos. Division of Pneumology, Heart Institute (InCor) School of Medicine, University of Sao Paulo, SP, Brazil

Introduction: Knowledge acquired in tobacco-related diseases and treatment are fundamental for futures physicians who will have to manage with this pandemic disease.

Objectives: To determine the prevalence of smokers, Shisha use, passive smoking; knowledge about tobacco-related diseases, smoking cessation techniques and treatment on medical students.

Methods: Cross-sectional survey randomly sample of 211 medical students from 3rd year of 2008 and 6th year of 2011. The questionnaire used was the self-administered Global Health Professional Students Survey (GHPPS) after translation and validation to Portuguese. The GHPPS was supplemented with questions about knowledge acquired.

Results: Responded 101 x 110 students 3rd/6th. Low prevalence of smokers among the male population with a fall in the 6th year (7.9 x 4.6%, p<0.001), female smoker. Current/past use of Shisha were higher in 3rd/6th (47.5% x 46.4%, p=0.522). The students have a Knowledge of Smoke Free Places in college, buildings and clinics, (45.4% x 91.8%, p<0.001). Curriculum and Training analyses about smoking showed a significant gain of knowledge on smoking cessation (9.9% x 98.1%, p<0.001); importance of educational materials to cessation (29% x 72.7%, p<0.001) and Non-nicotine treatment (46.5% x 99.1%, p<0.001). Diseases associated to smoking are well known, except tuberculosis (42.6% x 38.3%, p=0.523).

750s
Conclusions: Both non-smokers and smokers had normal lung function indices. Induced sputum increased knowledge about the curriculum, training, and smoking-related diseases.

2University of Latvia, EKMI, Riga, Latvia; 3P. Stradiņa, KUS, Riga, Latvia

Tobacco smoking: Still an important lifestyle component for adolescents and these future physicians have tools to act in the smoking pandemic.

Results: Lung function measurements, sputum induction (IS) and sputum cell anonymous questionnaires about tobacco use. The prevalence of smoking was relatively high in all age groups (21.8% for group A, 35.6% for group B). The prevalence of smoking was significantly lower in females compared to males (p = 0.05). Regression analysis showed significant dependency of FOXP3-positive T-regulatory cells from the number of macrophages of induced sputum (r² = 0.118; p = 0.030) from the number of neutrophils.

It is of great importance to be able to diagnose early inflammatory changes that can lead to COPD in airways of young cigarette smokers.

Agnese Kislina

The aim of this study was to analyze the cell spectrum of induced sputum from young cigarette smokers, with emphasis on T-regulatory cells. Methods: A self-administered questionnaire was distributed to house physicians, but also involve specific immune mechanisms with recruitment of T-reg lymphocytes. The lymphocyte response is probably adaptive.

P4064

Evaluation of cell spectrum in induced sputum of young cigarette smokers

Agnese Kislina1, Gunta Strazda2, Liga Balode3, Zane Sinikevica3, Darja Isajeva1, Sergejs Isajeva2, Normunds Jurka1, Immanuels Taivans3, Valentina Gordjusina4, Viesturs Silins3,4 University of Latvia, Latvia; Faculty of Medicine, Riga, Latvia; University of Latvia, EKMI, Riga, Latvia; P. Stradiņa, KUS, Riga, Latvia

Conclusions: Total ban doesn’t decrease initiation of tobacco use with shisha in Pakistani teenagers. Preventive campaigns are needed to inform adolescents that shisha is harmful and may be a gate for initiation of tobacco use, but, unfortunately, all budgets for this prevention has been cut down for 5 years in France.

P4067

Knowledge attitude and practice of shisha (water pipe) use in doctors

Ashok Kumar, Shaista Ghazal, Shaista Gharazi, Shamshuddin, Nusrat Idrees, Nadeem Rizvi, Chest Medicine, Jinah Postgraduate Medical Centre, Karachi, Sindh, Pakistan

Background: Tobacco use in the form of shisha has adverse effects similar to cigarette smoking.

Objectives: To assess the knowledge, attitude and practice of doctors about shisha(water pipe) use and its hazards as doctors serve as role model of society and can play a very important role in educating public.

Methodology: A self administered questionnaire was distributed to house physicians, postgraduate, medical officers and consultants in different teaching hospitals of Karachi.

Results: 343 doctors from different teaching hospitals of Karachi filled the questionnaire of which 170 were females. Approximately 29.5% doctors have used shisha some time in their life. Of total survey population 56.5% house officer, 73.9% postgraduates, 65.9% medical officers and 91.3% of consultants agreed that shisha contains tobacco (p value 0.001) and 58% house officers, 77% postgraduates 68.3% medical officers and 91.4% of consultants believed that it is harmful to health (p value < 0.001). Knowledge about hazards of passive shisha use was found to be very poor. Only 25.2% house officers, 40.5% postgraduates, 34.1% medical officers and 69.6% of consultants were confident that neonatal deaths are associated with passive shisha exposure (p value <0.001) while 51.9% house officers, 64.2% postgraduates, 53.7% medical officers and 87% of consultants believed that shisha exposure during pregnancy can lead to Sudden Infant Death Syndrome (p value 0.001). Conclusions: Our study indicates that there is lack of knowledge among doctors specially house officers regarding contents used in shisha and its hazardous effects on health. Steps should be taken for educating doctors especially juniors about different methods of tobacco use and its hazards.

P4068

Prevalence of hookah consumption in Tehran

Makan Sadegh1, Ali Abdolahim2, Mohammadreza Masjedi1,2 Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran; 3 Research Unit, Iranian Anti Tobacco Association, Tehran, Islamic Republic of Iran; Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran

Background and objective: Not much information is available in the literature.
411. Tobacco comorbidity

P4070 To assess the effect of smoking on cardiovascular system

Amrapala Gupta 1, Sushila Seel 1, Rajesh Gupta 2, Jyothi Behara 1, 2. 1Physiology, Pr BD Sharma PGIMS, Rohtak, Haryana, India; 2TB & Respiratory Medicine, Pr BD Sharma PGIMS, Rohtak, Haryana, India

Background: Smoking alters autonomic functions and increases adrenergic activity that predisposes to cardiovascular morbidity and mortality. Heart rate Variability (HRV) is a measurement of autonomic activity.

Methods: Study included 60 subjects in total, of which 30 (Test group-A) were chronic smokers with history of at least 10 pack years and 30 (Group-B) non-smoker controls. The HRV was recorded in the supine posture in relaxed state. We recorded the frequency domain analysis [low frequency domain (LF), high frequency domain (HF) and LF/HF ratio] for which five minute recordings were taken and data was generated using the Polyrite D system.

Results: There was a significant (P<0.001) decrease in heart rate with decreased RR interval was recorded as compared to control group-B. Along with, there was a decline in LF and HF domains. Difference was calculated between test group and control group.

Conclusion: This result indicates that smoking results in negative cardiac autonomic modulation and smoking cessation is recommended to prevent cardiac morbidity and mortality.

P4072 Spiroergometry among smoking and non-smoking patients

Tatiana Lefeva 1, Julia Krasnova2. 1Therapy, Academy of Advanced Medical Education, Pr. Park, Russian Federation; 2Gerontology, Academy of Advanced Medical Studies, Irkutsk, Russian Federation

Aim: To evaluate parameters of spirometry at smoking and non-smoking patients.

Materials and methods: 47 patients were examined (20-were smoking (an index of smoking 15 packs/year), 27-non-smokers). The mean age of the first group dominated by men (52.6 ± 7.4 years and second, 40.0 ± 9.5) years, (P<0.05). The next parameters of a spirometry were studied. Heart rates (HR), Sistolic blood pressure, Diastolic blood pressure, VO2peak, VCO2peak, VIEpeak, O2-puls, EQCO2, PET CO2rest.

Results: Characteristics of parameters of spirometry at smoking and non-smoking patients.

Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Smokers (n=20)</th>
<th>Non-smokers (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR rest</td>
<td>76.0±12.1</td>
<td>75.6±12.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HR maximum</td>
<td>145.1±18.9</td>
<td>155.4±13.6</td>
<td>0.04</td>
</tr>
<tr>
<td>HR 5 min of rest</td>
<td>111.5±15.4</td>
<td>104.6±16.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Sistolic blood pressure rest</td>
<td>114.6±12.9</td>
<td>106.9±12.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Sistolic blood pressure maximum</td>
<td>178.8±22.3</td>
<td>167.8±29.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sistolic blood pressure 5 min of rest</td>
<td>111.1±13.8</td>
<td>103.0±15.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure rest</td>
<td>86.1±9.5</td>
<td>83.6±9.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure maximum</td>
<td>109.3±12.6</td>
<td>100.9±14.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure 5 min of rest</td>
<td>88.2±10.5</td>
<td>79.6±10.5</td>
<td>&gt;0.006</td>
</tr>
<tr>
<td>Load maximum</td>
<td>113.8±27.5</td>
<td>120.4±27.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VO2peak</td>
<td>11.7±6.3</td>
<td>13.3±3.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VCO2peak</td>
<td>12.3±4.1</td>
<td>14.0±3.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VIEpeak</td>
<td>543.0±18.8</td>
<td>663.1±178.0</td>
<td>0.031</td>
</tr>
<tr>
<td>O2-puls</td>
<td>6.5±2.6</td>
<td>6.1±1.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>EQCO2</td>
<td>41.2±6.6</td>
<td>45.6±4.2</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>PET CO2rest</td>
<td>28.7±3.1</td>
<td>28.0±2.4</td>
<td>&gt;0.005</td>
</tr>
</tbody>
</table>

Conclusion: Smoking patients had higher indicators of HR on 5 minute of rest, sistolic blood pressure of rest diastolic blood pressure upon the maximum loading and on 5 min of rest than non-smokers.
P4073 The influence of active and former smoking on the amount and quality of sleep in an obstructive sleep apnea (OSA) population versus habitual snorers Oana-Claudia Deleanu1, Diana Pocora2, Ruxandra Ulmeeana1, Stefan Mihaucuet1a, Florin-Dumitru Mihaliant1. 1Institute of Pneumology “Marius Nasta”, University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania; 2Institute of Pneumology “Marius Nasta”, Bucharest, Romania; 3Institute of Pneumology “Marius Nasta”, Faculty of Medicine and Pharmacy, Oradea University, Bucharest, Romania; 4Clinical Hospital of Infectious Diseases and Pneumology “Victor Babes”, Timisoara, Romania

**Objective:** We analyzed effects of smoking and smoking status on sleep in 2 groups (OSA and habitual snorers) comparable regarding comorbidities and dependencies.

**Results:** We analyzed 71 OSA patients (18% women, 82% men) successfully CPAP treated (other pathologies excluded: 25/35% nonsmokers, 19/27% active smokers (YP=21±5.2;7,Fagerstrom=3.5±2.1), 27(38%) exsmokers (YP=25±9.1±18.8); mean values: age=54.3±13 years, Epworth=8±2.6±5.4 total sleep time=5.6±2h, arousal index=29±2.3±7h, AHI=38±1.5±36.6h. We compared OSA active smokers with control group of 11 active smokers snorers (2 women, 9 men, age=41.1±13.7 years, Epworth=4.09±3.6), YP=23±2.2±25.4, Fagerstrom =4.6±2.3±2, total sleep time=4±7±2.8h, arousal index=15.8±11.6h). OSA smokers sleep quality is affected vs. non-smokers (more arousals, p=0.02). There was no difference in total sleep time, efficiency, sleep latency, sleep stages or OSA severity (except worse nocturnal hypoapnea in active smokers: r=-0.49,p=0.03); no differences between active smoking vs. male sex, or between OSA and nonsmokers. YP index correlates with arousal index, but doesn’t correlate with nicotine dependence.

**Conclusion:** Smoking intensity and sleep quality (arousal index/correlated, unrelated to nicotine dependence. Studies are needed to prospectively assess effects of smoking on sleep and OSA using a non-smoking control group.

P4074 Effects of smoking and smoking cessation on decline in pulmonary function Shinobu Otsuna, Mie Aoki, Toshiyuki Ogasa. First Department of Medicine, Asahikawa Medical University, Asahikawa, Hokkaido, Japan

(Background) Natural course of pulmonary function after smoking cessation is still unclear. We sought to assess influences of smoking habits to lung function in subjects with various smoking habits.

**Subjects and Methods** Total of 860 subjects were recruited from patients who attended to rural primary care clinics except for respiratory disorders. Each participant was asked to answer the following questions: age, smoking habits, medical history, and forced vital capacity (FVC) and forced expiratory volume in second (FEV1).

**Results** Both %FEVI (measured FEVI/predicted FEVI X 100) in current smokers (CS) and %FEVI in ex-smokers (ES) were lower than %FEVI in non-smokers (NS). There was no difference in %FEVI among the subgroups divided by age both in current smokers and ex-smokers. Also, there was no difference in %FEVI among the subgroups divided by duration of smoking cessation in ex-smokers. Moreover, it was confirmed that age, highest amount of cigarette smoking were significantly related to FEVI both in male CS and male ES. In male CS, the estimated decline of FEVI per age was 2.6 mL. In male ES, the estimated decline of FEVI per age was 2.5 mL, and excess of decline pack-year of smoking was 1.5 mL. In female CS, the estimated decline of FEVI per age was 1.6 mL, and excess of decline pack-year of smoking was 1.3 mL.

**Conclusion** Our data suggested that influences of smoking on FEVI were observed even in healthy ex-smokers.

P4075 Prenosological diagnosis of respiratory function abnormalities in smokers Marina Seerzbaeva, Mikhail Pogodin, Nina Aleksandrova. Laboratory of Respiratory Physiology, Pavlov Institute of Physiology, St. Petersburg, Russian Federation

Chronic tobacco poisoning leads to the gradual development of various patholog-ical processes at the cellular, tissue, organ and system levels, but their clinical manifestations may have delayed effect. Prenosological diagnosis of respiratory function disorders in smokers is very important in order to promote an effective behavioral intervention for smoking cessation. The study was performed for evaluation of simple and noninvasive diagnostic methods of respiratory disorders in smokers. Maximal inspiratory pressure (MIP), peak inspiratory flow (PIF) and dSO2 may be adequate diagnostic methods for early detection of respiratory pathology in smokers. These methods can be used in routine clinical practice.

P4076 Comorbidity in smokers – A cumulative effect of exogenous and endogenic factors? Elvira Ivancheva1, Rosita Iavicnova2, Filip Stoy1, Vanya Youzorouka2, 1Pulmonology, Medical University, Plovdiv, Bulgaria; 2Pulmonology, Medical University, Sofia, Bulgaria

This work is an analysis of our studies and literary data about a cumulative effect of tobacco smoke and another risk factors and comorbidities. There is investigated the connection between COPD and COPD and lung cancer (COPD + Ca) (NS). There was no difference in %FEV1 among the subgroups divided by age both in current smokers and former smokers and %FEV1 in ex-smokers (ES) were lower than %FEV1 in non-smokers (NS). There was no difference in %FEV1 among the subgroups divided by age both in current smokers and male sex, or between OSA and nonsmokers. YP index correlates with arousal index, but doesn’t correlate with nicotine dependence.

**Conclusion:** Smoking intensity and sleep quality (arousal index/correlated, unrelated to nicotine dependence. Studies are needed to prospectively assess effects of smoking on sleep and OSA using a non-smoking control group.

P4077 High environmental tobacco smoke and other air pollutants exposure in patients with allergic rhinitis non smokers Dragica Peselj1, Ljudmila Nagorni-Obradovic1,2, Biljana Savic1. 1Institute of Pneumology “Marius Nasta”, University of Medicine and Pharmacy “Victor Babes”, Timisoara, Romania; 2Teaching Hospital of Allergology and Immunology, Clinical Centre of Serbia, Belgrade, Serbia

**Background:** Chronic exposure to cigarette smoke inhibits surface immunoglobulin-mediated responses in B cells. Immunomodulatory effects of cigarette smoke are evidence based and the effects of environmental tobacco smoke (ETS) on immune system are in focus of current research.

**Aim:** Aim of the study is to analyse tobacco smoking status in patients (Ps) with allergic rhinitis (AR) with special regard to ETS. **Methods:** In this observational questionnaire based study successive series of Ps treated for AR at two tertiary level health care facilities in Belgrade, Serbia, was enrolled from January 2010 to December 2011, and valid questionnaires were analyzed for Ps demographic and social data, and tobacco smoking status.

**Results:** Study group consisted of 182 Ps; average age: 36.2±12.50; male/female ratio: 0.75. Tobacco smoking status analysis showed: 12.6% current smokers, 15.4% former smokers, and 136/184 (72%) Ps non smokers. About two thirds of the ‘non smokers’ have been exposed to ETS while 166/182 (91.2%) Ps have been exposed to both tobacco smoke ingredients (at home and/or at working place), and to the other air pollution.

**Conclusion:** High proportion of AR Ps is exposed to tobacco smoke and/or the other environmental pollution, which might present a serious problem and challenge for further research in the field of immunomodulation.

P4078 Effectiveness of smoking cessation in patients with psychiatric disease Zeynep Pinar Östen, Elfet Sen, Bamu Eras Güllübay, Faten Alin Kabadab. 1Dipartimenti dell’Apparato Respiratorio, Chest Disease, Ankara University School of Medicine, Ankara, Turkey

**Background:** Smoking cessation treatment is considered to be less effective in patients with psychiatric diseases.

**Aim:** To evaluate the smoking cessation rate in patients with psychiatric dis-orders, compare the effectiveness between the different treatment modalities and demonstrate the discrepancies from other patients. **Methods:** From a total number of 609 active smokers; 52 with psychiatric diseas-es (most discriminant concomitant condition was depression) were prospectively evaluated between 2004 and 2010. Each patient answers the same questionnaire including smoking status and medical background. Nicotine dependence and CO of hypoxemia during any apnea than nonsmokers. Our results showed that the measurement of PIF, PEF, MIP and dSO2 may be adequate diagnostic methods for early detection of respiratory pathology in smokers. These methods can be used in routine clinical practice.
levels were evaluated. Smoking cessation program was administered individually according to the guidelines and all of the patients were followed at least 1 year.

**Results:** There was no difference between the groups in age, baseline Fagerstrom nicotine addiction score, exhaled carbon monoxide level and treatment protocols. However, total amount of smoked tobacco (27.8±12.1 pack-year) and cigarette consumption per day (21.1±10) was higher in patients with psychiatric diseases (p<0.01 for all). The cessation rates with or without psychiatric diseases were respectively 44.2% and 55.6%. Effectiveness of treatment modalities are 44.4% for nicotine replacement treatment (a total amount of 5.7% for the group without psychiatric diseases). The survey was conducted in closed, ethnically homogenic population of Kashubians.

**Conclusion:** Searching for CHRNA3, CHRNA4, CHRNA5, and CHRNB4 genes polymorphisms influencing nicotine dependence in the ethnic population of Kashubians, North Poland

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Genome wide association studies showed that genes encoding nicotinic receptor CHRN subunits might be potentially involved in the pathogenesis of nicotine dependence. We aimed to investigate whether polymorphisms in the sites rs12914008, rs16969968, rs2226196, rs578776, rs7148770 of CHRN, CHRNA3, CHRNA4 and CHRNA5 subunits influence nicotine dependence. The survey was conducted in closed, ethnically homogenic population of Kashubians. The study sample consisted of 45 unrelated subjects, daily or occasional smokers. Several variables of smoking habit were recorded, and the nicotine dependence was scored with the use The Fagerstrom Test for Nicotine Dependence (FTND). Genotyping was performed in blood samples, and genotypes were correlated with the severity of nicotine dependence with the use of multivariate logistic regression analysis.

**Results:** Distribution of genotypes for all polymorphisms did not deviate from expectations predicted by the Hardy-Weinberg equilibrium. We found that A allele carriers of rs16969968 polymorphism had higher risk of heavier smoking, i.e. 10 or more cigarettes per day, than G allele carriers (OR = 1.54; 95% CI: 1.00-2.35).

In the separate analysis, performed in the group of subjects with the history of smoking shorter than 5 years, higher risk of a stronger nicotine dependence (i.e. FTND score 4 or more) in A allele carriers of rs12914008 polymorphism than in G allele carriers was found (OR = 14.96; 95% CI: 1.42-158.0).

**Conclusion:** Polymorphisms in the sites rs16969968 and rs578776 of CHRN and CHRNA3 subunits genes may influence the severity of nicotine dependence.

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**Background:** We have previously reported at the 2011 ERS Annual Congress that early exposure to tobacco smoke significantly increased the prevalence of COPD. As a follow up, we hypothesized that COPD from early exposure to smoke may cause an increase of IMT that correlates with the increase in the prevalence of smoking-related vascular comorbidities. (Methods) We identified potential subjects into three groups: G1) history of COPD and early exposure; G2) history of COPD and non-early exposure; G3) subjects without COPD and analyzed the measurements IMT. IMT were measured using the longitudinal axis of the common carotid arteries from ultrasound. We defined early exposure as when habitual smoking started before age of 20. (Results) A total of 152 subjects (72±10 years old; SD) were enrolled into the study after informed consents were obtained. G1, 2, and 3 consisted of 41 subjects (age 68.4±9 yrs), 80 subjects (71.1±11), and 31 subjects (69±10) respectively. Maximum value of IMT in G1 was 1.34±0.12mm, G2 was 1.23±0.13, and G3 was 1.12±0.16. Groups with history of COPD had higher maximum value of IMT when compared with group without COPD. Furthermore, G1 demonstrated higher value when compared with G2, suggesting early exposure to smoke as possible etiology within subjects with COPD. (Conclusion) In subjects with COPD, early exposure promoted atherosclerotic changes, which may increase the likelihood of smoking-related vascular comorbidities such as cardiovascular and cerebrovascular diseases. Further studies are needed to elucidate the precise magnitude of the increase in risk of these comorbidities associated with COPD and early exposure.

**Conclusion:** This study aimed at evaluating the correlation between not smoking at home and intention to quit.

**Methods:** This descriptive cross-sectional study was carried out in Tehran in 2011, on 2,020 smokers. Information were collected by interviewers through a standardised questionnaire such as age of smoking onset, daily rate of smoking, price of cigarettes, using labeled or non-labeled tobacco products, history of quit attempts, cessation intention, water-pipe consumption, and knowledge about anti-tobacco laws.

**Objective:** This study aimed at evaluating the correlation between not smoking at home and intention to quit.

**Methods:** This descriptive cross-sectional study was carried out in Tehran in 2011, on 2,020 smokers. Information were collected by interviewers through a standardized questionnaire such as age of smoking onset, daily rate of smoking, price of cigarettes, using labeled or non-labeled tobacco products, history of quit attempts, cessation intention, water-pipe consumption, and knowledge about anti-tobacco laws.
and not smoking at home. Family members can have a positive role in encouraging considerable role in increasing the intention of its members for smoking cessation. Tobacco smoking at home can motivate smokers to quit smoking. Family has a significant association between tobacco smoking at home and intention to quit. Chi-Square test revealed a significant association between tobacco smoking at home and intention to quit.

Discussion: As this study and some other studies have shown, restrictions on tobacco smoking at home can motivate smokers to quit smoking. Family has a considerable role in increasing the intention of its members for smoking cessation and not smoking at home. Family members can have a positive role in encouraging other members to quit smoking or sustain their abstinence.

P4084 Mapping the tobacco retailers in Edirne, Turkey
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Objective: Smoking rate is on the rise in Turkey. Although many marketing bans have been effectively implemented, regulations related to retail tobacco outlets have gone unnoticed and have not been effectively supervised. In this study, we aim to manifest that a lack of legal regulation related to the high retail tobacco outlet density with displays.

Methods: In the center of Edirne, marketing environment, numbers and geographical distribution of retail tobacco outlets are documented and mapped with geographical information systems.

Results: There were 569 retail tobacco points of sale in 520 stores. We calculated one tobacco retail outlet per 270 people. This retail outlet density rate is above the country average and about four times higher than in Istanbul. Products especially attracting children, such as chocolates, sweet candies and chewing gums were set up near the tobacco stands and were easy for children to see and reach. It is seen on the city map that 47% of retail tobacco outlets are within 100 m to education, health, and sport facilities.

Conclusions: We concluded that one of the reasons of the increasing prevalence of cigarette use especially among adolescents in Turkey is deregulation of the retail tobacco marketing environment during privatization process of national tobacco monopoly. Using the mapping techniques can help to control retail marketing environment.

P4085 Smoking prevalence and practice in special categories: Taxi drivers
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The goal of the survey was to estimate the prevalence of tobacco consumption on taxi drivers and secondhand smoke (SHS) exposure in cars. The study is important because it is the first one made in Romania on this topic and there are a few of them reported in medical publication. There are decisions of local council on banning smoking in taxis for both driver and customer. The data were collected from a 5-10 min questionnnaire which contain demographic data, Fagerstrom Nicotine Dependence Scale and questions regarding smoking practice in the car. The questioners were directly distribute to taxi drivers from three large taxi companies from Bucharest.

Results: 100 questioners were collect for statistical analysis from 400 taxi drivers. The lot was made by 94/6men and 6/4women; average age 37.7±9.5±8.9years; driving experience averaged 6.7±4.4±5.5years; hey work in shifts: 7/1% only in day, 63/6% in night and 29/3% in alternative. The work years on night shift aver- age were 3.9±4.36. Smokers 70.7%, (average age 38.04±9.78) years Exsmokers 10.1%, Nonsmokers 19.2%. Number of cigarettes/day (0-5) 15.7%, 10/20 66.6% and > 20/515.7%. Nicotine dependence was high, 70% of smoker light their cigarette in the first 5 minutes of waking. 35% of smoke in the taxi, if the customer doesn’t express his opinion regarding smoking.

Conclusions: The prevalence of smoking is higher than the national average (30%). The study group consists of young people who work at night and have a high dependence on nicotine. There is company internal rules that bans smoking, so many taxi drivers refrain from smoking in taxis, but not when they don’t have client. Smoke free policy can support a smoking cessation program among them.

P4086 A survey to assess smoking awareness and attitudes of staff at a local hospital
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Objectives: To determine the smoking awareness levels in hospital staff. To assess the impact of smoking cessation programme (SCP) and other smoking cessation methods on smoking habits and attitudes of hospital staff.

Methods: A cross-sectional, descriptive, quantitative study was carried out. Data were collected using a semi-structured questionnaire. Staff were recruited from all hospital departments. A total of 462 person (95.95%) mentioned a history of smoking. There were 435 (92.4%) smokers who 261 (57.7%) had moderate or high nicotine dependence. A significant correlation was detected between first substance abuse experience or daily substance abuse during the first 2 years following smoking onset (P<0.001). Those who started smoking at a younger age in our study started substance abuse significantly sooner than others or developed a daily addiction to it. Using below formula, we can anticipate how long after smoking experience one would probably experience their first substance abuse (P<0.001).

First substance abuse experience age=7.7±2.78 (first smoking experience age)

Conclusions: A significant correlation exists between smoking and future substance use. Therefore, efforts must be made to prevent tobacco consumption in the first place. For those who are already smokers, preventive and supportive measures must be undertaken to prevent substance abuse especially in the first two years following smoking initiation.

P4087 Evaluation of smoking pattern and its correlation with addiction among substance abusers
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Introduction: Since tobacco consumption is not illegal, people are often not considering it as an addictive substance. It has been revealed that young smokers have a stronger desire and tendency to experience high risk behaviors and have a greater risk of substance abuse.

Objective: This study aimed at evaluating the pattern of smoking and its effect on initiation of substance abuse in those presenting to the rehabilitation centers and substance abuse clinics.

Materials and methods: In this descriptive cross sectional study, 487 cases referred to the rehabilitation centers and substance abuse clinics in Tehran were evaluated with a standard questionnaire.

Results: A total of 462 person (95.95%) mentioned a history of smoking. There were 435 (92.4%) smokers who 261 (57.7%) had moderate or high nicotine dependence. A significant correlation was detected between first substance abuse experience or daily substance abuse during the first 2 years following smoking onset (P<0.001).

Conclusions: A significant correlation exists between smoking and future substance use. Therefore, efforts must be made to prevent tobacco consumption in the first place. For those who are already smokers, preventive and supportive measures must be undertaken to prevent substance abuse especially in the first two years following smoking initiation.

P4088 Short-term effects of quitting smoking in TNF-α and interleukin-10 serum and nasal lavage levels
Marceli Rocha Lopes, Dionei Ramos, Rafaela Fagundes Xavier, Juliana Tyaki Ito, Fernanda Maria Machado Rodrigues, Juliana Nicolin, Alessandra Choqueita de Toledo, Ercy Mara Cipulo Ramos. Phisiotherapy, UNESP - São Paulo State University, Presidente Prudente, SP, Brazil

Some systemic benefits of quitting smoking are known, however, the immediate effects on inflammatory biomarkers have not been well described. The purpose of this study was to evaluate inflammatory biomarkers during a smoking cessation program (SCP). Twenty two abstinent smokers (age 50-55 years; 13-36 pack/year index; FEV1% 96±82 (104-80%) were included in this study. They were recruited from hospital staff. The measurements of TNFα and interleukin-10 (IL-10) serum and nasal lavage samples were evaluated at baseline and after 7, 15, 30 and 60 days of abstinence. The measurements of TNFα and interleukin-10 (IL-10) serum and nasal lavage samples were evaluated at baseline and after 7, 15, 30 and 60 days of abstinence.

Background: Rising smoking-related morbidity and mortality would be expected to lead to increased awareness among hospital staff regarding the harmful effects of cigarettes.

Climate and objectives: The aim is to assess the smoking habits of individuals working within a hospital setting who are directly or indirectly exposed to patients with smoking-related illnesses. The survey addresses health issues and attitudes towards smoking. The timing is opportune in that Mater Dei Hospital Malta is to be declared a totally smoke-free hospital.

Methods: A questionnaire was compiled, based on various tools validated in the literature. These were distributed to all members of staff at our General Hospital, targeting more than 3600 individuals.

Results: 27.1% of male and 24.8% of female staff are active smokers. Males were significantly (p=0.001) more likely to have started smoking at a younger age than females. Almost half find difficulty in refraining from smoking in forbidden areas. Only 22.2% of smokers refrain from smoking in hospital. The highest percentage of smokers are in the youngest age group (18-25 years). 10.4% of doctors and 23.6% of nurses are active smokers. 25.7% of non-smokers had previously smoked, the greatest incentive for quitting being for health reasons. Most members of staff are aware of the adverse effects of smoking and a number have symptoms suggestive of smoking-related pathology.

Conclusions: Hospital staff mirror the general population with respect to smoking habits and comorbidities. This is unacceptable and emphasizes the need to implement harsher measures whilst educating our hospital staff so that these in turn may serve as educators to patients and hospital visitors.
abstinence (p<0.0001). There was a significant decrease in TNF-α levels on nasal lavage in abstinent smokers after 60 days of abstinence (p=0.0186). For TNF-α levels on blond plasma and IL-10 on blond plasma and nasal lavage there was no observed significant difference. The abstinence promoted decreased exC0 and COHb levels after 7 days, decreased in TNF-α levels on nasal lavage in 60 days and of abstinence.

P4089
Is motivational Q-mat test useful to predict smoking cessation?
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Background: Smoking is one of the major causes of cancer, heart and pulmonary diseases, one of essential steps in tobacco control is persuading the smokers to quit smoking. Encouraging smokers to the quit can be possible if the smoker has enough motivation for quit. In this study we investigated abstinence rate after 6 months according to level of motivation to quit (Q-mat score) and level of nicotine dependency (Fagerstrom score).

Material and method: This study was conducted on the volunteers of smoking cessation clinic in Tehran. They underwent tests for nicotine dependence, motivation degree assessment by FT and Q-mat test respectively. Thereafter, smokers started the cessation program consisting in behavioral therapy and pharmacotherapy. Their quit rate was by verified by telephone and through exhaled co measurement after 6 months.

Results: In this study 345 volunteers were studied from which 311 (90.1%) male. The mean age was 37.6±11.04 years. After 6 months follow up abstinence rate was 39%. The mean of Q-mat score was 15.8±5.1 (14.9-16.7 CI 95%) in participants who stopped smoking and 15.4±5.1 (14.7-16.9 CI 95%) among participants who failed smoking cessation (p=0.4). The mean of FT was 5.2±2.6 (4.7-5.6 CI 95%) in participants who stopped smoking and was 6.2±2.6 (5.7-6.4 CI 95%) among participants failed (p=0.002).

Conclusion: The results of this study indicate that volunteers may have high participants failed (p=0.002).

P4090
Usefulness of paediatric dyspnoea scores for evaluative purpose in acute wheeze
Jolita Behkof, Irene Marjie Barrels, Roelien Reimink, Paul Brand. Princess Amalia Children’s Clinic, Isola Klinieken, Zwolle, Netherlands

Clinical dyspnoea scores are the most commonly used methods to assess wheeze severity and response to bronchodilator treatment in young children. We performed a prospective observational study to assess the (external) validity of 3 frequently used dyspnoea scores: Asthma Score (AS), Clinical Asthma Score (CAS) and Pulmonary Index (PI), before and after bronchodilator treatment. We studied 46 hospitalized children (0-8 yrs) with a wheeze exacerbation. Video and audio recordings of breathing pattern and lung sounds were made before and after salbutamol inhalation. 3 paediatricians and 4 nurse practitioners independently reviewed these recordings and rated the degree of dyspnoea using the three scores. This was repeated after 4 weeks to evaluate intra-observer reliability. Inter- and intra-observer reliability were evaluated by intraclass correlation coefficient (ICC, considered adequate when >0.70), responsiveness by Guyatt’s RR (considered adequate when > 1.96). Differences in scores within and between observers were larger than those before and after treatment.

Inter- vs intraobserver reliability and responsiveness of three dyspnoea scores

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<th>Interober ICC</th>
<th>Intraobserver ICC</th>
<th>Guyatt’s RR</th>
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<tr>
<td>AS</td>
<td>0.72</td>
<td>0.77</td>
<td>0.89</td>
</tr>
<tr>
<td>CAS</td>
<td>0.69</td>
<td>0.71</td>
<td>0.83</td>
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<tr>
<td>PI</td>
<td>0.61</td>
<td>0.66</td>
<td>0.51</td>
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We conclude that the poor within- and between-observer reliability of these three dyspnoea scores renders them invalid for use as an evaluative instrument in children 0-8 years of age with an acute wheeze exacerbation.

P4091
Clinical scores for the assessment of acute dyspnoea in wheezing children:
Systematic review
Jolita Behkof, Roelien Reimink, Paul Brand. Princess Amalia Children’s Clinic, Isola Klinieken, Zwolle, Netherlands

A reliable, valid, and easy-to-use assessment of the degree of wheeze-associated dyspnoea is important to provide individualised treatment for children with acute asthma, wheeze or bronchiolitis. We conducted a systematic review to assess validity, reliability, and utility of all available paediatric dyspnoea scores. We searched Pubmed, Cochrane library, National Guideline Clearinghouse, Embase and Cinahl for eligible studies. We included studies describing the development or use of a score, assessing two or more clinical symptoms and signs, for the assessment of severity of dyspnoea in an acute episode of asthma, wheeze or bronchiolitis in children aged 0-18 years. Study selection and data extraction was done independently by two reviewers. Validity, reliability and utility of the reviewed 32 children scores were assessed by 15 quality criteria for clinimetric studies. We retrieved 41 articles describing 32 dyspnoea scores. Thirteen scores were judged unsuitable for clinical use, because of insufficient face validity, use of items unsuitable for children, difficult scoring system or need of auscultation skills, leaving 19 possibly useful scores. The median number of quality criteria that could be assessed was 6 (range 5-10). The median number of positively rated quality criteria was 2 (range 1-5). In conclusion, none of the published dyspnoea scores has been sufficiently validated to allow for clinically meaningful use in children with acute wheeze. Proper additional validation of existing scores is warranted to allow clinicians and researchers to use the available paediatric dyspnoea score for clinical or research purposes.

P4092
Clinical predictive rules to identify preschool wheezers at risk for subsequent asthma: Can we rely on them? Could we improve their performance?
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Background: Various predictive rules have been developed to identify wheezy preschoolers at risk for persistent asthma. The aim of this study was to evaluate the performance of the asthma predictive index (API), modified API (mAPI), and PIAMA score, and to examine whether the presence of reversible airflow obstruction (RAO) could improve the prediction of later asthma.

Methods: This retrospective study included 32 children aged 6-8 years with recurrent wheeze who had regular follow-up for the last 4 years. Active asthma was defined as doctor-diagnosed asthma or wheeze that required long-term medication in the previous 12 months. RAO was defined as a bronchodilator response ≥80% for respiratory resistance and ≥35% for respiratory reactance determined with the forced oscillation technique (FOT).

Results: Active asthma was present in 32 children (34.8%). 21 children (22.8%) had positive API, 10 (10.9%) positive mAPI, and 55 (59.8%) had PIAMA score ≥ 20; RAO was documented in 25 children (27.2%). The stringent API had positive and negative likelihood ratio (LR+ and LR-) of 3.0 and 0.69 respectively. The mAPI had LR+ 1.6 and LR- 0.73, and the PIAMA score LR+ 1.5 and LR- 0.52. The combination of API (or mAPI) and RAO resulted in LR+ 3.8 and LR- 0.24 (LR+ 3.2 and LR- 0. 4), whereas the combination of PIAMA score and RAO resulted in LR+ 1.4 and LR- 0.39.

Conclusion: All tested indices had limited overall ability to predict –especially to rule-out– subsequent asthma in preschoolers with recurrent wheeze. Combination of asthma predictive models with FOT-determined RAO may improve the prediction of later asthma in wheezy young children.
Parents reported asthma symptoms in the past 12 months in 57 children. Asthma maintenance medication was used in the past 12 months in 38 children. The diagnostic questionnaire total score (0-100) was significantly different between children with (n=63) or without symptoms and/or asthma medication use at follow-up (54 versus 42, p=0.005). Sensitivity, specificity, positive and negative predictive values of the questionnaire were 40%, 82%, 69% and 56%, respectively.

Conclusions: These preliminary results show asthma symptoms and/or medication use at school age in half of the children with respiratory symptoms at preschool age. Further analyses of the final database are needed to draw definite conclusions with regard to the diagnostic accuracy of this newly developed diagnostic tool.

P4094
Usefulness of the asthma predictive index in clinical practice: A systematic review and clinical epidemiological analysis
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The Asthma Predictive Index (API) has been developed from follow-up data of the Childhood Asthma Study in Asthmatic Children (CASCACH). The API includes 5 symptom-patterns of wheeze that parents can use to identify their child’s asthma status into 7 categories. The most severe is the multiple-trigger pattern (3 or more symptoms in any 24h period). API scores range from 0-4 and were shown to be a good tool to predict disease course.

Objective: We investigated whether multiple-trigger wheezers were more likely to have abnormal pulmonary function in preschool wheezers.

Background: Multiple-trigger wheezers are commonly used among preschoolers with wheeze. However, symptom-patterns of wheeze have not been related to pulmonary function tests or markers of airway inflammation.

Methods: Twenty-six control subjects and 25 wheezers (11 episodic and 14 multiple-trigger wheezers) were tested. FEV1, FeNO and LCI did not differ significantly among episodic and multiple-trigger wheezers. The presence of current atopy was associated with higher FeNO (p=0.024) but did not influence pulmonary function and LCI significantly. Eight out of the 25 (32%) wheezers showed a significant increase in FEV1 and 15 out of the 25 (60%) wheezers showed a significant decrease in LCI, after administration of inhaled salbutamol.

Conclusions: Asthmatic children report significantly lower asthma control than their parents using the C-ACT, irrespective of the child’s age. This may indicate that parents underestimate asthmatic complaints of their children.

P4095
Pulmonary function and inflammation discriminated by symptom-pattern phenotypes in preschool wheezers
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Background: The discrimination of episodic and multiple-trigger wheezing is commonly used among preschoolers with wheeze. However, symptom-patterns of wheeze have not been related to pulmonary function tests or markers of airway inflammation.

Objective: We investigated whether multiple-trigger wheezers were more likely to have abnormal FEV1, increased ventilation inhomogeneity (LCI) and increased fraction of exhaled nitric oxide (FeNO) than episodic wheezers. We also investigated whether multiple-trigger wheezers were more likely to have a positive reversibility test, than episodic wheezers.

Methods: FEV1, LCI and FeNO were measured in healthy children and those with recurrent wheeze aged 4 to 6 years.

Results: Twenty-six control subjects and 25 wheezers (11 episodic and 14 multiple-trigger wheezers) were tested. FEV1, FeNO and LCI did not differ significantly among episodic and healthy preschoolers. On average, LCI was abnormal in 18 wheezers (72%). Multiple-trigger wheezers had an average increase of 3.1% (P=0.0001) in LCI, compared with episodic wheezers. FEV1 and FeNO did not differ significantly among episodic and multiple-trigger wheezers. The presence of current atopy was associated with higher FeNO and did not influence pulmonary function and LCI significantly. Eight out of the 25 (32%) wheezers showed a significant increase in FEV1 and 15 out of the 25 (60%) wheezers showed a significant decrease in LCI, after administration of inhaled salbutamol.

Conclusions: Multiple-trigger wheeze is associated with pulmonary function abnormalities independent of atopic status. LCI is the most sensitive indicator of abnormal pulmonary function in preschool wheezers.

P4096
The childhood asthma control test: Children versus parents
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Introduction: The Childhood Asthma Control Test (C-ACT) is a validated patient-completed questionnaire to assess asthma control in children 4-11 years, which is divided into two parts. One part is filled in by the child, the second part by the parent.

Objectives: To compare asthma control scores between children and their parents.

Methods: Asthmatic children 4-11 years and their parents visiting our outpatient asthma clinic in 2011, completed the C-ACT as part of routine patient care. Spearman correlation and Intraclass Correlation Coefficient (ICC) between C-ACT by child and parent were calculated. Both scores were expressed as percentage of the maximum and pair wise compared using the Wilcoxon Signed Ranks Test and a Bland-Altman plot.

Results: 272 children (aged 6.68 yrs, 66.8% male) and their parents participated. Correlation between C-ACT score between children and parents was moderate (r=0.72, p<0.001); the ICC was reasonable (0.77, p<0.001). Children scored median 75% (0-100) of the maximal score, whereas parents scored median 87% (0-100). On average children scored 8.5% lower than parents (p<0.001, see figure 1). The difference between children and parents was independent of the child’s age (p = ANOVA=0.804).

Conclusions: Asthmatic children report significantly lower asthma control than their parents using the C-ACT, irrespective of the child’s age. This may indicate that parents underestimate asthmatic complaints of their children.

P4097
Level of asthma control among asthmatic children in Thessaloniki area in northern Greece
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Background: In spite of the use of international guidelines for the diagnosis and treatment of asthma, there is continuing evidence of poor asthma control among asthmatic children. Level of asthma control has not been previously evaluated in Greece.

Aim: To evaluate the level of asthma control among asthmatic children in the city of Thessaloniki (Northern Greece).

Method: Parents of children > 2 years old with doctor’s diagnosis of asthma interviewed by the same physician using a detailed questionnaire including asthma symptoms, limitation of activities, need for rescue medication, asthma exacerbations and emergency visits. 365 children were examined either in Asthma Clinic, or the Emergency Department from November 2010 to May 2011.

Results: Mean age of the children was 7.8 years. 93/365 (25.48%) of them achieved adequate control of asthma, as defined by GINA (Global Initiative for Asthma). 176/365 (48 22%) had partly controlled asthma, whereas uncontrolled asthma was found in the 96/365 (26.3%) of the children. 104/365 (30%) of the study population had used rescue medication for more than two days during the previous week, whereas 70/365 (19.2%) of them reported limitation of activities and 62/365 (17%) had nocturnal symptoms within the previous month.

Conclusions: One out of four of the children suffering from asthma in Thessaloniki area achieves control of the disease. An increased use of rescue medication for more than two days was reported in 1/3 children, limitation of activities and nocturnal symptoms in around 1/5 of the children.

757s
Can response to inhaled corticosteroids in preschool children with recurrent wheezing predict asthma at age six years?

Safaa Wafy

Caregivers reported few problems due to their child’s asthma whereas

Conclusions:

(r= -0.168, p=0.35).

1Chest Department, Assiut University Hospital, Assiut, Egypt; 2Community and

wheezing predict asthma at age six years?

Can response to inhaled corticosteroids in preschool children with recurrent

Methods:

From the Asthma DEtection and Monitoring (ADEM) study, 160 recur-

rent wheezers aged 2-4 years (≥ 2 episodes, ISAAC questionnaire) received 200μg
diclohexamethone for eight weeks. Before and after treatment symptom score (in-

versely to severity), airway resistance (Rint) before and after and 300 μg Salbutamol,
Fractional exhaled Nitric Oxide (FeNO), and exhaled breath condensate markers
(pH, interleukin (IL) 1a, IL-2, IL-4, IL-5, IL-10, IL-13, IFNg, scCAM, and Eotaxin) were assessed. At the age of 6 years a final diagnose (asthma or transient wheezing) was based on symptoms, lung function, and medical use. Analysis was performed by logistic regression.

Results: At the age of 6 the study group consisted of 61 asthmatics and 99 transient wheezers. At the age of 2-4 years symptom score before (ORadjusted=0.86 95%CI=0.79-0.94, p<0.01) and after treatment (ORadjusted=0.88, 95%CI=0.81-0.96, p<0.01), and prebronchodilator Rint after treatment (ORadjusted=2.80 95%CI=1.77, 51, p=0.04) were significantly associated with asthma at the age of 6 years. However, all parameters tested did not change during treatment.

Conclusions: In recurrent wheezing children, asthma at 6 years was associ-

ated with more severe symptoms before and after ICS treatment and increased prebronchodilator airway resistance after ICS treatment at 2-4 years of age.

P4099 Asthma-related quality of life in children: Correlation with asthma control and lung function

Sandra Klaisen-Beeren1, Peter Merkus2, Anneke Lansdorfs3, Hein Brandelli4

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Introduction: Children with asthma often have sleep disturbances, absence from school and limitations of physical activity that may reduce their quality of life (QOL). Therefore, asthma-related QOL is an important endpoint in childhood asthma.

Objectives: To assess QOL in children and adolescents with asthma, and to correlate QOL with asthma control, lung function and FENO.

Methods: QOL was assessed by caregivers of asthmatic children aged 4-11 yrs and by adolescents with asthma (12-18 yrs) using the Pediatric Asthma (Care-

givers) Quality of Life Questionnaire (PAQLQ). PAQLQ scores were correlated with asthma control (assessed by the (Childhood) Asthma Control Test (C-ACT) and GINA classification) and with FEV1 and FENO.

Results: 221 children (mean age 10.5 yrs, 148 male, n=76 >11 yrs) participated. Median FEV1 was 97.1% (59.139) and median FENO 18.6 ppb (4-170). Median PAQLQ score of caregivers was 6.46 (3.69-7), with median sub domain scores of 6.75 (activity) and 6.44 (emotional). Median PAQLQ score of adolescents was 6.18 (3.52-7), with sub domain scores of 6.10 (symptoms), 5.40 (activity) and 6.88 (emotional). Median PAQLQ score in children with controlled asthma (n=43) was 6.85 (5.54-7), in partly controlled asthma (n=84) 6.52 (4.23-7) and in uncontrolled asthma (n=85) 5.78 (3.52-7) (<0.05). PAQLQ scores correlated strongly with C-ACCT scores (r=0.60, p<0.05), but not with FENO (r=0.048, p=0.49) or FEVER (r=-0.186, p=0.35).

Conclusions: Caregivers reported few problems due to their child’s asthma whereas adolescents reported lower QOL, in particular on activity. Pediatric asthma QOL correlated strongly with asthma control, but not with FENO and FEV1.

P4100 Assessment of quality of life in asthmatic children. A case- control study

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Introduction: Health-related quality of life (HRQL) has become an increasingly important issue in the management of asthma and it is now often used to evaluate the effectiveness of antiasthma drugs.

Objective: To assess impairment in QOL in asthmatic children and to determine the influencing factors.

Methods: 230 asthmatic outpatients, aged 7-18 years, from chest outpatient clinic in school health insurance, Assisi, compared with another 272 non asthmatic pa-

tients. Two questionnaires were used for each patient: asthma questionnaire and St George’s Respiratory Questionnaire (SGRQ) to assess QOL.

Results: Asthma affected boys more than girls (62.2% and 37.8%). The mean age of asthmatic children was 9.1±2.1 years. Allergic rhinitis were highly significantly associated with asthmatic patients. About 40% diagnosed as uncontrolled asthma based on their night awakening, 70% >26.5% based on their activity limitation and daytime symptoms. Severe asthma reported in 42.6%. Asthma affects quality of life of all patients. There were significant differences between the two groups as regard Symptom, Activity, Impact and Total score (all P < 0.0001) of St George’s. There was a negative correlation between asthma severity and quality-of-

life score. Allergic rhinitis, was strongly and negatively associated with the overall SGRQ score (p=0.038). Lower QOL was associated with school absence, younger (<11 yrs) and among patients with poor adherence/illiterate patient. Asthma affected all life style of the majority of patients as, physical exercise limitation, sleep disturbance, and emotional function etc.

Conclusion: Bronchial asthma in our community affected QOL of children, so reduce asthma severity and improve asthma symptoms attempts to improve their QOL.

P4101 Effect of asthma control and quality of life on the use of alternative medicine

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Asthma is the most common chronic lower respiratory tract disease of childhood. It may affect the quality of life of the child and the parents. Nowadays, use of alternative treatment (AT) methods are increased in treatment of asthma and/or relief of symptoms. But there are limited studies showing the efficiency of AT and evaluating the association between asthma control and AT usage. We investigated the prevalence of AT usage and effect of AT usage on asthma control and quality of life in patients with asthma.

Study included 80 patients with asthma followed up in Pediatric Pulmonology Department. “Pediatric Asthma Quality of Life Questionnaire” (PAQLQ) was used to evaluate the quality of life. “Asthma Control Test” (ACT) and “Asthma Control Questionnaire” (ACQ) were used to measure asthma control.

Mean age of the patients were 9.2±4.3. 63.8% of the patients used at least one method of AT in their life before the recommended treatment. The most commonly used methods were: carbolic molasses (36.3%), herbs (26.3%), quails (25.2%), honey in black radish (15.1%), olive oil (15.0%), garlic (5%), respectively. Of whole, 59.6% of the patients got benefit from AT. Mean score of PAQLQ was 5.9±1.0. Parents with younger kids were found to use more AT methods (p=0.002). There were no association between the use of AT and time of the diagnosis of asthma, time of anti-inflammatory drugs usage, PAQLQ, ACT and ACQ (p>0.05).

In conclusion, AT is frequently used in our patients. We found that there was no effect of level of asthma control and quality of life on preferring AT.

P4102 Allergy and asthma severity

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Background: Asthma, allergic rhinitis (AR) and atopic dermatitis (AD) are multifactorial illnesses determined by complex interplay between genetic and environmental factors with different phenotype expression. The majority of asth-

mas have AR and studies have shown that treatment of AR helps control asthma symptoms. The objective of this study was to evaluate if the presence of AR and/or AD interfere with asthma severity.

Methods: We evaluated 1,350 asthmatic children aged 0 – 18 years (median 9 years), attending Health Center Nis. These data were collected by standard protocol and registered in a computer data base. Asthma diagnosis and severity were established by GINA (1995) criteria. Skin prick tests (SPT) were performed with common aeroallergen extracts and tests were considered positive if wheal diameter greater than or equal 3 mm. Data were analyzed by chi square test.

Result: Asthma severity was mild in 61.8%, moderate in 28.0% and severe in 10.2%. Male to female ratio was 1.3:1. AR was present in 59% of the patients, 72% in 6.2% , and both AR and AD in 2.1%. Regardless asthma severity there was no difference in the frequency of AR and/or AD among asthmatics. SPT was positive to at least one allergen in 78% of patients. The frequency of SPT positivity was 58% in mild asthma and increased to 85% in severe asthma (p<0.001).

Conclusion: Asthma severity was not related to the presence of AR and/or AD in this group of asthmatic children, but there was a relationship in the frequency of positive skin tests according to asthma severity.
Table 1. Coefficient of variation for delivered dose at each time delay/flow rate combination (n=10)

<table>
<thead>
<tr>
<th>Time delay (s)</th>
<th>Flow rate (L/min) combination</th>
<th>Coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diamond</td>
<td>Z-Stat</td>
</tr>
<tr>
<td>(0/5)</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>(5/5)</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>(10/15)</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>(0/15)</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>(5/15)</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>(10/15)</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>(0/30)</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>(5/30)</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>(10/30)</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Drug deposits were analyzed using HPLC. Results are presented as coefficient of variation of the delivered doses.

The co-efficient of variation was highest for the conventional VHC for all test conditions. Use of an anti-static VHC can minimize variability (improve reproducibility) in delivered dose under in vitro test conditions.

Figure 1. Left: Facemask seal leakage (%); Top right: SAM 0; Bottom right: SAM 1.

There was a wide variation in leakage from different VHC facemasks and also between SAMs. The smallest amount of leakage for both SAMs was seen with the OptiChamber Plus Z-Stat and conventional AeroChamber Plus (Z-stat and AC Plus; Philips Respironics, Respironics New Jersey, Inc., Parsippany, NJ, United States), followed by the OptiChamber Diamond with LiteTouch facemask.

**Table 1. Coefficient of variation for delivered dose at each time delay/flow rate combination (n=10)**

P4104

**In vitro comparison of the effect of inhalation delay on the variability of the delivered dose from valved holding chambers**

Dark Von Hollen, Paul Hancock, Ross Hatley, Kurt Nikander

Philips Respironics, Respirro New Jersey, Inc., Parsippany, NJ, United States; Respirro Respiratory Drug Delivery (UK) Ltd, Chichester, West Sussex, United Kingdom

The valved holding chamber (VHC) has been designed to optimize delivery for those using pressurized metered dose inhalers (pMDIs). We tested the effects on delivered dose of increasing delay between pMDI actuation and flow through the VHC, using both anti-static and conventional VHCs.

Ten anti-static Diamond (Diamond; Philips Respironics) VHCS, anti-static AerocChamber Plus (Z-Stat and conventional AerocChamber Plus; Z-stat and AC Plus; Monaghan Medical Corp.) VHCs were washed and air dried and six HFA albuterol sulfate pMDIs (ProAir HFA, 90 μg albuterol, Teva Specialty Pharmaceuticals LLC) were primed before use. For each run the pMDI was actuated into the VHC, after a delay of 0, 5 or 10 s flow through the VHC and attached filter occurred at an extraction flow rate of 5, 15 or 30 L/min for 10 s. The pMDI was actuated 10 times for each of the 10 VHCs of each brand at each delay/flow rate combination.

P4105

**Hypothalamic-pituitary-adrenal axis suppression in children at Cape Town allergy units – Prevalence and predictive factors**

Ekheder Zeiling1, Carl J. Lombard2, Galal3, Stephen Hough4, Elvis Iruuen5, Eugenine Weinberg5,1, Paediatric Endocrine Unit, University of Stellenbosch, Cape Town, Western Cape, South Africa; 3 Paediatric Endocrine Unit, Medical Research Council, Cape Town, Western Cape, South Africa; 1 Paediatric Endocrine Unit, University of Stellenbosch, Cape Town, Western Cape, South Africa; 2 Pain Clinic, University of Stellenbosch, Cape Town, Western Cape, South Africa

**Background:** Hypothalamic-pituitary-adrenal axis suppression (HPAS) is generally thought to be rare in children treated with corticosteroids (CS), since HPAS may be partially masked by recovering HPA function.

**Objective:** To determine the prevalence & predictive factors for HPAS in children treated with CS at the allergy clinics in Cape Town.

**Methods:** 143 asthmatic children, 5-18 years old, on inhaled CS (ICS) with additional CS were recruited. Clinical features compatible with HPAS were documented: Daily and cumulative CS dose, adherence, asthma score and lung functions were recorded. A metapyrone test was performed if the 0:00 h cortisol (C) was > 8nmol/l. Spearman correlation coefficients (r) were calculated between the post-metapyrone (PMTP) ACTH, 11-deoxycorticosterone (11DOC), 11DOC+C, and each variable. A multiple linear regression model of ΔACTH & a logistic regression model for HPAS were developed.

**Results:** Prevalence: All HPAS 65.1 (56.5-72.9)%; low (PMTP 11DOC, 11DOC + cortisol) 33.3 (23.7-40.9)%; low (PMTP ACTH, 11DOC, 11DOC + cortisol) 16.3 (9.3-23.3)%; hypocortisolism 6.1 (1.8-10.5)%.

**Conclusions:** About 2/3 of asthmatic children on CS may have a degree of HPAS. In one third the asthmatics may still be suppressed while hypothalamic-pituitary function may have recovered. Predictive factors for HPAS are concomitant use of BMI, adherence to ICS and NS.

P4106

**Fatigue: A symptom of asthma in children?**

Ghislaine van der Zande1, W.B. Vreede1, H. Heneweer3, 1 Paediatric Pulmonology, DeKinderkliniek, Almere, Netherlands; 2 Master Program Physician Assistant, Hogeschool Utrecht, Netherlands

**Introduction:** In children with symptoms of fatigue asthma is frequently diag-
nosed. However fatigue is not mentioned as a symptom in definitions of asthma in children.

**Aim of the study:** Exploration of the consistency between the symptom fatigue and the diagnosis asthma in children. Consequently asthma can be diagnosed earlier and faster and the care for these patients will improve.

**Method:** A retrospective analysis of the files of 440 patients between the age of 5 and 18 years with the diagnosis Asthma de Novo between May 15th 2009 and May 15th 2011. The data of patient characteristics, pulmonary function tests and symptoms were analyzed.

**Results:** There was an uneven distribution between boys (58%) and girls. The boys had a average age of 9.9 years, the girls of 11.0 years. In both groups the various pulmonary function parameters were abnormal. 52% of the patients complained of fatigue. The distribution of symptoms in boys and girls is equally.

**Conclusion:** Fatigue is the most frequently mentioned symptom of asthma in children, after complaints during exercise, dyspnea and coughing. Fatigue is not a specific symptom. The results can therefore only be an assumption. It is recommended to involve asthma in the differential diagnosis of unexplained fatigue in children.

**P4108**

**Role of MgSO4 in PICU management of children with status asthmaticus**

Shahid Sheikh1, Nadeem Khan 2, Melissa Frasure 3 , Nancy Ryan-Wenger4, Karen McCoy 1, 4

1Division of Pulmonary Medicine, Department of Pediatrics, Nationwide Children Hospital and Ohio State University, Columbus, OH, United States; 2Division of Critical Care, Department of Pediatrics, Nationwide Children Hospital and Ohio State University, Columbus, OH, United States; 3Division of Respiratory Care, Nationwide Children Hospital, Columbus, OH, United States; 4Division of Nursing Research, Nationwide Children Hospital, Columbus, OH, United States.

**Background:** This retrospective study was done to understand the use of MgSO4 for treatment of children with status asthmaticus in a pediatric intensive care unit (PICU).

**Methods:** Charts of all patients ≥5 years of age admitted to the PICU with status asthmaticus, at Nationwide Children’s Hospital, Columbus, OH, between 2000-2007 were reviewed.

**Results:** Among 222 encounters, 203 received continuous albuterol, 216 received IV steroids, 113 receive Terbutaline, 17 received mechanical ventilation, and 57 status asthmaticus, at Nationwide Children’s Hospital, Columbus, OH, between May 15th 2009 and May 15th 2011. The data of patient characteristics, pulmonary function tests and symptoms were analyzed.

**Patients characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>254 (56%)</td>
<td>186 (42%)</td>
</tr>
<tr>
<td>Age</td>
<td>9.9 (SD 3.1)</td>
<td>11.0 (SD 3.6)</td>
</tr>
<tr>
<td>FEV1 in %</td>
<td>92.4 (42.35%)</td>
<td>95.8 (38.13%)</td>
</tr>
<tr>
<td>PD20 mcg</td>
<td>853</td>
<td>713</td>
</tr>
<tr>
<td>Fatigue</td>
<td>127 (50.0%)</td>
<td>101 (54.3%)</td>
</tr>
</tbody>
</table>

**P4110**

**Quality of life after acute bronchiolitis in infancy**

Leif B. Rolfsjord1,2, Kai-Håkon Carlsen1,2, Egil Bakkeheim1, Karl C. L. Carlsen1,2, Department of Paediatrics, Oslo University Hospital, Oslo, Norway; 2Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway.

**Background:** Acute bronchiolitis, parental allergic disease, atopic eczema, male gender and parental stress are risk factors for asthma development. Quality of life (QoL) may be reduced in children with allergic disease, but prospective studies on risk factors for reduced QoL in infants are lacking.

**Aim:** Are asthma risk factors, apart from acute bronchiolitis associated with QoL nine months after hospitalization for bronchiolitis? The Infant Toddler Quality of Life Questionnaire (ITQOL(TM)) was sent to parents of 405 hospitalised infants included in a randomized clinical trial testing the efficacy of racemic adrenaline, the Bronchiolitis All SE-study. The 13 domains were analyzed by multiple linear regression including age at hospitalization, gender, atopic eczema, parental asthma and parental allergic rhinitis (risk factors).

**Results:** Risk factors were similar for the 209 infants (mean age 13.2 months) who did and the 196 who did not return the questionnaire. Reduced QoL was found for atopic eczema (Table 1), parental asthma and female gender (four, two and one domain, respectively), but increased in children with parental allergic rhinitis (one domain).

**Effect on atopic eczema on QoL adjusted for asthma risk factors**

<table>
<thead>
<tr>
<th>Atopic eczema associated with</th>
<th>Change in QoL (95% CI)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>-9.8 (-16.4, -3.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Growth and development</td>
<td>-4.5 (-8.1, -1.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Discomfort</td>
<td>-14.5 (-25.7, -3.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Getting along</td>
<td>-12.5 (-18.7, -6.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multiple regression of the risk factors, results of atopic eczema.
P4111
Respiratory complication in children with dengue
Lucia Azevedo, Daniel Leal, Ana Menezes, Selma Sias, Miguel Aide, Gesmar Herdy. Department of Pediatrics, Federal Fluminense University, Niterói, RJ, Brazil

Dengue, emerging infectious disease, has been presenting more severe in the last years. In children this diagnosis is difficult. The morbimortality is related to the early recognition and appropriate management. The goal is to know the clinical and laboratory features of children with dengue, hospitalized in the pediatric emergency of the Antonio Pedro University Hospital. Were analyzed from 2006 to 2010 the records of 63 children, 25 (39.7%) of them with respiratory complication. All had pleural effusion: 17 (68%) for the right and 8 (32%) bilateral. The age ranged between 2 and 12 years (mean = 8.2), the most was female (66%). The symptoms were: fever, abdominal pain, vomiting and headache. All had leukopenia and 23 (92%) thrombocytopenia. Ascite was found in 19 (76.6%) and thickening of the gallbladder in 5 (20%). Hypoalbuminemia in 15 (60%) and enzyme liver abnormalities in 21 (84%). The analysis was similar to that reported in the literature differing only in sex.

P4112
Additive effect of air pollution particulate matter and cigarette smoke on pneumococcal adhesion to lower airway cells
Reetika Suri1, Nasem Mushiq1, Richard Wain2, Jonathan Grigg1. 1Centre for Paediatrics, Blizzard Institute of Cell and Molecular Sciences, London, United Kingdom; 2Centre for Immunology and Infectious Disease, Blizzard Institute of Cell and Molecular Science, London, United Kingdom

Air pollution particulate matter (PM) and cigarette smoke (CS) are associated with increased vulnerability of children to bacterial pneumonia. In epidemiological studies, PM and CS are considered independent variables. We previously reported that PM10 (PM diameter <10 μm) increases pneumococcal adhesion to lower airway cells. Here we assessed whether PM and CS additively increase the susceptibility of airway epithelial cells to pneumococcal infection. Monolayers of the alveolar epithelial cell line A549 were exposed to sub-optimal doses of PM10 or cigarette smoke extract (CSE) for 3 h. The pollutants were washed off and cells exposed to Streptococcus pneumoniae for 2 h at a multiplicity of infection (MOI) of 100. After virus washing, cells were detached and lysed. Adherent bacteria were assessed by quantitative culture. Data were compared by T tests.

Both PM10 and CSE stimulated pneumococcal adhesion. An additional increase in pneumococcal adhesion was caused by PM10 and CSE combined. No decrease in viability was observed by light microscopy. The data suggests that PM10 and CSE additively increase vulnerability of airway cells to pneumococcal infection. If confirmed in animal models, additive effects of PM10 and CSE should be considered in epidemiological studies. Individuals at risk are likely to be living in countries with high PM levels and high incidence of indoor smoking.

P4113
Neutrophil count trends in BAL samples from children being investigated for chronic cough
Vanessa Alegre1, Grace Choi2, Konstantinos Dourou3, Mark Everard1. 1Academic Unit of Child Health, Sheffield University, Sheffield, United Kingdom; 2School of Medicine, Sheffield University, Sheffield, United Kingdom; 3Respiratory Paediatrics, Sheffield Children’s NHS Foundation Trust, Sheffield, United Kingdom

Introduction: Investigating probable persistent bacterial bronchitis (PBB) with a bronchoscopy allows the identification of infectious agents and quantification of cellular responses in the paediatric population who rarely expectorate sputum under the age of 10.

Methods: Bronchoscopies in children carried out 2010-11 were identified and a retrospective case notes analysis done to identify those performed because of chronic cough or proven/probable PBB. Bronchoalveolar lavage (BAL) samples were analysed for standard bacterial culture, viral PCR and neutrophil count (%). Results: 70 bronchoscopy BALs were analysed: 18.6% positive for bacteria and viral culture (B pos/V pos); 35.7% positive for bacteria but negative for viruses (B pos/V neg); 21.4% negative for bacteria but positive for viruses (B neg/V pos); 24.3% negative for both (B neg/V neg). Analysis of the BAL neutrophil count (%) was performed with one-way ANOVA and Cuzick’s test for trend. For the reasons of analysis the 4 groups were ordered as follows: group 1: B pos/V pos; group 2: B neg/V pos; group 3: B neg/V neg; group 4: B pos/V neg. The 4 groups differ significantly (means ± SD: 45.7±30.7, 18.6±21.4, 20.4±22.9, 11.6±15.2, for groups 1, 2, 3, and 4, respectively, p<0.001). Furthermore, a significant trend was found across the 4 ordered groups (p<0.001).

Conclusion: The presence of bacteria and viruses is associated with a significantly more neutrophils and thus a greater degree of inflammation than that induced by bacteria alone and could explain why recurrent viral infections are a feature of PBB.
Conclusion: Our results suggest that sodium sulfite may potentiate the activity of RV-induced diseases by increasing the production of IL-8, RANTES, and IP-10.

P4116 Differential responses of monolayer and differentiated airway epithelial cell cultures to NTHi infection
Kirst Wilson1, Lynne Bingle2, Colin Bingle2, Mark Everard3. 1Infection and Immunity, University of Sheffield, United Kingdom; 2Clinical Dentistry, University of Sheffield, United Kingdom; 3Paediatric Respiratory Medicine, Sheffield Children’s Hospital, Sheffield, United Kingdom.

The innate defence functions of the lung require a patent airway epithelium and infections are often associated with epithelial defects and phenotype alterations. Non-typeable Haemophilus influenzae (NTHi) one of the first bacterial species to infect children, reduces innate defences, allowing further colonisation with other pathogens, including RSV. We have established NTHi infections of lung derived cell lines and primary airway cells in differentiated cultures prior to the establish-ment of secondary infections with RSV as a model for paediatric RSV infection. A549, H292 and primary airway epithelial cells were grown in monolayer cultures in transwell inserts. Differentiated cultures of tracheobronchial epithelial (TBE) cells were grown at the ALI using established methods. The apical compartments of established cultures were infected with increasing doses of GFP tagged NTHi and followed for up to 7 days. Infection and cell viability was determined using confocal microscopy and bacterial counts at each time point. A549 and H292 cells, and undifferentiated primary cells became heavily infected and by day 7 almost complete loss of cells was associated with a loss of viable bacteria. Cytokine array studies showed that these cultures mounted limited cytokine responses. The ALI TBE cell cultures had an enhanced ability to overcome the same bacterial infections and this was associated with a marked cytokine response. This data suggests that differentiated epithelial cell cultures have an enhanced ability to overcome bacterial infection compared to monolayer cultures of epithelial cells. This is likely due to the innate defensive shield secreted from these complex cultures.

P4117 Video-assisted thoracoscopic surgery (VATS) and percutaneous drain insertion (PDI) in childhood empyema
Ira De Schutter1, Elke De Wachter1, Jan Lamote2, Joyce Raymond Punzalan1, 2Department of Pediatrics, Our Lady of Lourdes Hospital, Manila, Philippines; 1Department of Pediatrics, Our Lady of Lourdes Hospital, Manila, Philippines; 3Paediatric Respiratory Medicine, Universitair Ziekenhuis Brussel (UZ Brussels), Belgium; 4Department of Thoracic Surgery, Universitair Ziekenhuis Brussel (UZ Brussels), Belgium; 5Centre for Outcomes Research and Laboratory for Experimental Surgery, Universitair Ziekenhuis Brussel (UZ Brussels), Belgium.

Introduction: Pediatric parapneumonic effusion (PPE) incidence increases.
Aims: To compare different treatment options in children with PPE.
Methods: Retrospective analysis of children with PPE, admitted from 01/01/2007-30/11/2011. PPE definition: ≥1cm fluid on US or CT, and/or an opacity on chest X-ray of ≥50% of the hemithorax. Exclusion criteria: age <6, trauma, thoracotomy.
PDI and VATS were performed on clinical indication. VATS was reserved for patients (pts) with insufficient clinical improvement.
Results: Pts were treated as follows: Group A: no PDI/VATS. Group B: PDI. Group C: VATS. Group D: PDI followed by VATS.
Results: 49 pts were treated, included 35/24/26, median age 3.3y (range 0.8-14.8y); 15, 12, 11, and 11, in group A, B, C, and D, resp. Age, sex ratio and inflammatory parameters were similar in all groups.
Total length of stay (LOS) was similar for groups B, C and D, but shorter for group A (22 vs 18d, p=.023). Oxygen need was also shorter in group A compared to groups B and C (p<0.0000002384). Effective sputum induction was noted in both groups but earlier in group A (22 vs 18d, p=0.023). Oxygen need and fever resolved earlier after intervention in group C than in group B (3 vs 8d, p=0.009 and 1 vs 6d, p=0.04, resp). Time to drain removal, LOS and duration of antibiotic treatment after intervention (3 vs 6d, p<0.001; 11 vs 18d, p=0.004, and 10 vs 18d, p=0.001) were shorter in group C than in group B. ICU stay after intervention was similar in the 3 groups.
Conclusions: VATS is a good treatment option for PDI in children with PPE. Clinical improvement was faster with VATS than with PDI, indicating that early performed VATS might shorten LOS and duration of antibiotic treatment.

P4118 Cyst hydatid patients in a pediatric pulmonology department in Turkey
Ayse Tana Aslan, Ayse Tanin, Elke De Wachter1, Jan Lamote2.

Cystic hydatid patients in a pediatric pulmonology department in Turkey

P4119 Adjunct treatment of pneumonia in children 6-18 years old using a hand held sputum induction device
Mary Aimee Uson1, Anjanette De Leon1, Bobby Balet1, Leslie Mac Domagas2, Joyce Raymond Punzalan1, 1Department of Pediatrics, Our Lady of Lourdes Hospital, Manila, Philippines; 2Department of Pediatrics, Our Lady of Lourdes Hospital, Manila, Philippines.

Pneumonia is consistently a leading cause of mortality and morbidity in the Philip-pines; treatment is mainly antimicrobial. Lung Flute is a safe, hand held device that helps effective induction of sputum. The objective of this study is to assess the effectiveness of Lung Flute in sputum induction for relief of cough in children 6-18 years old admitted for Pediatric Community Acquired Pneumonia (PCAP). PCAP B and PCAP C. Children ages 6-18 years old admitted with a diagnosis of PCAP B or PCAP C were included. Patients diagnosed with PCAP A, PCAP D and hyperreactive airway were excluded. Each subject was enrolled to Lung Flute group or Control group by systematic randomization. Patients in the Lung Flute group used Lung Flute 3x a day in addition to the treatment provided by the physician. Pretested questionnaire on cough was answered by both groups. McNemar test was used. Of the 35 subjects (CI 80.0%, alpha error 0.05), there were more males than females (27:8 yrs of age). Majority admitted were diagnosed with PCAP B in Lung Flute group (73.4%) and Control group (85%). There was significant decrease in the frequency of cough on Day 2 (p value 0.048954) and significant improvement on the quality of cough on Day 2 (p value 0.002627) and Day 3 (p value 0.02961). Significant improvement on the quality of life on Day 1 and Day 2 was seen (p value 0.0008483, p value 0.002, p value 0.0000002384). Effective sputum induction was noted in both groups but earlier improvement was seen in the Lung Flute group. Lung Flute is an effective device in sputum induction and may someday be used as adjunct treatment of pneumonia.

P4120 Clinical characteristics of pediatric patients affected with human Metapneumovirus who needed hospital admittance in the western region of Guatemala
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Introduction: Human Metapneumovirus (hMPV) was described for the first time in 2001 by van den Hoogen et al. as a cause of bronchiolitis in children, although a world spread pattern, very little is known about its epidemiological behavior in latinamerican countries.
Aim: To review the clinical characteristics of children who needed admission to our hospital due to a respiratory infection caused by hMPV.
Methods: We included in this review all pediatric patients admitted during 2010 & 2011 suffering from a viral respiratory tract infection, and had a polymerase chain reaction positive to hMPV in a nasopharyngeal aspirate, sent to the CDC in the US, for its accurate classification.
Results: We reviewed 102 clinical files. 56 were female, mean age 16 months. Three symptoms were predominant in these patients: fever (n=89), cough (n=86) and respiratory distress (n=57). An alveolar radiological pattern on chest X-rays was seen in 57% of the cases. White blood cell counts were normal although a discrete neutrophilia was observed in most cases. C reactive protein mean value 27 mg/dl. None required mechanical ventilation. Mean time hospitalization was 7.4 days. There was no mortality reported in all cases. During the year 2011, no hMPV infection was recorded, despite an intensive epidemiological surveillance.
Conclusions: hMPV is still an important cause of respiratory infection in children. Even though, during this review the mortality rate was null. It called our attention the bi annual pattern of appearance of this virus, because we did not record any...
Acute lower respiratory tract infection and vitamin D status in children

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Childhood acute lower respiratory infection (ALRI) is one of the most common reasons for morbidity and mortality especially in developing countries. Predisposing factors include season, nutrition, suboptimal immunization, lower socioeconomic status, prematurity, underlying disease, tobacco exposure and vitamin D deficiency. Vitamin D deficiency is defined as 25(OH)D < 20 ng/ml, whereas vitamin D insufficiency is defined as 25(OH)D 21-30 ng/ml. In a study in Turkey the incidence of vitamin D deficiency in children was found 8% and insufficiency 25.5%.

In this study we aimed to describe vit D status in children with lower respiratory infection. Between November 2010 and February 2011 63 children with acute lower respiratory infection between 0.5-5 years of age and 59 age matched children without respiratory symptoms were enrolled in the study. Both study and control groups received vitamin D prophylaxis for one year and they have no predisposing factors for ALRI. Vitamin D status of children with acute lower infection (mean 34.9 ng/ml) were compared with children without ALRI (mean 37.2 ng/ml). No difference was found between the patient and the control group (p=0.38). In the patient group 17 patients diagnosed to have ALRI again after February 2011 – after one year period. In terms of ALRI recurrence, statistically significant difference was found between vitamin D status normal and insufficiency patients (p= 0.003).

In conclusion although there was no association between vitamin D status and childhood ALRI, significant association was found between vitamin D status and ALRI recurrence. Larger serial studies are needed for precise results.

Mycoplasma pneumoniae infection affects total eosinophil count, the serum level of ECP, and interleukin-5 in atopic children

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Background: A number of studies have outlined mechanisms by which mycoplasma infection may promote allergic lung inflammation. In addition, there is increasing evidence from human studies suggesting that mycoplasma infection contributes to asthma exacerbations, and severity with the change of cytokines. The present study evaluated the change of serum levels of eosinophil count, eosinophil cationic protein, and interleukin-5 in atopic children with Mycoplasma pneumoniae infection.

Method: We recruited 137 children including 44 atopic children with mycoplasma pneumonia (Group 1), 34 non-atopic children with mycoplasma pneumonia (Group 2), 25 children with viral pneumonia (group 3), 34 non-atopic children with viral pneumonia with mycoplasma infection (Group 4). The change of total eosinophil count, serum levels of interleukin (IL)-5, eosinophil cationic protein were measured at admission and at recovery for each group by using commercial ELISA.

Results: The serum level of IL-5 at admission was increased at recovery in group 1 (114±51.1 pg/ml at admission, 143±26.5±68.4 pg/ml at recovery). However, Buserum eosinophil cationic protein concentrations were increased at clinical recovery compared to the mean serum concentration at admission (49.5 pg/ml at admission, 37.9 pg/ml at recovery in group 1; 38.2 pg/ml at admission, 27.8 pg/ml at recovery).

Conclusion: The outcomes of the present study implied changes of eosinophil and its mediators during Mycoplasma pneumonia infection may be associated with the mechanism by which the Mycoplasma pneumoniae contribute to the development of airway hyperresponsiveness.

Is there a delay in diagnosis of post infectious obliterative bronchiolitis (PBO)?

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Background: PBO, or an orphan lung disease results following an antecedent severe viral or lower respiratory tract infection (LRTI), commonly due to adenovirus. The clinical symptoms of PBO are non-specific. This may result in a significant delay in diagnosis.

Methods: We retrospectively examined the medical records of children with PBO to determine the time from initial illness to diagnosis based on clinical and radiological criteria as follows:

1. History of antecedent viral LRTI
2. Evidence of airway obstruction (clinical or spirometry)
3. Radiological investigations consistent with PBO

Results: Of the nine cases identified over last 17 years, adenovirus was the main organism implicated in the initial infection in keeping with description in literature. Common referrals were for difficult or severe wheeze, exercise limitation, recurrent respiratory infections or bronchiectasis. The diagnosis was made earlier in children who had a persistent oxygen requirement or were admitted under the care of respiratory paediatricians.

Conclusions: There is a significant delay in diagnosis of PBO in our experience. Severe LRTI especially with adenovirus and a prolonged oxygen requirement at initial presentation followed by persistent respiratory symptoms should prompt further investigations Confirmation of the diagnosis leads to better understanding of the disease for the child with the opportunity to network with other children with rare diseases, could lead to potentially disease modifying treatment like Azithromycin and avoid unnecessary treatment for asthma.

Pneumatoceles that required surgery in childhood: Report of 2 cases

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Pneumatoceles are thin-walled filled with air cystic lesions that have been recognized as a potential complication of pneumonia. Although, they are usually asymptomatic, they may enlarge and compress the adjacent lung and mediastinum. The aim of this report is to describe 2 cases of severe pneumonia complicated by pneumatoceles that required surgical intervention.

Case 1
A one year old girl presented with a 2 day history of pyrexia. Radiological investigation revealed a right sided consolidation with pleural effusion. Pleural fluid culture revealed staphylococcus aureus. Antibiotic treatment and drainage failed and a CT scan on day 21 revealed an enlarging pneumatocele on the right causing mediastinal shift. The child developed acute respiratory failure; Successful decompression of the pneumatocele was achieved after initial urgent needle aspiration. Radiologic resolution was complete 2 months post initial presentation.

Case 2
A previously healthy 8 month old boy was admitted to our institution with a tension pneumatocele following a severe necrotic pneumonia. Blood culture was positive for Pneumococcus type 3F. On auscultation there was dramatically decreased air entry on the left side. CXR and CT revealed hyperinflation,large air cyst causing mediastinal shift to the right. Conservative management was initially attempted, but when oxygen saturation decreased dramatically surgical excision (pneumonectomy) was decided. The patient is now asymptomatic 2 months post discharge.

Conclusions: Tension pneumatoceles, although rare, are a serious complication of pneumonia that may need surgical intervention when the patient is in critical condition.

414. Issues in neonatal and paediatric intensive care

Educating fellows in CanMEDS physician roles via a quality improvement-based curriculum

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Background: Of the many CanMEDS physician roles that have been adopted by European medical educators, evidence suggests that several may be particularly challenging to teach and assess, namely: Health Advocate, Collaborator, Scholar and Manager.

Objective: Since Quality Improvement (QI) activities have been shown to provide medical residents a means by which to learn skills relevant to the above CanMEDS roles, we sought to determine whether a QI-based curriculum would afford our fellows a robust, level-appropriate and assessable learning experience.

Methods: Our fellows participated in our division-level program of continuous quality improvement. In doing so, they learned and applied QI principles as they developed an evidence-based respiratory treatment protocol (RTP) intended to reduce the incidence of chronic lung disease (CLD) among neonates born at <29 weeks gestation. To assess fellow competence in CanMEDS roles, the fellowship program directors maintained educational portfolios for each fellow, including self-reflections, competency-based evaluations and evidence of scholarship.

Results: Our fellows successfully implemented their RTP, then collected, analyzed
and reported outcomes data to division leadership. Our fellows’ RTP reduced the incidence of CLD nearly 50% within one year, results they have presented at
Board of Pediatrics.

**Conclusion:**
We developed a disease-specific instrument to measure HRQL in children with BPD aged 4 to 8 years old. The clinical impact method and item analysis were used to reduce items.

**Results:**
51 children participated in the study: 20 in item generation and 31 in item reduction. 130 items were identified. With the clinical impact method 53 items with an overall importance (OI) > 0.75 were selected. Three items with highest OI were ‘easily distracted’ (2.52), ‘having a cold for longer period of time’ (2.39) and ‘coughing’ (2.39). After item analysis, 47 items remained in the questionnaire.

**Conclusion:**
This is the first time the development of a disease-specific instrument to measure HRQL in BPD has been undertaken. The items in the developed questionnaire have clinical impact. The next step will be to determine validity of these items.

**P4129**
Development of a quality of life instrument for children with bronchopulmonary dysplasia

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**Introduction:**
Bronchopulmonary dysplasia (BPD) is a common complication of premature birth. It is associated with prolonged hospitalization, long-term pulmonary morbidity and an increased risk for adverse neurodevelopmental outcome. The impact of these complications on health-related quality of life (HRQL) is not known because there is no disease-specific instrument to measure HRQL available.

**Aim:**
To develop a disease-specific questionnaire to measure HRQL in children with BPD aged 4 to 8 years old.

**Methods:**
Participants: children aged 4 to 8 years old with BPD. The first steps in the development of a HRQL instrument are item generation and item reduction.

Sources for item generation were literature, expert opinion and parents of participants. For item reduction, parents indicated how much the items affected the HRQL of their child. The clinical impact method and item analysis were used to reduce items.

**Results:**
51 children participated in the study: 20 in item generation and 31 in item reduction. 130 items were identified. With the clinical impact method 53 items with an overall importance (OI) > 0.75 were selected. Three items with highest OI were ‘easily distracted’ (2.52), ‘having a cold for longer period of time’ (2.39) and ‘coughing’ (2.39). After item analysis, 47 items remained in the questionnaire.

**Conclusion:**
This is the first time the development of a disease-specific instrument to measure HRQL in BPD has been undertaken. The items in the developed questionnaire have clinical impact. The next step will be to determine validity of these items.
prospectively defined a hypoxic episode as three consecutive measurements (at 0, 15, and 30 minutes) of \( O_2 \) sat >92%, the upper limit of the RTP. During E1 and E2, \( O_2 \) sats 92% were detected manually by the bedside nurses. During E3, the DST analyzed clinical data and automatically notified the charge nurse of a patient’s hypoxic episode. We retrospectively compared the rate of hypoxic episodes of each epoch, using the Chi-squared test to determine statistical significance.

**Results:** Neonates treated during E3 experienced fewer hypoxic episodes than those treated during E2 (17 v. 24 episodes per 1000 \( O_2 \) sat measurements; p < 0.0001). These rates were lower than that of E1 (41 episodes per 1000 \( O_2 \) sat measurements; p < 0.0001).

**Conclusion:** Use of a DST was associated with less frequent episodes of hypoxia among premature neonates and seemed to enhance the efficacy of a respiratory treatment protocol.

**P4131**

**G-CSF administration improves chronic lung disease caused by exposure to high-concentration oxygen in neonatal mice**

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**Background:** Chronic lung disease (CLD) is a condition that results from the inflammation-induced destruction and developmental arrest of the lungs of premature infants. To date, there is no effective treatment for CLD. Hematopoietic stem cells have been reported to differentiate into pulmonary type II epithelial cells. It is known that G-CSF acts on hematopoietic stem cells to mobilize them in the peripheral blood. It has also been reported that G-CSF exerts anti-inflammatory effects. In this study, we investigated whether G-CSF administration could improve a mouse model of CLD caused by exposure to high-concentration oxygen.

**Methods:** Neonatal mice within 24 hours after birth were placed in 80% oxygen or room air for 21 days. From day 23, pups were administered 0.5 microgram/g of G-CSF or saline for 5 days. The lungs were removed in postnatal week 6, and lung sections were stained with HE and Masson’s trichrome and immunostained for PCNA and α-SMA for histology.

**Results:** Compared with the control groups, the oxygen-exposed groups showed a similar morphological change. The oxygen-exposed, saline administered group showed a significantly improvement in pulmonary epithysma than the oxygen-exposed, saline administered group. There were no significant differences in staining with Masson’s trichrome nor immunostaining for PCNA and α-SMA.

**Discussion:** G-CSF administration significantly improved a mouse model of CLD. It is unclear whether G-CSF-mobilized peripheral blood stem cells differentiated into pulmonary epithelial cells, whether G-CSF induced the proliferation and differentiation of type II epithelial cells, or whether G-CSF exerted anti-inflammatory effects.

**P4132**

**Gestation at delivery and outcome in CDH infants following fetoscopic tracheal occlusion**

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**Background:** Newborns with congenital diaphragmatic hernia (CDH) suffer substantial morbidity and mortality. In non-randomised studies, fetal endoscopic tracheal occlusion (FETO) was shown to reduce the duration of mechanical ventilation, use of high frequency oscillation (HFO) ventilator and survival to discharge was lower (18% versus 82%, p = 0.011). The preferred intervention for infants born with the Pierre Robin Sequence (PRS). It is the preferred intervention for infants referred to our institution for respiratory assessment.

**Aim:** To determine if timing of 1st NPA insertion affects duration of hospitalization for infants with PRS referred to RGHSC.

**Methods:** A retrospective case note review of the management of infants referred to RGHSC with PRS from Oct 2009-Oct 2011 was performed.

**Results:** 12 infants were included in this study. 7/12 infants were successfully discharged with NPA support. In 57 infants 1st NPA was inserted within 48hrs of admission and discharge occurred at a median of 15 days. In the other 2 infants, NPA was not inserted until day 6 & 10 of admission respectively. Only these 2 infants required nasaogastic feeding on discharge. Parental training commenced on average 5 days later and these infants required up to a week longer in hospital. These delays did not however, impact on the timing of eventual cleft surgery. 3/12 infants were preterm and could not be managed initially with NPA due to small size. These infants all required a period of non-invasive ventilation and also had a longer hospital stay.

**Conclusions:** Our results suggest that delayed insertion of NPA in infants with PRS may result in later establishment of oral feeding and prolonged hospitalization. NPA insertion within 48hrs of admission is suggested as optimum. Preterm infants are also considered as requiring a longer hospital stay with an alternative approach to airway management.

**P4134**

**Respiratory dead space but not neonatal lung disease is associated with lung clearance index in preterm neonates**

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**Background:** Neonatal lung disease (NLD), gestational age per se (GA) and breathing pattern may influence gas mixing efficiency in neonates.

**Aim:** To assess the effect of NLD, GA and breathing pattern on the lung clearance index (LCI) in preterm and term neonates.

**Methods:** 236 preterm (GA 23-36 w) and 232 term healthy control infants from two centres (Berne and Perth) were studied at a mean (standard deviation) postmenstrual age of 43.4 ± 3.5 in quiet unsedated sleep using multiple breath washout (MBW) with 4% sulphur hexafluoride and a mainstream ultrasonic flowmeter (Spironos Exhalzner D, Ecomedics AG, Duernen, CH). Functional residual capacity (FRC) and LCI were calculated from the washout trace. Tidal volume (VT), respiratory rate (RR) and respiratory dead space (Vd) estimated from the mole mass signal were calculated during 30 s of tidal breathing prior to MBW. We used multivariable linear regression to analyse outcomes.

**Results:** Only RR (R²=0.04, p<0.001) and Vd/Vt (R²=0.16, p<0.001) were positively associated with LCI. No other factors including presence of bronchopulmonary dysplasia, days of supplemental oxygen, GA, body size and body proportions at birth and at test were significantly related to LCI. After adjusting for Vd/Vt, RR was no longer significantly associated with LCI.

**Conclusions:** Vd/Vt is associated with LCI in preterm neonates and should be considered as a relevant factor when assessing and interpreting LCI in infants. The effect size of this association is moderate.

**P4135**

**Effect of the level of volume-targeted ventilation on the spontaneous respiratory activity of infants born at term**

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Premature-born infants frequently breathe while being mechanically ventilated. The pattern of their respiratory efforts with ventilator inflation influences outcome, in particular active expiration leading to pneumothorax.

**Aim:** To compare patient-ventilator interactions in infants born at term at different levels of volume-targeting (VT).

**Methods:** 15 infants, median gestational age 38 (range 34-41) weeks were studied at a median postnatal age of five days. The infants were studied at VT levels of 4 and 6 ml/kg, applied in random order. Five infants were on conventional ventilation (CMV) and 10 on triggered ventilation (PVT). Oesophageal, gastric and airway pressures, flow and volume were simultaneously recorded for at least five minutes at each VT level; 50 consecutive breaths were analysed at each VT level.

**Results:** In the infants studied on CMV, active expiration was more common at
a VT level of 4 ml/kg than at VT levels of 0 and 6 ml/kg (p=0.0001), whereas in infants on PTV, active expiration was significantly lower at 4 ml/kg than at VT levels of 0 and 6 ml/kg (p=0.0001) (Table). At each VT level, the occurrence of active expiration differed significantly between ventilator modes.

<table>
<thead>
<tr>
<th>CMV</th>
<th>PTV</th>
<th>p</th>
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<tbody>
<tr>
<td>No VT</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>VT 4 ml/kg</td>
<td>77</td>
<td>37</td>
</tr>
<tr>
<td>VT 6 ml/kg</td>
<td>42</td>
<td>48</td>
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</table>

Data are presented as % of inflations associated with active expiration.

Conclusion: The underlying mode of ventilation significantly influences whether low compared to higher levels of volume targeting will increase active expiration.

P4136
Optimal PEEP in the first week of life in mechanically ventilated extremely preterm newborn infants: Clinical setting vs. optimal setting as registered by forced oscillation technique (FOT)
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Recently it has been shown that the use of forced oscillation technique (FOT) allows identifying an optimal open-lung PEEP minimizing mechanical stress to the lungs (Kostic P, Crit Care. 2011).

The aim of this study is to characterize the optimal mechanical PEEP settings in the first week of life in mechanically ventilated preterm newborns and to compare it to the PEEP set by current clinical approach.

Four preterm newborns (GA=23-27wks, BW=679-946g) were studied at the first, third and seventh day of life. PEEP was increased by 2cmH2O above the clinically set PEEP and then decreased by four 5-minute steps of 1cmH2O. For each step the total respiratory input reactance (Xrs) at 10Hz was measured at end-expiration by sinusoidal FOT. The optimal mechanical PEEP was defined as the PEEP at which the maximum of Xrs was reached (Dellacà’, Int Care Med, 2011).

Mean±SD values of the clinically set PEEPs and the mechanically optimal PEEPs are shown in the figure.

The higher inter-subject and day-by-day variability of the mechanically optimal PEEP suggests that FOT could help in fine tuning PEEP settings related to the lung mechanical changes over time in each patient. Future studies will be address whether setting the mechanically optimal PEEP could be beneficial from a clinical point of view.

P4137
Computerized quantification of wheezing in neonates: Relationship with conventional lung function parameters
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Objective: Computerized respiratory sound analysis has been used to evaluate wheeze in infants, but it is not known whether the acoustic detection of wheeze is associated with impaired lung function. The present study aimed to investigate the relationship between wheeze detection and conventional parameters of lung function testing (LFT).

Methods: Computerized lung sound analysis with quantification of wheezing (PulmoTrack®) was performed in 78 neonates at a median (IQR) postmenstrual age of 48 (44-59) weeks and a body weight of 4818 (3835-6140) g. In the same session, LFT was performed which included bodyplethysmography, tidal breathing measurements, SF6 multiple breath washout, measurement of respiratory mechanics by the occlusion test, forced expiratory flow (V’maxFRC) by rapid thoracobulbinal compression and capillary blood gas analysis.

Results: Wheezing >5% of the breathing cycle was detected in 41/78 (53%) infants, 18/78 (23%) had inspiratory and 29/78 (37%) expiratory wheezing. Infants with and without wheezing did not significantly differ in postmenstrual age and body weight. Inspiratory wheezing had no relationship with LFT parameters. In contrast, infants with expiratory wheezing had significant changes in their breathing pattern and respiratory mechanics with increased iTEF/TE (p=0.034), end-expiratory flow (TEF10, p=0.027), airway resistance (p=0.005) and respiratory resistance (p=0.036).

Conclusion: Computerized wheeze detection is easy to perform in unsedated infants during natural sleep and may help to identify infants at risk of obstructive airway disease.

P4138
HRVC is the commonest rhinovirus group detected in children admitted to a paediatric intensive care unit with respiratory illnesses
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Introduction: Respiratory viruses account for a significant proportion of acute admissions to the paediatric intensive care unit (PICU). Acute respiratory illnesses (ARI) represent 10-15% of all admissions to PICU. Recent studies have shown that human rhinovirus (HRV) was the most frequent virus detected in severe cases of ARI admitted to a PICU. There has been no study to date examining the prevalence of HRV groups (including the newly discovered HRVC group) in children admitted to a PICU.

Aim: The aim of this study was to determine the prevalence of different HRV groups in children with respiratory illnesses admitted to a tertiary PICU.

Methods: Nasopharyngeal aspirates (NPA) and clinical information were obtained from children admitted with respiratory illnesses to PICU between March 2009 and July 2011. RNA was extracted from NPA, and reverse transcribed. From cDNA, a 2-step PCR of the HRV 5’NCR was used for HRV detection, and sequencing for typing.

Results: NPA from 229 children admitted to PICU were analysed. HRV was the commonest virus, being present in 93 (40.6%) samples examined, followed by respiratory syncytial virus (RSV) which was identified in 50 (21.8%) samples. Of the 77 NPA available for HRV typing, HRV was found to be the commonest HRV group detected, representing 42 (54.5%) of the samples identified. HRV groups was found in 32 (41.5%) and HRVB in 3 (4%) of the samples analysed.

Conclusions: This study demonstrated that HRV is the commonest virus identified in children admitted to a tertiary PICU with a respiratory illness. In addition, HRVC was the commonest HRV group detected across all respiratory illness.

P4139
Use of high flow nasal oxygen (HFNO) for bronchiolitis in a general paediatric ward: Preliminary experiences
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Background: Viral bronchiolitis is a leading cause of hospitalisation. Interventions to reduce morbidity are challenging. We evaluated HFNO in infants with acute bronchiolitis on a general paediatric ward. Previous HFNO experience has been in a PICU or HDU settings.

Aim: To assess responses to HFNO in previously well children and in those with underlying co morbidity.

Methods: Prospective study between November 2011 and February 2012. Inclusion criteria were patients needing >30% FiO2 or a RR(respiratory rate)>60/minute.

Results: Nine previously well infants, mean age 40 days (range 10-120 days) were commenced on HFNO. Mean RR and pulse rate prior to initiating HFNO was 73 and 146 respectively. Mean oxygen requirement was 37%. 5 patients had observations done before 2 hours and then between 2-4 hours. A reduction in mean RR to 54 at 2 hours and 47 at 4 hours was observed. The mean pulse rate reduced to 132 and 102. Mean oxygen requirement was higher at 2 hours (43%) but reduced at 4 hours (32%). No significant change in blood gases noted. 8 children responded well to HFNO. One patient required nasal CPAP.

Five children with underlying co morbidities and acute bronchiolitis were started on HFNO. These children were older, mean age 270 days (range 60-630). Of these 5, 3 deteriorated on HFNO and required escalating interventions.

Conclusion: In previously well infants with bronchiolitis, HFNO is safe in a general paediatric ward setting and offers clinical benefits within 2-4 hours. Children with underlying disorders may not respond as well and if no improvement is seen within 4 hours, stepping up treatment may be desirable.

766s
P4140
The evaluation of lung function measured by impulse oscillometry method in very low birth weight born children at preschool age
Meral Ozer1, Ayse Gunfener2, Zeynep Seda Uyan1, Ayse Sevim Gokalp1, Nazan Kavas1, Gulcan Turker1, Ayse Engin Arisoy1, 1Neonatology, Kocaeli University, Kocaeli, Turkey; 2Pediatric Pulmonology, Kocaeli University, Kocaeli, Turkey.

Introduction: Chronic lung disease is one of the most important complications of prematurity and results in short and long-term morbidity. Survival of more prematurely born babies leads to an increase in the incidence of bronchopulmonary dysplasia (BPD).

Aim: To evaluate the lung function of babies who were born under birth weight of 1500 grams using impulse oscillometry in preschool age.

Methods: Eighty-six children who were 3-6 years old and followed in our neonatology clinic (born under birth weight of 1500 grams) were enrolled in the study as the patient group and 40 term-born healthy children as the control group. The demographic data of the patients, duration of mechanical ventilation and oxygen therapy and presence of BPD were recorded. After routine physical examination, lung functions of children were measured by impulse oscillometry. The data were evaluated by SPSS 16 program.

Results: Forty-nine (57%) of 86 patients were non-BPD, 20 were mild BPD, 14 were moderate BPD and 3 were severe BPD. Weight and height of premature and control groups were similar. There was a statistically significant difference between the two groups in terms of resistance (R5,R10,R20), reactance (X5,X10,X20) and resonant frequency (fres). The airway resistance was significantly higher and reactance was significantly lower in the premature group. However, there was no difference between BPD and non-BPD groups.

Conclusion: Although premature babies can catch-up their peers at 3-4 years old in terms of their body percentiles, their lungs still reflect the traces of prematurity.

P4141
Effects of salbutamol therapy on pulmonary mechanics and chronic lung disease in very low birth weight infants
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Background: To determine the changes in pulmonary mechanics before and during salbutamol therapy and to evaluate the effect of salbutamol on the duration of mechanical ventilation in very low birth weight (VLBW) ventilator-dependent infants.

Methods: A prospective single-centre trial was conducted. Forty-three patients (birth weight 600 to 1500 g, gestational age 24 to 32 weeks) who failed to be weaned from the respirator at 7 to 14 days of age were enrolled; 23 infants received a 7-day course of salbutamol (2.5 mg 4 times per day via nebulizer) and 20 patients were in the control group. A similar mean airway pressure (MAP) and fractional inspired oxygen concentration (FiO2), respiratory system mechanics (tidal volume (VT), respiratory compliance (Cr) and respiratory resistance (Rrs)) were measured before and on days 2, 5, and 7 of the study.

Results: There was a significant increase in Crs and VT in the salbutamol group as compared with the control group (P<0.001). No major changes in Res were observed. Salbutamol therapy significantly decreased FiO2 and MAP (P<0.001) and facilitated successful weaning from mechanical ventilation. In addition to a shorter duration of mechanical ventilation (P<0.01), the occurrence of CLD (FiO2 > 0.21 at 36 weeks of corrected gestational age, chest x-ray changes and Rrs changes) was significantly decreased in the salbutamol group (P<0.01).

Conclusions: Our study indicate that salbutamol therapy in VLBW infants significantly improves lung’s mechanics and facilitates extubation in infants and reduces the duration of mechanical ventilation and decreases CLD (at 28 days and 36 weeks) in a population of VLBW infants.

P4142
In vitro assessment of elastance unloading and work of breathing during proportional assist ventilation
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Proportional assist ventilation (PAV) is a patient-triggered mode in which the elastic and resistive work of breathing (WOB) can be unloaded. The unloading level is set with the aim of achieving an optimal balance of the WOB between the ventilator and the patient. In vitro studies, however, have shown that during PAV, there are trigger delays and the pressure wave forms of the ventilator and lung models differ which may influence the relationship between the level of unloading and the WOB of the patient and ventilator.

Aim: To assess the WOB of the ventilator and a lung model with increasing amounts of elastance unloading.

Methods: A dynamic lung model, with a compliance of 0.4ml/cmH2O, was connected to a Stephanie ventilator in PAV mode. Elastance unloading was applied in stepwise increments and pressure, flow and tidal volume were recorded. Pressure-volume loops were constructed, from which the WOB was calculated for the ventilator and the lung model.

Results: The median tidal volume of breaths analysed was 3.75 (range 3.1 to 4.4) ml. As the elastance unloading was increased, the lung model showed a greater reduction in the elastic WOB than the increase of WOB of the ventilator.

The WOB in the lung model, however, was underestimated by the distortion of the inflation pressure waveform due to the trigger delay.

Conclusion: Although elastance unloading during PAV enables transfer of the WOB from the patient to ventilator, the infant has no support during the trigger delay, thus the benefit is over-estimated.

P4143
Changes in respiratory system reactance (Xrs) during the first lung volume recruitment in preterm lambs on high frequency oscillatory ventilation (HFOV)
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The aim of this study was to assess the dynamic changes in respiratory mechanics during the first stepwise increase of mean airway pressure (MAP) in preterm lambs receiving HFOV. Six 132d preterm lambs were commenced on HFOV at MAP of 14 cmH2O and frequency (fosc) of 10Hz. Five min after birth MAP was increased up to 30 cmH2O in 2-min steps of 4 cmH2O. At the beginning (t0) and at the end (t1) of each step fosc was reduced to measure Xrs at 5Hz. Lung volume (VL) changes were simultaneously measured by electrical impedance tomography.

VL monotonically increased during the recruitment manoeuvre (RM). In average only the 22±2% (mean±SD) of the total change occurring at each step immediately followed the change in MAP, while the remaining 78±2% occurred over the next 2 min. Xrs at first decreased, then it increased over time stabilizing to a higher value compared with the lower MAP step.

Changes in respiratory system reactance (Xrs) during the first lung volume recruitment in preterm lambs on high frequency oscillatory ventilation (HFOV)
414. Assessment of physical activity, exercise, muscle function and clinical characteristics as outcomes in physiotherapy and rehabilitation

P4144

Adequate physical activity in students with and without asthma

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Background: Early youth is decisive for the adoption of opinions concerning the physical activity which contributes to the decrease of death risk due to chronic diseases.

Aim: To examine differences in physical activities in young students with and without asthma.

Method: 578 Physical Therapy students in Athens, Greece, aged 18-30 (± 2.07) participated in the study. Adequate physical activity was assessed according the guidelines of the American Cardiology Association and the American College of Sports Medicine (yes-no). Differences in physical activity between students with and without asthma were examined through χ².

Result: 40% of the total sample reported diagnosed asthma. Adequate physical activity was stated by 40% of students with asthma and by 55.3% of students without asthma. No significant differences were found in physical activity between the two groups (p > 0.05). Students with asthma didn’t differ in physical activity regarding gender. BMI, sleep duration, alcohol consumption, income, and health-belief (p>0.05), while they differed as for smoking (p=0.018). Students without asthma didn’t differ (p > 0.05) in physical activity with regard to BMI, sleep duration, alcohol consumption smoking, income, and their health-belief, while they revealed differences as for sex (p>0.001).

Conclusion: The results of the present study in one hand are encouraging because students with asthma were as active as those without asthma, but in the other hand they are disappointing because both groups didn’t meet American guidelines for the adequate physical activity that have shown to contribute to chronic illnesses prevention.

P4145

Cardiorespiratory fitness, pulmonary function and C-reactive protein levels in adults with diabetes

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Background/Aim: Diabetes Mellitus (DM) is associated with impairment of cardiopulmonary fitness and pulmonary function; increasing evidences have suggested that comorbidities and systemic inflammation may be involved. The objective of this study was evaluate changes in metabolic variables, C-reactive protein (CRP) levels, cardiopulmonary fitness and pulmonary function in DM patients compared with healthy subjects.

Methods: 19 men with diabetes (49.2±2 years) and 19 healthy control subjects (51.4±7 years) were studied. All subjects performed a spiroergometry and an incremental cardiopulmonary exercise test on a cycleergometer with electromagnetic breaking (workload increases, range 13-22W/min). Cardiopulmonary data were continuously collected with a metabolic unit. Heart rate (HR) was continuously monitored.

Results: See table 1.

Table 1. Lung function, physical capacity parameters and CRP levels

<table>
<thead>
<tr>
<th>Control (n=19)</th>
<th>DM (n=19)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.66±0.15</td>
<td>0.88±0.21</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.73±0.01</td>
<td>8.39±0.36</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>104.0±23</td>
<td>103.4±3.0</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>99.3±2.5</td>
<td>103.9±3.0</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.84±1.2</td>
<td>82.6±9.9</td>
</tr>
<tr>
<td>PEF 25-75% (pred)</td>
<td>100.0±16.6</td>
<td>115.6±5.8</td>
</tr>
<tr>
<td>PEF (% pred)</td>
<td>94.7±5.0</td>
<td>89.9±3.5</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>149±3</td>
<td>139±2</td>
</tr>
<tr>
<td>Work load (Watts)</td>
<td>156±5</td>
<td>135±3</td>
</tr>
<tr>
<td>RER</td>
<td>0.80±0.02</td>
<td>1.14±0.03</td>
</tr>
<tr>
<td>VO2peak (ml/kg/min)</td>
<td>24.17±0.7</td>
<td>18.91±0.7</td>
</tr>
<tr>
<td>VO2at 40%VO2peak</td>
<td>14.11±0.8</td>
<td>12.17±2.5</td>
</tr>
</tbody>
</table>

Conclusion: The cardiopulmonary fitness is reduced in patients with diabetes but the spirometric values are preserved, and the CRP did not differ of the control subjects.

P4146

Respiratory function, functional capacity, and physical activity in patients with scleroderma

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Aim: Scleroderma is a chronic multisystem disease of unknown origin, characterized by fibrosis on the connective tissue of skin and internal organs. Because of pulmonary involvement, patients’ exercise tolerance is poor and functional capacity is impaired. The purpose of this study was to compare lung function, functional capacity, and physical activity, between patients with scleroderma and healthy controls.

Materials and methods: Ten scleroderma patients (9F, 1M, 53.3±9.4 years) and ten healthy controls (9F, 2M, 54.5±12.6 years) participated in the study. Pulmonary function test was performed using spirometry. Functional capacity was evaluated using six-minute walk test (6MWT). Heart rate, oxygen saturation, dyspnea and fatigue perception using modified Borg Scale was recorded before and after the test. Subject’s physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ).

Results: All scleroderma patients involved in this study had preterminal lung involvement. The FEV1, FEF25-75%, and 6MWT distance were significantly lower in patients with scleroderma (p<0.05). The %6MWT distance of the patients was 64.5±22.3%. Oxygen desaturation, dyspnea and fatigue perception at the end of 6MWT were significantly higher in patients with scleroderma as compared with the healthy controls (p<0.05). The IPAQ moderate physical activity score and IPAQ total score were significantly lower in patients with scleroderma (p<0.05).

Conclusions: Lung function, functional exercise capacity, and physical activity level are adversely affected in patients with scleroderma. Exercise training programs may be useful in scleroderma patients.

P4147

Effects of exacerbation risk on symptoms and clinical characteristics in patients with bronchiectasis

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Aim: Exacerbations may deteriorate symptoms and clinical features in patients with bronchiectasis. The purpose of this study was to investigate effects of exacerbation risk on muscle strength, exercise capacity, dyspnea, fatigue, and quality of life in patients with bronchiectasis.

Methods: Fifteen low risk patients (0 exacerbation per year) and 15 high risk patients (>1 exacerbation per year) participated in this study. Lung function, quadriceps muscle strength (hand held dynamometer), dyspnea (modified Medical Research Council dyspnea scale, MRC), fatigue (Fatigue Severity Scale, FSS), exercise capacity (six-minute walk test, 6MWT), and cough specific (Leicester Cough Questionnaire, LCQ) and general (Nottingham Health Profile, NHP) were determined.

Results: No significant difference was found in lung function between the groups (p>0.05). Number of females was significantly higher in high risk group as compared to low risk group (p<0.05). Quadriceps muscle strength, 6MWT distance, and LCQ physical score were significantly lower; and MRC, FSS score, and NHP energy, emotional reactions, pain, physical mobility, and total scores were significantly higher in high risk bronchiectasis patients than those of low risk patients (p<0.05).

Conclusion: High risk of having exacerbations adversely affects quadriceps strength; exercise capacity, dyspnea and fatigue perception, and cough specific and general health in patients with bronchiectasis. Number of exacerbations in the previous year may be a determinant of characteristics and function in bronchiectasis.
P4148 Comparison of functional capacity, muscle strength, body composition in patients with cystic fibrosis, non-cystic bronchiectasis and healthy controls
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Aim: We aimed to compare functional capacity, respiratory and peripheral muscle strength, and body composition in patients with cystic fibrosis, non-cystic bronchiectasis and healthy controls.

Methods: 43 with bronchiectasis, 36 patients with cystic fibrosis, and 35 age-sex matched controls were included. Body composition was evaluated using bioelectrical impedance analysis. Pulmonary function test was performed. Respiratory muscle strength (MIP and MEP) was evaluated using a mouth pressure device, quadriceps muscle strength using a dynamometer, functional capacity using six-minute walk test (6MWT).

Results: The weight, height, body mass index (BMI), and fat free mass, pulmonary functions, MIP and MEP, quadriceps muscle strength, 6MWT distance, were significantly lower in patients with bronchiectasis and cystic fibrosis compared with healthy controls (p<0.05). 24 patients (56%) with bronchiectasis, 23 (64%) patients with cystic fibrosis had malnutrition. 12 (28%) bronchiectasis, 16 (44%) cystic fibrosis patients’ MIP were weaker than 95%CI (80-150 cmH2O) of the controls. 8 (19%) bronchiectasis, 8 (22%) cystic fibrosis patients’ 6MWT distance were shorter than 95%CI (576-871 m) of the controls. 9 (21%) bronchiectasis, 7 (19%) cystic fibrosis patients’ quadriceps muscles were weaker than 95%CI (160-500 N) of the controls.

Conclusion: Body composition, pulmonary function, respiratory and peripheral muscle strength and functional capacity are impaired in bronchiectasis and cystic fibrosis patients. Malnutrition may lead these impairments. Pulmonary rehabilitation programs should be adjusted to improve these outcomes.

P4149 Periperal and respiratory muscle strength in pulmonary artery hypertension
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Background and aim: Pulmonary arterial hypertension (PAH) is a rare pulmonary vascular disease characterized by increased pulmonary arterial pressure. The PAH patients experience dyspnea and fatigue limiting performance in activities of daily life. The aim of this study was to compare lung function, respiratory muscle strength, and peripheral muscle strength between patients with PAH and healthy subjects.

Materials and methods: Seventeen patients with PAH (4 M, 13 F) and fifteen age-matched healthy controls (7 M, 8 F) participated in this study. Pulmonary function test was performed using spirometry. Respiratory muscle strength was measured using a mouth pressure device. Lower and upper peripheral muscle strength was measured from quadriceps femoris, shoulder abductors a hand held dynamometer, and hand grip was recorded.

Results: The mean pulmonary arterial pressure was 65.57±31.77 mmHg in PAH patients, maximal inspiratory pressure was significantly correlated with mean pulmonary arterial pressure (r=0.67, p<0.05). The mean maximal inspiratory (p=0.0001) and expiratory muscle pressures (p=0.001) of patients with PAH were significantly lower than those of healthy controls. Quadriceps muscle force (p=0.05), shoulder abduction force (p=0.001), and hand grip force (p=0.018) were significantly lower in patients with PAH as compared with healthy controls.

Conclusions: High pulmonary arterial pressure results in reduced peripheral, inspiratory and expiratory muscle strength. Effects of respiratory and peripheral muscle training in patients with PAH needs further investigation.

P4150 Comparison of exercise capacity, pulmonary functions, respiratory and peripheral muscle strength between patients with idiopathic pulmonary arterial hypertension and Eisenmenger syndrome
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This study was designed to compare exercise capacity, pulmonary functions, respiratory and peripheral muscle strength between patients with idiopathic pulmonary arterial hypertension (IPAH) and Eisenmenger syndrome. Thirty-three patients with PAH of either IPAH (mean age 45.31; 12 female and 4 male) or Eisenmenger syndrome (mean age 38.41; 10 female and 7 male) were studied. Exercise capacity was determined by using six minute walk test. Also pulmonary functions, respiratory muscle strength (maximal inspiratory (MIP) and maximal expiratory (MEP) pressure) and handgrip strength were measured. Unpaired-t, Mann-Whitney and Fisher’s exact tests have been used for the statistical analysis of the data. There were no significant differences in exercise capacity, respiratory and peripheral muscle strength between the two groups. FVC% (p=0.0025), FEV% (p=0.001) and PEF% (p=0.02) of patients with Eisenmenger syndrome were significantly lower than those of patients with IPAH. In conclusion: exercise capacity, respiratory and peripheral muscle strength were similar for patients with Eisenmenger syndrome compared to those IPAH. In addition, the present study provides evidence that pulmonary functions are reduced in patients with Eisenmenger syndrome compared with IPAH.

P4151 Associations between measurements of health related quality of life (HRQoL) and physical activity (PA) in patients with interstitial lung disease (ILD)
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Background: ILD is a diverse group of interstitial lung diseases characterized by an impaired alveolar diffusion capacity of oxygen. PA relates to HRQoL in these patients. The aim of this study was to investigate associations between HRQoL, and PA.

Methods: We studied 54 patients with ILD (Age: 64±11 years; FVC: 81±25%; DLCO: 45±13% of the controls was assessed by the Chronic Respiratory Disease Questionnaire (CRDQ) and the Saint Georges Respiratory Questionnaire (SGRQ). The SenseWear Armband was used to assess PA. Mean steps (STEPS) and moderate intensity activity (MOD PA) were calculated over 7 consecutive days.

Results: Baseline characteristics are presented in Table 1.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Male (n=30)</th>
<th>Female (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±10</td>
<td>64±11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26±5</td>
<td>24±4</td>
</tr>
<tr>
<td>Exercise capacity (6MWT) (m)</td>
<td>312±115</td>
<td>267±108</td>
</tr>
<tr>
<td>Dyspnea (CRDQ)</td>
<td>86±17</td>
<td>88±16</td>
</tr>
<tr>
<td>Fatigue (CRDQ)</td>
<td>86±17</td>
<td>88±16</td>
</tr>
<tr>
<td>Total (CRDQ)</td>
<td>86±17</td>
<td>88±16</td>
</tr>
<tr>
<td>Activity (SGRQ)</td>
<td>86±17</td>
<td>88±16</td>
</tr>
<tr>
<td>Total (SGRQ)</td>
<td>86±17</td>
<td>88±16</td>
</tr>
<tr>
<td>Steps (STEPS)</td>
<td>8671±3341</td>
<td>7255±3341</td>
</tr>
<tr>
<td>MOD PA (Steps)</td>
<td>24±38</td>
<td>24±38</td>
</tr>
</tbody>
</table>

Conclusion: The SGRQ and CRDQ are measuring similar concepts but HRQoL is unrelated to PA levels in patients with ILD.

P4152 Thoracicabdominal dysynchrony and it relationship with muscle strength in patients with COPD: Preliminary results
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Background: Upper limbs (UL) exercises can generate thoracoabdominal dyssynchrony (TD), which increase the dyspnea in patients with COPD. However, it is unknown the influence of posture and inspiratory muscle strength (IMS) in TD.

Aim: To verify the TD in rest and UL exercises comparing sitting and standing postures.

Methods: Fifteen patients with COPD (FEV1 47±15%; age 66±9; MIP 58±21cmH2O) performed flexion-extension exercises at the shoulder (1), above the shoulder (2) and horizontal abduction-adduction (3) in sitting and standing postures. The respiratory inductive plethysmography was performed (LifeShirt) and the Borg scale was reported. The PhRIB (Phase Relation during Inspiration),
Conclusion: These preliminary results suggest that upper limb exercises cause TD independent of the postures adopted. In addition, the results suggest that the inspiratory muscle weakness seems get worse the dysynchrony.

The Correlation between Daily Physical Activity using a Compact Accelerometer and Clinical Parameters in Patients with COPD

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Background: In patients with chronic obstructive pulmonary disease (COPD), inspiratory muscle weakness seems get worse the dysynchrony. The ventilatory reserve may be related to better physical fitness, and hence to a lower chance of hyperinflation.

The Maximum voluntary ventilation is a better correlate of energy expenditure during simple activities of daily living than measures of airflow obstruction or respiratory muscle strength in patients with COPD.

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Background: In patients with chronic obstructive pulmonary disease (COPD), the relationship between energy expenditure (EE) and measures of lung function has attracted attention. Weak to moderate associations were demonstrated between daily EE and measures of respiratory muscle strength, maximal voluntary ventilation (MVV), inspiratory capacity (IC) and forced expiratory volume in one second (FEV1) in patients with moderate to severe disease. However, as this earlier work measured EE over a 12-hour period, it is unclear to what extent the EE elicited during individual and simple activities of daily living were associated with these measures of lung function.

Objective: To explore the extent to which energy expenditure (EE) elicited during individual and simple activities of daily living is associated with different measures of lung function in patients with COPD.

Methods: Thirty-six patients (20 males; FEV1 48 ± 23.3%; GOLD classification I – 5 patients, II – 11, III – 7, IV – 7; BMI 21.8 ± 3.2 kg/m2) using a single-axis accelerometer (LifePodder, Suzuken, Japan) for 1 month. Five EE measures were monitored: total energy expenditure (kcal/day), number of steps per day, walking distance (meters/day), and the time spent performing PA (minutes/day) at light (below 3 metabolic equivalent values [METs]) and moderate (3–6 METs) intensities.

Results: There was no difference in dyspnea in both groups. Table 1 summarizes the results.

P4154

Correlation between daily physical activity using a compact accelerometer and clinical parameters in patients with COPD

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Background: Physical activity (PA) monitoring is becoming increasingly important in patients with COPD. However, the correlation between clinical parameters in COPD and PA has not yet been well studied.

Objective: To evaluate the correlation between PA using a compact accelerometer and clinical parameters in patients with COPD.

Methods: We studied daily physical activity in 30 stable COPD patients (29 males; 72.1 ± 9.5 years of age; %FEV1 54.8 ± 23.3%; GOLD classification I – 5 patients, II – 11, III – 7, IV – 7; BMI 21.8 ± 3.2 kg/m2) using a single-axis accelerometer (LifePodder, Suzuken, Japan) for 1 month. Five PA measures were monitored: total energy expenditure (kcal/day), number of steps per day, walking distance (meters/day), and the time spent performing PA (minutes/day) at light (below 3 metabolic equivalent values [METs]) and moderate (3–6 METs) intensities.

Results: Significant differences (p < 0.05) were observed between GOLD classifications for age, BMI, MRC scale, %FEV1, six minute walk test (6MWT; distance, oxygen saturation (SpO2), heart rate, dyspnea and leg fatigue on Borg scale), and nutritional conditions (serum pre-albumin, transferrin, and retinol-binding protein [RBP]).

Conclusion: Borg scale, although not significantly different among GOLD classifications, and MRC scale were strongly correlated with PA.

What is the relationship between inspiratory capacity and different measures of exercise capacity in patients with COPD?

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Background: Inspiratory capacity (IC) is an indirect measure of pulmonary hyperinflation in patients with chronic obstructive pulmonary disease (COPD), and may be a limiting factor to exercise capacity in this population. However, the relationship of IC with exercise capacity still needs to be better explored.

Objective: To investigate the relationship between inspiratory capacity and different measures of exercise capacity in subjects with COPD.

Methods: Thirty patients with COPD (18 men, 66 ± 8 years, forced expiratory volume in the first second [FEV1] 40 ± 14%pred) were studied. Inspiratory capacity was assessed by post-bronchodilator spirometry, whereas exercise capacity was assessed by the following three tests: six-minute walking test (6MWT), incremental symptom-limited cycle ergometry test (ISL) and constant work rate cycle ergometry test (CWR), all tests performed according to international guidelines.

Results: In the 6MWT, IC (in liters) explained 18% (p = 0.02) of the distance walked, whereas in the ISL it explained 23% (p = 0.008) of maximum work load and 19% (p = 0.02) of heart rate reached at the end of the test. In the CWR, IC showed only a simple negative correlation with oxygen saturation at the end of the test (r = 0.48).

Conclusion: The inspiratory capacity significantly contributes, albeit modestly, to some key variables of exercise capacity tests. This indicates that a greater ventilatory reserve may be related to better physical fitness, and hence to a lower chance of hyperinflation.

P4154

Sensation of leg effort at rest is related to lower peripheral muscle strength in patients with COPD

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Introduction: Sensation of leg effort (SLE) is known as a limiting factor in exercise capacity during a maximal exercise test in patients with COPD. The Borg scale scores this discomfort of the peripheral muscles before and during an exercise test. A high score in a maximal exercise test is known to correlate with lower skeletal muscle strength. However some patients experience SLE already at rest before the exercise test and other do not.

Objective: To evaluate if SLE at rest before exercise also could be related to peripheral muscle strength.
Methods: Data of 26 patients in a pulmonary rehabilitation program was analyzed. The Borg scale SLE before the maximal incremental exercise test. Isometric quadriceps force was assessed by a computerized dynamometer during a voluntary maximal isometric contraction with the hip at 90° and the knee at 60° flexion. The highest value was taken.

Results: SLElis light to moderate inversely correlated with isometric quadriceps force which is expressed as the percentage of strength compared to that of a healthy individual (Pearson r=0.408; p=0.039).

Conclusions: Lower quadriceps force seems to relate to higher leg effort compared to those who do not experience any leg discomfort at all. However due to the great range in quadriceps force, it is necessary to objectively measure quadriceps force to have a good clinical impression of patient’s peripheral muscle strength.

P4157 Measurement of quadriceps strength in patients with COPD using a rig-supported handheld dynamometer  
Wei Yee James, David Jolliffe, Kamrul Islam, Beverley MacLaughlin, Christopher Griffiths, Maxine Gibbon, Jonathan Feng, Dylan Morrissey, Adrian Martineau. Centre for Primary Care and Public Health, Bart's and the London School of Medicine and Dentistry, Whitechapel, London, United Kingdom

Background: Quadriceps strength (QS) predicts prognosis in COPD. Measurement using a non portable isokinetic dynamometer (ID) is the gold standard. Handheld dynamometers (HHD) are portable, but measurements of QS obtained using a HHD may be affected by operator strength. We therefore constructed a portable rig that can be bolted to a chair to support a HHD, and evaluated its performance in measurement of QS in COPD patients.

Objectives: To determine whether use of a rig to support a HHD reduces inter-observer variability in QS measurement, and generates data which correlate with those obtained using an ID.

Methods: Two operators (A-male, BMI 25.5 kg/m²; B-female, BMI 19.3 kg/m²) measured QS using unsupported HHD (12 patients) and rig-supported HHD (15 patients); values obtained for each patient were compared between operators. QS was then measured in 30 patients using both rig-supported HHD and ID; values obtained for each patient were compared between methods.

Results: Measurements of QS obtained using unsupported HHD differed between operator A vs. B (mean QS 49.5 kg vs 35.3 kg respectively; 95% CI for difference 0.9 to 1.7); however, they were highly correlated (r=0.96; 95% CI 0.95 to 0.97, p<0.001).

Conclusions: Use of a portable rig to support a HHD in the measurement of QS in COPD patients eliminates observer effects, and generates values which correlate highly with those obtained using the gold standard methodology.

P4158 A comparison of pulmonary function, functional exercise capacity and sleep quality in patients with chronic obstructive pulmonary disease and obstructive sleep apnea syndrome  
Ebra Cakir, Nurel Bellur1, Hulya Arıkan1, Nazife Vardar Yaglı1, Sema Saviç1, Melda Sağlam1, Deniz İnal-Ince1, Hakan Çalışkan1, Meral Bosnak-Güçlu1, Sadik Arıcı2, Lutfi Cıhapaşaoğlu1, 1Department of Physiotherapy and Rehabilitation, Hacettepe University, Faculty of Health Sciences, Ankara, Turkey; 2School of Physiotherapy and Rehabilitation, Dokuz Eylul University, İzmir, Turkey; 3Department of Physiotherapy and Rehabilitation, Gazi University, Faculty of Health Sciences, Ankara, Turkey; 4Department of Chest Medicine and Sleep Center, Diskapi Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey; 5Department of Chest Medicine, Hacettepe University, Faculty of Health Sciences, Ankara, Turkey

Aim: Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS) are two diseases that are characterized by obstruction of pulmonary airways. The aim of this study was to compare pulmonary function, functional exercise capacity and sleep quality in patients with COPD and OSAS.

Materials and methods: Twenty-five COPD patients (21 M, 4 F) and 25 OSAS patients (16 M, 9 F) participated in the study. Pulmonary function were measured using a spirometer. Functional exercise capacity was evaluated using a six-minute walk test (6MWT).

Results: Par-Parameters of pulmonary function, 6MWT distance and %6MWT distance were significantly lower in patients with COPD than those of OSAS (p<0.05). In patients with COPD, Borg dyspnea and fatigue were significantly increased and oxygen saturation was significantly decreased during 6MWT compared with OSAS patients (p<0.05). The PSQI sleep duration score was significantly lower, and PSQI sleep disturbances and subjective sleep quality scores were significantly higher in patients with COPD as compared to OSAS patients (p<0.05).

Conclusion: Pulmonary function and functional exercise capacity deteriorated in patients with COPD compared to OSAS patients. Exercise dyspnea and fatigue increases and oxygen saturation decreases in patients with COPD. In comparison with COPD patients, sleep duration and subjective sleep quality are adversely affected in patients with OSAS. Differences in sleep quality and exercise rat-

P4159 Evaluation of preoperative and postoperative exercise capacity by using six-minute walk test  
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The aim of this study was to evaluate preoperative and postoperative exercise capacity of the patients by using six-minute walk test (6MWT) in patients electively undergone coronary artery bypass surgery. Twenty-nine patients whose mean age was 68.69 enrolled to the study. 6MWT was done at two time set (before operation and at discharge from hospital). Heart rate, blood pressure and oxygen saturation levels was noted, level of dyspnea and fatigue determined by Borg scale before and after test and walking distances recorded after six minutes. Walking distance was 349 meters (66% of predicted values) before operation and 284 meters (54% of predicted values) after operation. Decrease of walking distance after operation was statistically significant (among measured and predicted levels, p<0.0001). Heart rate (p=0.0002), systolic blood pressure (p=0.0002), level of fatigue (p=0.008) was significantly increased before and after operation and also diastolic blood pressure (p=0.01) was significantly increased after operation after 6MWT. Decrease of oxygen saturation was significant both the tests before and after operations (p=0.02, p=0.01). Although heart rate, blood pressure, level of fatigue changes before and after 6MWT was not significant before and after CABG, decrease of oxygen saturation after CABG was significant (p=0.004). Conclusion of this study, CABG significantly reduces exercise capacity in the early postoperative course and although this reduce, similar increase of cardiopulmonary parameters and decrease level of oxygen saturation at the end of 6MWT emphasize that exercise induce cardiopulmonary overload in the post operative course.

P4160 Using the six-minute walk test to assess exercise capacity in people with pulmonary hypertension  
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Introduction: The aim of the study was to determine if there was a difference in six-minute walk distance (6MWD) when two six-minute walk tests (6MWTs) were performed in people with pulmonary hypertension (PH) prior to attendance at the PH clinic.

Methods: Participants with PH performed two 6MWTs for the first time prior to attendance at the PH Clinic. The tests were performed on a 32 metre continuous track in an outpatient hospital setting using standard instructions and encouragement.

Results: 212 participants completed two 6MWTs [mean (SD) age 57 (16) years; BMI 27 (6) kg/m²]. Using the better 6MWT the mean distance was 438 (139) metres and 6MWT % predicted was 87% (24). There was a significant increase in 6MWD on the second 6MWT [mean difference (95% CI): 16 m (9 to 23); p<0.0001] with 66% of participants walking further on the second walk than the first walk. There were no adverse events during testing.

Conclusion: In people with PH, when a second 6MWT was performed the increase in walk distance was significant but small. This may indicate that one test at baseline may be adequate.

P4161 Effects of radical treatment in patients with intrathoracic cancer  
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Introduction: In patients (pts) with intrathoracic cancer radical treatment aims to prolong life and restore quality of life. Data on its effect on exercise capacity and muscle force are limited.

Aim: To investigate the effect of radical treatment on exercise capacity, muscle force and quality of life in pts with newly diagnosed intrathoracic cancer.

Methods: Exercise capacity, peripheral muscle force and quality of life were assessed before and after radical therapy. Data are presented as median with 95% CI.

Results (table): 117 pts (86 male, age: 64 y (77 - 87); BMI; 25 kg/m² (18 - 34); 40% COPD; 35 PY (0 - 70); 105 NSCLC, 6 SLC and 6 mesothelioma were enrolled: 50% underwent surgery as sole therapy, 12% surgery + chemotherapy, 24% chemotherapy + radiotherapy, 10% surgery + chemotherapy + radiotherapy
and 4% radiotherapy only. 24 pts dropped out and 18 are still under treatment. The maximal exercise capacity and 6MW distance decreased significantly after treatment (from 100 Watt (48 - 184) to 82 Watt (38 – 147) and from 515 m (388 - 632) to 482 m (328 – 617)), respectively. Fatigue and pain increased significantly after treatment: FACT-F from 9 pnts (3 - 30) to 13 pnts (3 - 33) and VAS pain from 1 pnts (0 - 9) to 2 pnts (0 - 8).

Conclusion: Radical therapy for intractable cancer significantly decreases exercise capacity, muscle force, and increases pain and fatigue. Mature data on all pts will be available at the meeting.

P4162
Oxygen uptake is slower than heart rate on kinematics in recent myocardial infarction patients
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Background: The heart rate (HR) and oxygen uptake (VO₂) on-kinetics analysis provides information about the individual response to aerobic exercise, which may be reduced after recent myocardial infarction (MI), mainly due to impairment in the oxygen transport system.

Design: To determine whether the HR and VO₂ onset dynamics were affected by recent MI, we evaluated the VO₂ and HR on-kinetics in three groups of subjects with preserved ventricular (VF) and pulmonary function (PF).

Methods: Eight men (49±8 years) with a recent MI (RMI), eleven men (52±7 years) with a late MI (LMI) and ten apparently healthy men (48±8 years) (CG) underwent to PF assessment, ramp cardiopulmonary exercise test (CPX) and two constant workload exercise tests (CWETs) on treadmill at moderate and high workloads, corresponding to 75% and 125% of the gas exchange threshold identified at CPX. VO₂ was registered breath-by-breath and analyzed after smoothed by moving averages of 8 respiratory cycles. HR was recorded by digital telemetry system. A monoeponential fit was applied to analyze VO₂ and HR on-transient response to the first seconds of the CWETs. Intragroup and intergroup comparisons were performed (p<0.05).

Results: RMI group presented rVO₂ slower than tHR at moderate and high workloads. All groups presented faster tHR and VO₂ at moderate when compared to high workload.

Conclusion: Recent uncomplicated MI patients present slowing of VO₂ at aerobic exercise, which suggests impairment of oxygen delivery and extraction mechanisms.

P4163
Exercise induced dyspnea among 12-13 year old children
Heneke Johansson, Hans Hedenskog, Christer Janson, Leif Nordang, Lennart Nordvall, Katarina Norlander, Margareta Emntner.

Introduction: Many children are limited in their physical activity because of exercise induced dyspnea (EID).

Aim: The aim was to investigate the prevalence of EID, asthma and physical activity level among a population of 12-13 year old children in Uppsala, Sweden.

Method: A questionnaire was sent to 3815 parents asking them to answer the questions together with their child.

Results: The response rate was 61% (n=2312). EID during the last 12 months was reported by 14.3% (n=330) (girls 16.9 vs. boys 11.8%, p=0.001). Of all the children reporting EID, 48% reported wheezing and 30% rhinits during the last year, and 39% had ever had physician diagnosed asthma. Children with EID and asthma used bronchodilators and inhaled corticosteroids (ICS) to a larger extent than children with EID but no diagnosis of asthma (bronchodilators: 27.3 vs. 11.3%, p=0.001 and ICS: 31.2 vs. 4.4%, p=0.001). Only 12.4% of the total population (n=2312) reached the international physical activity recommendations (≥ 1 hour/day, 7 days/week on a moderate to vigorous level). 13% among children with EID and 12.3% in children without EID reached the recommendations (p=0.72).

Conclusion: Self reported exercise induced dyspnea is common in children and the majority of those children do not have an asthma diagnosis or asthma treatment. Only a minority of Swedish children have a self reported physical activity level that is in line with international recommendations.

416. Prognosis of lung cancer

P4164
Expression of macrophage migration inhibitory factor (MIF) in the serum and lung tissues in patients with non-small cell lung cancer (NSCLC)
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1 Pulmonary Department, The 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; 2 Clinical Laboratory, The 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; 3 Department of Pathology, The 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Objective: To study the expression of MIF in the serum and lung tissues of patients with NSCLC.

Methods: Eighty-eight patients of the 1st affiliated hospital of Sun Yat-sen university with diagnosis confirmed by pathology were recruited from 2011.10 to 2012.3, including 66 patients with NSCLC (group A) and 22 patients with benign lung lesions (group B). ELISA was done to compare serum MIF level in these two groups and in 30 healthy individuals. Immunohistochemistry (IHC) was done to compare the expression of MIF between group A and B. The correlation between serum MIF level and high expression rate in lung tissues was analyzed.

Results: The serum MIF level in group A was significantly higher than healthy control (4.79 Vs 10.69/mg/mL, P<0.001), but not significantly higher than group B (14.79 Vs 13.68/mg/mL, P=0.580). Among group A, the serum MIF level in patients with advanced stage (stage III and IV) was significantly higher than those with early stage (stage I and II) (17.53 Vs 10.54/mg/mL, P<0.001). The MIF high expression rate in the lung tissues of group A was markedly higher than group B (30.3% Vs 4.5%, P<0.014). Among group A, there was significantly higher MIF expression rate in patients with advanced stage compared with those with early stage (42.1% Vs 14.3%, P=0.015). The serum MIF level had a positive correlation with MIF expression rate in the lung tissues in patients of group A (P<0.05).

Conclusions: The serum MIF level had a positive correlation with MIF expression rate in lung cancer tissues. Both of them help to predict NSCLC clinical stage and histological grade. MIF is a good histological biomarker of NSCLC.

P4165
Clinical implication of stem cell markers in N2 positive non-small cell lung cancer
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Introduction: Non-small cell lung cancer (NSCLC) is one of the most commonly diagnosed malignancies and the leading cause of death worldwide. Cancer stem cells (CSC) are proposed to be responsible for metastasis and chemoresistance.

Material and methods: 72 patients were diagnosed with N2 positive NSCLC. They underwent surgical resection from 2006 to 2007 in Asan Medical Center, Seoul, Korea. Immunohistochemical staining for CD133, CD44, CD24, CXCR4, Nanog, Oct4, ABCG2, E-cadherin, vimentin, and Ki-67 was performed.

Result: Most frequently expressed CSC marker in primary tumor specimens of NSCLC was CXCR4 (92.2%), followed by CD44 (29.2%), CD24 (12.5%), and ABCG2 (9.7%). However, other markers such as CD133, Nanog, and Oct4 were not expressed. E-cadherin was expressed in 86.1% of primary tumor specimens, while vimentin was expressed in 20.8%. Cell proliferative marker, Ki-67, was expressed in 16.7% of primary tumor tissues. As for specimens of lymph nodes, most frequently expressed marker was CXCR4 (93.1%), followed by CD44 (15.2%), ABCG2 (12.5%), and CD24 (10%). In 85.1% of lymph node specimens, E-cadherin was positive. Vimentin was positive in 17.9%. Among the patients showing CD44 positivity in primary tumor specimens, 70% were negative for CD44 expression in lymph nodes. Survival analysis revealed that CD44 expression is a favorable prognostic factor for overall survival (p=0.024). Multivariate analysis using Cox-regression showed that NSCLC patients with CD44 positivity have trend towards increased overall survival.

Conclusion: Various CSC markers are expressed in patients with NSCLC. Immunoreactivity for CD44 is a positive prognostic factor for survival in N2 positive NSCLC.
P4166
Association of XPD and CDA polymorphisms with clinical outcome in non-small cell lung cancer in a Chinese population
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XPD plays a key role in the repair of DNA and platinum resistance lesions. Cytidine deaminase genes decide the velocity of catalytic activity. This study aims at investigating the relationship between the XPD, CDA genotypes and the outcome in NSCLC patients. We used RFLP to evaluate genetic polymorphism of the XPD Asp312Asp, XPD Lys75Gln, CDA Lys27Gln and CDA Ala170Thr in 93 NSCLC patients treated with cisplatin-gemcitabine regimen. 44% of patients carrying XPD 312A/Gln had progression of disease, whereas 55.6% with heterozygous XPD 312A/Gln had progression of disease as well. There were no significant correlation between XPD 312A/Gln and clinical benefit (p=0.32). 52.94% of patients with wild-type had clinical benefit (PR and SD). 56.9% of patients carrying XPD 751Lys/Gln responded to therapy. There was no difference between different genotype (p=0.517). But the difference of OS between XPD 312A/Gln and XPD 312A/Gln was very significant (20.0 months vs 12.4 months, p=0.04).

P4167
The metallopeptidase neprilysin is a hypoxia-induced prognostic factor in lung adenocarcinoma
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Identification of hypoxia-induced pathways might lead to novel therapeutic targets in solid cancers. A comparative expression profiling study was performed in hypoxic and normoxic ex vivo cultured lung cancer fragments with preserved tumor stroma and 3D-structure. A considerable overlap was found between hypoxia-regulated genes from the ex vivo lung cancer model and published hypoxia-signatures. The stem cell marker neprilysin (membrane metallo-endopeptidase, MME, CD10), which was consistently up-regulated by hypoxia in the histological subtypes in our study, has not been reported so far to be hypoxia-induced in cancer. Neprilysin has been shown to be expressed by stroma cells, e.g. cancer-associated fibroblasts. Immunohistochemistry for neprilysin in fresh NSCLC specimens and normoxic or hypoxic fragments revealed a localization in both, stroma cells and neoplastic tumor cells. To assess a possible role of neprilysin in lung cancer progress we analyzed the association of neprilysin expression and overall survival in NSCLC patients from public microarray datasets. High expression of neprilysin was significantly associated with poor overall survival in 182 adenocarcinoma patients in a multivariate meta-analysis (p=0.00012) and in adenocarcinoma patients from two individual datasets. As a conclusion, neprilysin is a hypoxia-induced, independent adverse prognostic factor in surgically treated lung adenocarcinoma patients. The results of this study suggest an important role of stroma-derived hypoxia-induced factors for lung cancer progression.

P4168
Prognostic value of ERCC1 expression in advanced non-small cell lung cancer (NSCLC)
Jens Konigsmark1, Torsten Blum1, Daniel Minch2, Andreas Roth2, Christian Böck3, Wolfram Gruening4, Catharina Creulow5, Sergio Griff6

Background: The immunohistochemical (IHC) detection of the “excision repair cross-complementation group 1” (ERCC1) protein in resected NSCLC is prognostically relevant. Pts with ERCC1-neg. tumors appear to benefit from adjuvant cisplatin-based chemotherapy (CTX), whereas pts with ERCC1-pos. tumors do not. Aim: We compared survival of pts with non-operated NSCLC III/IV according to the four tumor subtypes in our study, has not been reported so far to be hypoxia-induced in cancer. Neprilysin has been shown to be expressed by stroma cells, e.g. cancer-associated fibroblasts. Immunohistochemistry for neprilysin in fresh NSCLC specimens and normoxic or hypoxic fragments revealed a localization in both, stroma cells and neoplastic tumor cells. To assess a possible role of neprilysin in lung cancer progress we analyzed the association of neprilysin expression and overall survival in NSCLC patients from public microarray datasets. High expression of neprilysin was significantly associated with poor overall survival in 182 adenocarcinoma patients in a multivariate meta-analysis (p=0.00012) and in adenocarcinoma patients from two individual datasets. As a conclusion, neprilysin is a hypoxia-induced, independent adverse prognostic factor in surgically treated lung adenocarcinoma patients. The results of this study suggest an important role of stroma-derived hypoxia-induced factors for lung cancer progression.

Methods: We analyzed 398 pts (m=248, f=150) newly diagnosed with NSCLC stage III/IV between 10/2009 and 12/2010. Prospectively, ERCC1 expression determined by IHC was measured and indicated as H-score. Pts where no IHC and/or H-score could be performed were excluded.

Results: 271/398 cases (68%) were suitable for IHC. 175/271 (65%) of tumors were ERCC1 pos., 96/271 (35%) ERCC1 neg. 177/271 (65%) received platinum. Survival times in days were (mean ± SEM): platinum+ERCC1+: 404±25 (n=67); platinum+ERCC1+: 346±23 (n=110); platinum-ERCC1-: 144±23 (n=29); platinum-ERCC1-: 268±33 (n=65). In Cox hazard regression analysis, the factors platinum+ (p<0.001) and ERCC1 (p=0.01) were not independent (p=0.001, interaction term).

Conclusions: Pts with palliative platinum-based Ctx for advanced NSCLC had significantly longer OS when the tumor showed no significant ERCC1 expression. In pts who did not have platinum-based Ctx, the absence of ERCC1 expression was prognostically unfavorable. This study confirms observations from adjuvant therapy also for palliative Ctx.

P4169

EGFR mutations are associated with sensitivity to tyrosine kinase inhibitors (TKI) in patients with NSCLC. Studies point to different outcome to TKI treatment according to exon mutation.

Aim: Understand how different EGFR mutations predict TKI response and affect survival.

Methods: Records review of NSCLC patients with EGFR study (2006-2011). Epidemiological, clinical and outcome information was analyzed using SPSS19.0

Results: Of 409 patients studied 53 were EGFR-positive. After exclusion of 1 drug-resistant patient (exon 20) and patients who did not use TKI or had TKI as 1st therapeutic, 22 patients were considered - 50% male, 67.5±9.8, 59.1% non-smokers.

Progression-free survival (PFS) was better in exon 19 mutations (p=0.04). Survival after TKI (STKI) was better in 18 and 19 mutated patients (no statistical difference - p=0.06).

In non-surgical stages (72.8%), exon 19 mutated patients had better global survival (GS), STKI and PFS than others (p<0.05).

Table 1

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<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
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<tr>
<td>% patients</td>
<td>13.6</td>
<td>40.9</td>
<td>9.1</td>
<td>36.4</td>
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<tr>
<td>STKI (m)</td>
<td>25.6 (15–46.1)</td>
<td>25.4 (18.2–33.3)</td>
<td>10.3 (4.5–16.5)</td>
<td>11.6 (7.7–17.4)</td>
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<tr>
<td>PFS (m)</td>
<td>22.1 (0–18.8)</td>
<td>8.0 (12.8–31.8)</td>
<td>7.1 (5.1–9.1)</td>
<td>8.6 (4.8–12.3)</td>
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Table 2. Stages IIIB/IV

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<th>18</th>
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<tr>
<td>GS (m)</td>
<td>23.8 (0–64.8)</td>
<td>50.5 (17.8–83.2)</td>
<td>34.2 (8.6–60.0)</td>
<td>21.4 (7.7–35.0)</td>
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<tr>
<td>STKI (m)</td>
<td>14.1 (0–39.6)</td>
<td>19.8 (12.1–27.5)</td>
<td>10.3 (4.0–16.5)</td>
<td>11.3 (6.4–16.1)</td>
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<tr>
<td>PFS (m)</td>
<td>10.1 (0–27.4)</td>
<td>11.8 (9.2–26.2)</td>
<td>7.1 (5.1–9.1)</td>
<td>8.1 (5.6–12.8)</td>
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Associating patients with exons 18 and 20 (described as less predictive of therapeutic outcome) GS29.1, STKI12.2 and PFS8.6 months, all higher than values found for exon21(p<0.05).

Conclusions: Exon 19 mutation conferred better prognosis to patients treated with TKI. Exons 18 and 20 (22.7%) were not associated with worse prognosis than exon 21. Although this is a small group we believe that is worth to maintain analysis of the 4 exon mutation.

TUESDAY, SEPTEMBER 4TH 2012
Prognostic value of fluorine-18 fluoroethylguanine (18-FDG) positron emission tomography imaging in patients with non-small cell lung carcinoma Ahmet Yildirim 1, Fatma Yildirim 1, Sevket Orakci 1, Umit Ozgur Akdemir 1, Can Ozturk 1, 1Department of Pulmonary Medicine, Gazi University Faculty of Medicine, Ankara, Turkey; 2Department of Pulmonary Medicine, Dr. Suat Seren Education and Research Hospital For Chest Diseases and Thoracic Surgery Hospital, Izmit, Turkey; 2Department of Nuclear Medicine, Gazi University Faculty of Medicine, Ankara, Turkey

To determine whether the amount of 18-FDG maximum standardized uptake (SU-Vax) value on the PET/CT imaging at the time of presentation has prognostic significance in patients with non-small cell lung cancer (NSCLC). Patients and methods: A retrospective review identified 142 patients with NSCLC who underwent 18-FDG PET/CT study at the time of diagnosis. Extensive clinical data, including tumor histologic cell type, stage at presentation, treatment, and SU-Vax values in the primary tumor were recorded and survival was examined. Results: Total 142 patients were included the study. 32 patients of them have stage I and II. The median SU-Vax of early stage patients is determined 13.5. Early stage patient population was subdivided into two groups according to the median value for survival. The median survival of the 17 patients with the primary tumor having an SU-Vax between 13.0 was 19.0 months. There was no statistical differences between two groups (p=0.483). The 110 patients were on advanced stage (stage III and IV). Using the median SU-Vax of 12.5, the patient population was subdivided in two groups. The median survival of the 54 patients with the primary tumor having an SU-Vax less than 9.5 was 12.0 months whereas the median survival of the 56 patients with the primary tumor having an SU-Vax of 9.5 was 11.0 months. There was no statistical differences between two groups (p=0.266).

Conclusion: 18-FDG SU-Vax uptake of the primary lesions in patients with a new diagnosis of NSCLC does not have a significant relationship with survival.

EpCAM-positive circulating cells in lung cancer patients Joanna Domagalska-Koloszy1, Tomasz Skirecki 1, Grazyna Hosier 2, 1Pneumonology, Medical University, Warsaw, Poland; 2Laboratory of Flow Cytometry, Ceneter of Postgraduate Education, Warszaw, Poland

Lung cancer is a very aggressive neoplasm characterized by high metastatic potential which is the main cause of therapeutic failures. The exact cell of origin of metastasis is not known, however several markers for them have been proposed. Recent research indicates that a rare subpopulation of the CTCs (Circulating Tumor Cells) can be detected in tumor tissue, lung tissue and peripheral blood by flow cytometry with anti-EPAM antibody and to investigate its clinical significance.

Forty-one patients diagnosed with lung cancer were enrolled into this study. Patients did not receive anticancer treatment prior to the study. The cells bearing EpCAM were detected in tumor tissue, lung tissue and peripheral blood by flow cytometry with anti-EPAM FITC antibody, analyzed in FACScantoll, BD flow cytometer. EpCAM+ cells were detected in the tumor tissue with higher proportion than in adjacent lung parenchyma and with higher proportion in adenocarcinoma (AC) than in squamous cell (SCC) type. The median proportion of circulating EpCAM+ cells was 0.0026% (260 per ml). No difference was found between SCC and NOS. The fraction of EpCAM+ cells was higher in the patients with AD and without SCC (0.0130 vs 0.0027%), was significantly lower in the blood of patients with advanced disease (IBB, IV) when compared with lower stages (I-IIIA) (0.0018 vs 0.00067%, 230 vs 504 cell per ml) and was significantly lower in patients with metastases compared to those without metastases (0.0015% vs 0.0046%, p=0.012).

Our study confirmed the presence of a rare subpopulation of the CTCs of the EpCAM-positive cells in lung cancer patients with significant differences related to histological type and stage of the disease.

Independent prognostic und predictive value of blood vessel invasion (BVI) in curatively (R0) resected stage II and IIIA non-small cell lung (NSCLC) cancer patients: Dieter Wuerflein 1, Wolfgang M. Bruckel 1, Dietmar Kraus 2, Christian Meyer 1, Manfred Wagner 1, Joachim H. Ficker 1, 1Department of Internal Medicine 3, Klinikum Nuernberg, Germany; 2Department of Thoracic Surgery, Klinikum Nuernberg, Germany; 3Klinikum Nuernberg, Inst. of Pathology, Nuernberg, Germany

Objective: A single center study was conducted to identify the prognostic and predictive role of blood vessel invasion (BVI) in surgically R0 resected stage II and IIIA non-small cell lung cancer patients.

Methods: A total of N=105 consecutive patients who had undergone complete (R0) resection for stage IIA/IIIA primary non-small cell lung cancer (NSCLC) between 01/2008 and 12/2010 at the Lung Cancer Center Nuernberg were evaluated. All pathological specimens were examined for evidence of BVI.

Results: The baseline clinical data showed no significant differences between patients with and without positive invasion (tumor/necrosis; N=64) and patients without BVI (N=49). Patients with BVI had a significantly longer tumor-free survival (13.5 vs. 11.7 months; p=0.003). 18-FDG SUVmax values in the primary tumor were recorded and survival was examined. The cumulative 2-year survival rate was 64% (95% CI of ratio 1.00 – 1.79) was significantly associated with shorter survival, while the effects of patients presented any co-morbidity at the time of diagnosis and 14.3% of them had 3 co-morbidities. Multiple Cox’s proportional hazard model was performed to evaluate the impact of co-morbidity on survival.

Results: The median survival for all patients was 9.3 months (range: 0.12 – 7.06), and the cumulative 2-year survival rate was generally poor (<1%). Multiple Cox’s proportional hazard model showed that only the patients with the major co-morbidity group of 'endocrine, nutritional and metabolic disease and immunity disorder’ was the significant risk factor to shorten the survival for non-surgical NSCLC which raises special attention for better supportive or palliative care for lung cancer patients with this type of co-morbidity.

High mRNA expressions of KLF2 improve post operative prognosis of pulmonary adenocarcinoma correlation with chemokine receptor CCR7 and genetic mutations of p53 Meiji Iinokura 1, Yuya Terashima 2, Masato Shingyoji 1, Toshihiko Iizasa 1, Hisuki Kimura 1, 1Department of Thoracic Disease, Chiba Cancer Center, Chiba City, Japan; 2Department of Molecular Preventive Medicine, The University of Tokyo, Bunkyo-ka, Tokyo, Japan

Purpose: Chemokines and chemokine receptors not only have the powerful ability to influence of tumor metastasis and tumorigenesis, but also act as anti-tumorgenic ability. Lung Kunreppel-like factor (KLF, KLF2) is a member of the family of the Krueppel-like factors (KLFs). KLF2 was initially described as a lung-specific transcription factor. KLF2 is reported to regulate some malignant cells. We examined and evaluated the effect of KLF2 on pulmonary adenocarcinoma and the relationship of their mRNA expression with CCR7, EGFR and p53 genetic mutations in pulmonary adenocarcinoma.

Results: KLF2 mRNA expression was up-regulated in these patients. The mRNA expression of KLF2 was significantly good prognosis than the groups of low expressions (p= 0.0066, HR= 2.008, 95% CI of ratio 1.215 to 3.319). The expression of KLF2 mRNA had significantly good prognosis than the groups of low expressions (p= 0.0066, HR= 2.008, 95% CI of ratio 1.215 to 3.319). The expression of KLF2 mRNA had significantly good prognosis than the groups of low expressions (p= 0.0066, HR= 2.008, 95% CI of ratio 1.215 to 3.319). The expression of KLF2 mRNA had significantly good prognosis than the groups of low expressions (p= 0.0066, HR= 2.008, 95% CI of ratio 1.215 to 3.319). The expression of KLF2 mRNA had significantly good prognosis than the groups of low expressions (p= 0.0066, HR= 2.008, 95% CI of ratio 1.215 to 3.319).
P4175 Prognostic impact of nestin expression in resected large cell neuroendocrine carcinoma of the lung
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Data of patients with LCNEC and NS CLC with neuroendocrine differentiation after surgical resection in comparison to surgical resection in NSCLC. There are no studies that have shown prognosis similar to this of patients with SCLC and worse prognosis was observed in patients with LCNEC. Nestin expression in tumor cells was immunohistochemically studied in 30 patients with resected LCNEC, and its associations with clinicopathologic parameters were evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of nestin expression on survival. Nestin expression was observed in 8 of the 30 (26.7%) LCNECs. Clinicalpathologically, no significant association between nestin expression and age, gender, smoking habits, p-TNM stage, tumor size, or nodal status was observed. On survival analysis, nestin expression was significantly associated with a poorer prognosis in patients with LCNEC (P = 0.016). Multivariable analysis confirmed that nestin expression increased the hazard of death after adjusting for other clinicopathologic factors (HR= 3.53; 95% CI, 1.21-10.3).

The present study suggests that nestin expression is a prognostic indicator of a poorer survival probability in patients with resected LCNEC, although its prognostic significance still requires confirmation with larger patient populations. This study was approved by Kitasato university human ethics committee.

P4176 The impact of neuroendocrine differentiation in the prognosis of non-small cell lung cancer
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Introduction: Large cell carcinomas with neuroendocrine differentiation (LCNEC) consist a distinct subcategory and represent 2-3% of lung cancers. Retrospective studies have shown prognosis similar to that of patients with SCLC and worse prognosis after surgical resection in comparison to surgical resection in NSCLC. There are data showing that perioperative chemotherapy especially platinum based combinations, improves survival.

Aim: Examine the overall survival (OS) between patients with LCNEC and NSCLC with neuroendocrine differentiation and the progression free survival (PFS) according to the stage and the therapy applied.

Method: Data of patients with LCNEC and NSCLC with neuroendocrine differentiation were collected from June 2005 to December 2010.

Results: Data from 26 patients were collected, men median age 62 years old. 15 had LCNEC and 11 NSCLC with neuroendocrine differentiation, 6 at stage I-II and 10 at stage IV. The majority were confronted with multimodal therapy (surgery, radiotherapy, chemotherapy). The median OS was 15 months for LCNEC and 15.5 months for NSCLC with neuroendocrine differentiation (95% CI). There was no difference between LCNEC and NSCLC with neuroendocrine differentiation for stages I-II (p=0.814) and IV (p=0.563) respectively. The median OS for all patients was 3.5 months and the median PFS 2.5 months (95% CI). Totally 12 patients received systematically sandostatin-LAR and 14 did not receive without difference found in OS (p=0.140).

Conclusions: Randomised trials are needed in order to prove which therapeutic intervention is the most proper and which chemotherapeutic combination is the best for lung cancer with neuroendocrine differentiation.

P4177 Long-term outcomes and prognostic factors for neuroendocrine G1 and G2 lung tumors
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Background: Bronchial neuroendocrine G1 and G2 tumors show a favorable outcome. However, survival depends on several prognostic factors such as histological subtype, nodal involvement and other predictors.

Objectives: The presented study aimed to evaluate the long-term outcomes, survival rates and prognostic factors after resection of G1 and G2 neuroendocrine lung tumors according to the 7th edition of the TNM staging system.

Patients and methods: We conducted a retrospective review of 246 consecutive patients who underwent surgical treatment for G1 and G2 neuroendocrine tumors of the lung between 1998-2010.

Results: 246 patients (63% women) with G1 and G2 neuroendocrine lung tumors underwent thoracotomy. G1 tumors were found in 205 (83%) patients, while 41 (17%) had G2 disease. Follow-up was 65±±40.3 months. In the total study cohort with analysed 5- and 10-year survival: G1 bronchopulmonary tumor (survival 96% and 94%) was significantly different (p<0.001) from G2 bronchopulmonary tumor (survival 87% and 46%), stage I survival (94% and 85%) was significantly different (p=0.02) from stage >I (survival 86% and 59%), nodal involvement (survival 83% and 57%) was significantly different (p=0.02) in comparison to patients without nodal involvement (survival 94% and 84%), distant metastases (survival 80% and 27%) was significantly different (p=0.001) compared to patients without distant metastases (survival 94% and 84%).

Conclusions: Prognosis was influenced by histological subtype, stage of disease, occurrence of symptoms before operation, lymph node involvement and distant metastases.

P4178 The increase of circulating B7-H4-expressing CD68+ macrophage correlated with clinical stage of lung carcinoma
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Purpose: To investigate the B7-H4-expressing TAM in a series of 56 cases of lung carcinoma.

Methods: Tissue samples were obtained from patients with lung cancer, who underwent lobectomy surgery. B7-H4-expressing TAM was observed by confocal microscopy. B7-H4-expressing macrophage (CD68+ cells) in peripheral blood was measured among patients with lung cancer, patients with tuberculosis and healthy donors by two-color flow cytometry. Correlation of B7-H4-expressing CD68+ macrophage with histological types, tumor size and lymph node metastasis was assessed.

Results: Lung cancer are infiltrated with Tumor-associated macrophages (CD68+ cells) that expressed B7-H4. The circulating B7-H4-expressing CD68+ cells were higher in the lung cancer group than in the tuberculosis group. The number of B7-H4-expressing CD68+ cells was positively correlated with tumor size and lymph node metastasis, and the tumor size. The proportion of B7-H4 positive CD68+ cells among CD68+ cells was also greater in late stage lung cancer than in early serious stage lung cancer. The intensity of B7-H4 staining was significantly correlated with lymph node metastasis, and the tumor size. Expression of B7-H4 was significantly higher in CD68+ cells from the late stage lung cancer (stage III-IV, n=36) as compared with the CD68+ cells from early stage lung cancer (stage I-II, n=20).

Conclusion: It is suggested that lung carcinomas increase B7-H4-expressing macrophages, which might favor tumor progression.

P4179 Prognostic value of SUVmax in patients with lung cancer who underwent surgical treatment
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Introduction: The metabolic activity of a tumor can be measured by the Standardized Uptake Value (SUV) of F-2-deoxy-2-fluoro-D-glucose (FDG), which may provide prognostic information.

Objective: To analyse the prognostic value of SUVmax in surgically treated patients with lung cancer.

Methods: The patients included were selected from a database of patients with lung cancer, between 2007 and 2010, who underwent surgical resection with performance of PET with quantification of SUVmax prior to surgery.

Results: 26 patients underwent surgical resection of lung lesion, with mean age 64±12.2 years, 16 (61.5%) were male. 23 underwent pre-surgical PET. The value of SUVmax was accessed in 21: 9 (42.9%) adenocarcinoma, 8 (38.1%) carcinoid tumors, 2 (9.5%) squamous cell carcinoma and 2 (9.5%) NSCLC. The mean SUVmax was 5.4±4.4. In carcinoid tumors the mean SUVmax was 3 and in NSCLC 6.9, adenocarcinoma 7.3 and squamous cell carcinoma 5.5. The pre-surgical stage was IA 6 (28.6%), IB 12 (57.1%), IIB 1 (4.8%) and III in 2 (9.5%). After surgery, staging was distributed as follows: IA 8 (38.1%), IB 7 (33.3%), IIA 1 (4.8%), IIB 1 (4.8%) and IIIA 4 (19%). Disease being occurred in 4 and upstaging in 4, with mean SUVmax of 2.2 and 3.2, respectively. With respect to surgical stage, the average SUVmax was 6.1 in stage III, 5.2 in stage II and 5.3 in stage I. Recurrence was observed in 2 (9.5%), with SUVmax of 5.6 and 1.9. The median follow-up was 23.4 months and no deaths were reported.

Conclusion: Although limited by a small sample size, higher values of SUVmax in patients with post-surgery upstaging, in adenocarcinoma and in more advanced stages was observed in this study.
Conclusions: Most of our patients had advanced disease and despite the use of TKIs in selected patients the prognosis remained poor. Common mutations were deletions in exon 19 and point mutations in exon 21.

P4181
One year survival differences of EGFR- and KRAS-mutated advanced non-small cell lung cancer (NSCLC) compared to the wildtype population
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Introduction: With investigation of the complex relationship between EGFR-related biomarkers and response to tyrosine kinase inhibitor (TKI) novel therapies for NSCLC have been established. In numerous clinical studies the effect of TKIs in patients with activating EGFR mutations is proven by a better progression free survival (PFS) while the prognostic value of KRAS mutations remain vague. The current study in our clinic retrospectively analysed the one year survival of patients with NSCLC and an activating EGFR- or KRAS-mutation.

Methods: Within 15 months until Dec 2010, all subsequent biopsies of newly diagnosed NSCLC (n=753) were tested for the ability to be analysed by Sanger- and Pyrosequencing for the presence of EGFR mutations and by LightCycler Real-time PCR for the presence of KRAS mutations. The obtained data were correlated with the centre-bound tumour registry for survival data and analysed by Kaplan-Meier estimator.

Results: In a total of 552 cases with NSCLC, EGFR mutation was present in 27/552 (4,9%, male n=10) and KRAS mutation in 85/552 cases (15,8%, male n=43). In advanced NSCLC (IIIb/IV), 16/27 patients had an EGFR mutation and 46/85 had KRAS mutation. The one year survival of advanced NSCLC and EGFR mutation was 11/16 (68,8%) vs. 5/16 (31,3%) without mutation. Stratifying according to KRAS it was 15/46 (32,6%) vs. 27/552 (4,9%, male n=10) and KRAS mutation in 85/552 cases (15,8%, male n=43). 19/154 (12,3%) patients had an activating KRAS mutation. The one year survival of advanced NSCLC and KRAS mutation was 27/552 (4,9%, male n=10) and KRAS mutation in 85/552 cases (15,8%, male n=43).

Conclusion: Comparable with previous reports, the one year survival of NSCLC with EGFR mutation is improved whereas the one year survival with KRAS mutations seems to be poorer.

P4182
Recruitment of podoplanin positive cancer-associated fibroblasts in metastatic lymph nodes predicts poor prognosis in pathological N2 stage III lung adenocarcinoma
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Background: Cancer-associated fibroblasts (CAFs) directly communicate with cancer cells and play important roles in cancer progression. Recent studies have reported that primary cancer tissue with podoplanin-expressing CAFs predicted a poorer outcome among stage I lung adenocarcinoma patients. However, whether podoplanin(+)CAFs can also be recruited into metastatic lymph nodes and influence the prognosis remains unclear.

Methods: We selected 112 patients with pathological N2 stage III lung adenocarcinoma and examined the podoplanin expression of CAFs and their prognostic impact in primary and metastatic N2 lesions.

Results: A significant positive correlation was found in podoplanin expression in CAFs between primary and metastatic lesions (P = 0.001). The differences in overall survival of patients with podoplanin-positive/negative CAFs in their primary lesion was not correlated (P = 0.927). In contrast, patients with podoplanin(+)CAFs in metastatic lymph nodes had a shorter overall survival than those without podoplanin(+)CAFs (P = 0.003). In multivariate analyses, podoplanin(+)CAFs in metastatic lymph nodes were a significantly independent risk factor for a poor outcome (P = 0.007).

Conclusions: Our study indicated podoplanin(+)CAFs in metastatic lymph nodes was a significant prognostic factor for overall survival among pathological N2 stage III adenocarcinoma patients.

P4183
Immunohistochemical expression of Bcl-2 and p53 in patients with lung cancer: Correlation with survival time
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Background and aims: Bcl-2 and mutated p53 genes are the most relevant proteins involved in apoptosis and tumor development. The aim of this study was to determine the Bcl-2, p53 and Ki-67 expression and their impacts on survival time in patients with lung cancer.

Material and methods: 127 patients with lung cancer (IC), 87 with non-small cell lung cancer (NSCLC) and 40 with small cell lung cancer (SCLC) were stained immunohistochemically on paraffin-embedded tissue, using specific monoclonal antibody for Bcl-2 and p53.

Results: The differences in apoptotic marker expression between NSCLC and SCLC were revealed: p53 expression is seen more frequently in NSCLC patients (46/87; 52,87%). Bcl-2 expression is seen in 26/40 (65,0%) SCLC patients, and only in 27/87 (31,03%) with NSCLC (p=0,000). The Kaplan-Meier survival analysis demonstrated that Bcl-2 positive SCLC patients had poor survival status (Log Rank=20,137, p=0,000). In NSCLC patients only p53 immunoreactivity was associated with shortened survival (log Rank=6,534 p=0,011). Multivariate analysis showed that over-expression of Bcl-2 and p53 were independent prognostic marker for poor survival in the patients with SCLC (HR=6,02 p=0,000), and NSCLC (HR=1,547 p=0,049), respectively.

Conclusions: The results indicated that aberrant expression of p53 and Bcl-2 have a strong effect on survival and prognosis in patients with NSCLC and SCLC and reflect their different pathogenesis.

417. Screening, diagnosis, staging and treatment strategies for lung cancer

P4184
Validation of CALIPER (Computer-aided lung informatics for pathology evaluation and rating) for the non-invasive assessment of pulmonary nodules of the adenocarcinoma spectrum
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Rationale: The growing utilization of high-resolution computed tomography (HRCT) for clinical diagnosis and lung cancer screening results in identification of pulmonary nodules of unknown clinical significance. Non-invasive strategies...
for the individualized management of these lesions are required. In a pilot study we have demonstrated the consistent classification of pulmonary nodules of the adenocarcinoma spectrum using CALIPER.

Methods: Two pulmonary pathologists independently assessed histopathologic tissue invasion in 72 surgery resected pulmonary nodules (≤ 3cm) of adenocarcinoma spectrum from 88 patients. Based on consensus, all lesions were categorized as either NINN-<5mm invasive, n=60 (>5mm invasion, n=66). CALIPER mapped the individual HRCT voxels (pre-operative HRCT) within all the nodules to one of the previously identified 9 unique radiologic patterns. The nodules were categorized as INV or NINV based on the relative distribution of the patterns. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for CALIPER-based detection of tissue invasion were calculated.

Results: Sensitivity, specificity, PPV and NPV were respectively 98.5%[90.7-99.9%], 66.7%[24.1-94%], 97%[88.7-99.4%] and 80%[30-98%]. Only one case was identified as NINV by CALIPER and as INV by the pulmonary pathologists.

Conclusion: CALIPER represents a promising tool size for automated nodule detection of pulmonary nodules of the adenocarcinoma spectrum. Further prospective and retrospective validation of our data is currently ongoing.

P4185 Probability of malignancy based on automatic segmentation and software measurements of nodules in the Danish lung cancer screening trial (DLcST)
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Introduction and aim: With the widespread use of chest CT in clinical and setting screening pathways nodules are detected more frequently than ever, and the risk of malignancy needs to be determined.

Materials and methods: In DLcST, 4,104 current and former smokers, with a history of at least 20 pack years and age between 50-70 years, were randomized to either five annual multi-slice low-dose CT screenings or no screening. All participants had an annual visit to the screening clinic where lung function tests and questionnaires concerning health, lifestyle, smoking habits and psychosocial consequences of screening were performed. All scans were double-read by two experienced researchers and size were registered. Nodules between diameters of 5-15 mm were considered indeterminate, and re-scanned after three months. Participants with nodules larger than 15 mm were referred to diagnostic workup, as were those with growing nodules. Lung cancer was diagnosed by pathological evaluation.

Using volumetric software nodules were segmented automatically and for the solid and sub-solid components mass and volume were calculated as well as the largest axial diameter. All automated nodule-segmentations were visually reviewed for correctness and adjusted if needed.

Results and conclusion: We are currently analyzing the data by logistic regression with nodule size and outcome and nodule measurements, as age, sex, smoking status and history and COPD-status as explanatory variables. The results will be presented at the ERS 2012 in Vienna.

P4186 Emphysema, COPD and lung cancer screening. Update of an ongoing study
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Recently, screening with low-dose CT (LDCT) has been shown to reduce mortality from lung cancer. We reported that emphysema on a LDCT, but not COPD (FEV1/FVC <70%), is associated with an increased risk of lung cancer. We present an update of our screening study.

Data comes from a prospective cohort of an ongoing lung cancer screening study held at our center. From 2000 to 2011, current and former smokers of at least 40 years of age and at least 10 pack-years of smoking were recruited. All had annual LDCTs and most a baseline spirometry. Lung cancer incidence density and its association with risk factors were calculated with logistic regression.

From a cohort of 2697 subjects, 1925 (25% females) who had LDCTs and a history of at least 20 pack years and age between 50-70 years, were randomized to either five annual multi-slice low-dose CT screenings or no screening. All participants had an annual visit to the screening clinic where lung function tests and questionnaires concerning health, lifestyle, smoking habits and psychosocial consequences of screening were performed. All scans were double-read by two experienced researchers and size were registered. Nodules between diameters of 5-15 mm were considered indeterminate, and re-scanned after three months. Participants with nodules larger than 15 mm were referred to diagnostic workup, as were those with growing nodules. Lung cancer was diagnosed by pathological evaluation.

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Results and conclusion: We are currently analyzing the data by logistic regression with nodule size and outcome and nodule measurements, as age, sex, smoking status and history and COPD-status as explanatory variables. The results will be presented at the ERS 2012 in Vienna.
Patients (2.6%) with ischemic stroke as leading event (n=23, 1.2%), followed by LC (SCLC 10.3%, NSCLC 89.7%). Arterial TEE were documented in 51 patients (median survival 283 days vs. 479 days).

**Introduction:** The objective of this study was to evaluate the diagnostic performance of 18F-fluorodeoxy-glucose-Positron Emission Tomography with integrated contrast enhanced Computed Tomography (FDG-PET/CT) as a routine diagnostic tool in a Rapid Outpatient Diagnostic Program (RODP) for patients referred on the basis of a chest X-ray suspicious of lung cancer.

**Methods:** A retrospective chart study was conducted of all patients referred to the two-day RODP of our tertiary care university clinic between 1999 and 2009 after an abnormal chest X-ray. We analyzed timeliness of care and the diagnostic performance of FDG-PET/CT to differentiate between malignant and benign lesions.

**Results:** In 386 patients available for analysis, 260 patients were diagnosed with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) of both subtypes; 23 patients had another type of malignancy. 78 patients had certain benign disease, and in 45 patients the diagnosis was not pathologically confirmed but a median 24.5 months follow up confirmed a benign outcome. Sensitivity, specificity, negative predictive value, positive predictive value and accuracy of FDG-PET/CT to differentiate lung cancer from benign disease were 97.7%, 60.2%, 92.5%, 84.0% and 95.7% respectively. For lung cancer patients, median referral time was seven days, diagnostic delay was 2 days and therapeutic delay 19 days.

**Conclusion:** FDG-PET/CT in an RODP setting for suspected lung cancer has high performance in detecting cancer and facilitates timely care.

**P4192**

A proposal in small cell lung cancer staging according to TNM system

**Background:** Many pts with limited disease [LD] behave similarly to those with extensive disease [ED] from the prognostic point of view. On the other hand, a proportion of pts with ED SCLC behave similarly to those with LD. Moreover, the 7th (IASLC) TNM classification has not been evaluated with recent, large scale studies in SCLC.

**Patients and methods:** In this retrospective analysis 764 pts with proven SCLC were included managed with the same therapeutic protocols based on platinum analogues. Of these pts, 278 (36.4%) had LD, while 486 (63.6%) had ED. This classification was based on the following investigations: chest radiography, computed tomography of chest, abdomen and brain, thoracic bronchoscopy, isotope bone scan, sputum cytology and haematological and biochemical profile. We also grouped the pts according to new TNM classification (seventh edition).

**Results:** A statistically significant difference was found in survival among the LD SCLC pts with (IA + IB), (IIA + IIB + IIIA) and IIIB stage (p < 0.001). Similarly, we found a statistically significant difference in survival in ED SCLC pts with (IA + IIB + IIIB) and IV stage (p < 0.001).

**Table 1. Survival according to the stage of the disease**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Number of patients</th>
<th>Median survival (days)</th>
<th>95% CI</th>
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<tr>
<td>Stage IA + IB</td>
<td>40</td>
<td>512</td>
<td>419.029–604.971</td>
</tr>
<tr>
<td>Stage IIA + IIB + IIIB</td>
<td>211</td>
<td>348</td>
<td>296.630–399.370</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>136</td>
<td>277</td>
<td>214.959–339.041</td>
</tr>
<tr>
<td>Stage IV</td>
<td>377</td>
<td>236</td>
<td>220.387–251.613</td>
</tr>
<tr>
<td>Total</td>
<td>764</td>
<td>286</td>
<td>270.474–301.526</td>
</tr>
</tbody>
</table>

**Conclusions:** A new classification of SCLC can be proposed which includes four stages based on TNM classification of NSCLC. (Stage IA+IB, (Stage IIA+IIB+IIIA), (Stage IIB) and (Stage IV)).
Results: ECOG performance status was related with both mean survival and disease-free survival time (respectively p=0.011 and p=0.044). 148 patients were grouped by using 1975 TNM and 2009 IASLC staging systems. According to survival analysis, disease-free survival was not related with stage but mean survival analysis revealed that stage 3 cases had significantly worse survival compared to stage 1 cases (p=0.005).

Conclusion: According to our results, survival was significantly worse in stage 3 patients and patients with poor performance status.

P4194 The role of pequi fruit (Caryocar brasiliense Camb) pulp oil, as a natural source of antioxidants, in experimental lung cancer
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Background: Caryocar brasiliense Camb, most known as pequi, is a Brazilian fruit that has high levels of antioxidants properties. The aim of this study was to evaluate the antioxidant activity of the pequi oil.

Methods: 18 male BALB/c mice was studied: 14 animals received by gavage 0.5g/kg/day of pequi oil (Control + CBCoil = 4) during 75 days. After 15 days, 10 mice received two doses of 1.5g/kg intraperitoneal of urethane (Urethane + CBC oil = 10). The other 4 animals were only submitted to the two doses of urethane (Urethane group = 4). After 75 days, these groups were sacrificed. An antioxidant activity of pequi oil was evaluated in the lung tissues by the biochemical TBARS test (Thiobarbituric acid-reactive substances) and DNA damage by the comet test method.

Results: The lung parenchyma from the Urethane groups without oil and with oil showed necrotic formations induced by the chemical carcinogenesis in contrast with Control + CBC oil group. The image analysis of the comet assay showed a statistical significant decreased of the DNA damage cells in the Urethane + CBC oil group when compared with urethane group. TBARS test showed a significant decreased of the lipid peroxidation in the Urethane + CBC oil group, similar as values of the Control + CBC oil, when compared with Urethane group.

Conclusion: We conclude that the different natural antioxidant components found in the pequi oil are efficient to diminish the oxidative stress status and the DNA function with statistically significant improvement in emotional and global health scales, mean value for each scale was calculated pre and post ablation. The paired t test was used to assess statistical significance of the results. This revealed statistically significant improvement in emotional function (p =0.023) and the global health scales (p = 0.008).

Conclusion: This retrospective study demonstrates that patients undergoing ablation therapy for primary and secondary lung cancer describe overall improved function with statistically significant improvement in emotional and global health scales.

P4195 Is surgical resection of M1a lung adenocarcinoma with metastatic pleural nodules really a useless choice?
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Introduction: Infections are important causes of morbidity and mortality in lung cancer patients. The myelotoxicity caused by the administration of either the chemotherapeutic regimens or the radiotherapy increases the risk of potentially life-threatening infection.

Methods: This prospective study included all patients with lung cancer who referred with signs or symptoms of infection between September 2009 and October 2011. Data concerning patient’s history, disease’s diagnosis, management and therapy’s signs, symptoms and documentation were collected.

Results: Seventy one patients with lung cancer were enrolled with febrile episodes and/or microbiologically or otherwise documented infection. Forty six patients (64.8%) presented with non-small cell lung carcinoma, while 22/71 patients (31%) and 3/71 patients (4.2%) had small cell lung cancer and mesothelioma respectively. Fifteen patients (21.1%) presented with FN and totally 43/71 (60.6%) patients required hospitalization for parenteral therapy upon admission. The predominant site of the infections was the lung in 59/71 patients (83.1%). In the hospitalized setting 3 episodes of bacteremia with Staphylococcus aureus were reported and microbiologically documented infections accounted for 26.7% of the hospitalized patients. The overall mortality rate was 9.8%, while only 1 patient died in the outpatient setting despite the antibiotic therapy.

Conclusion: This study showed that the early detection and control of infection in lung cancer patients receiving therapy may improve their survival. Recognition of predisposing factors for infections and possible therapy toxicities should be evaluated carefully.

P4196 Evaluation of quality of life in patients with primary and metastatic lung cancer following radiofrequency ablation
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Objective: Radiofrequency ablation (RFA) is an increasingly utilised treatment option for high risk patients with primary lung cancer and metastatic lung disease. We assessed quality of life in patients who were undergoing RFA for primary and secondary lung cancers at this institution in patients deemed unfit for surgical intervention.

Materials and methods: 55 patients, (42 primary lung cancer and 13 metastatic lung tumours) were entered into the study. One standard instrument was used to measure quality of life, the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30). An integrated system for assessing health-related quality of life of cancer patients. All procedures were performed by a single operator. All patients were clinically and radiologically followed-up in a standardised way, all questionnaires were collected by a single associate pre treatment and one year post ablation. Data was analysed using the Stata version 10 software.

Results: The EORTC scores were calculated for the six functional scales, the role, social, emotional, physical function, emotional functioning and global health scales, mean value for each scale was calculated pre and post ablation. There was a reported improvement in all four scales after ablation. The paired t test was used to assess statistical significance of the results. This revealed statistically significant improvement in emotional function (p =0.023) and the global health scales (p = 0.008).

Conclusion: This retrospective study demonstrates that patients undergoing ablation therapy for primary and secondary lung cancer describe overall improved function with statistically significant improvement in emotional and global health scales.
P4198 Determinants of relapse and survival in completely resected non-small cell lung cancer

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Introduction: Lung resection is the treatment of choice in Non-Small Cell Lung Cancer (NSCLC). Besides TNM staging, other features have been reported as significant prognostic factors.

Aim: To analyze factors affecting relapse and survival in NSCLC after complete resection.

Methods: A retrospective study was conducted, including patients with NSCLC completely resected in the last 12 years. Clinical and histological factors were assessed and its influence on survival free of relapse and overall survival was determined.

Results: 160 patients were included, 77.5% male and 22.5% female, with a median age of 65 years. Relapse occurred in 69 patients (median survival free of relapse - 56 months). At univariate analysis, an association was found between reduced survival free of relapse and age >62 years, clinical tumor size >4cm, clinical TNM stage >IB, clinical T1, clinical N0, pathological TNM stage >IB, pathological T2, pathological N0 and vascular invasion. At multivariate analysis, tumor size >4cm (p=0.004), pathological TNM stage >IB (p=0.023) and vascular invasion (p=0.024) were associated to a reduced survival free of relapse. 64 patients died (median overall survival – 112 months). At univariate analysis, an association was found between reduced overall survival and age >62 years, clinical tumor size >4cm, clinical TNM stage >IB, clinical N0, pathological TNM stage >IB, pathological T2, pathological N0, vascular invasion and poor differentiation of tumor. At multivariate analysis, only pathological TNM stage >IB (p=0.024) remained a poorer overall survival factor.

Conclusion: Besides TNM staging, other factors are important on relapse and survival and should be considered for adjuvant therapy.

P4199 Therapeutic options for operated adenocarcinoma patients in stages I or II

Anastasios Palamidas1, Stefan Krüger1, University Clinic RWTH, Aachen, Germany

Aim: To analyze factors affecting relapse and survival in NSCLC after complete resection.

Methods: A retrospective study was conducted, including patients with NSCLC completely resected in the last 12 years. Clinical and histological factors were assessed and its influence on survival free of relapse and overall survival was determined.

Results: 160 patients were included, 77.5% male and 22.5% female, with a median age of 65 years. Relapse occurred in 69 patients (median survival free of relapse - 56 months). At univariate analysis, an association was found between reduced survival free of relapse and age >62 years, clinical tumor size >4cm, clinical TNM stage >IB, clinical T1, clinical N0, pathological TNM stage >IB, pathological T2, pathological N0 and vascular invasion. At multivariate analysis, tumor size >4cm (p=0.004), pathological TNM stage >IB (p=0.023) and vascular invasion (p=0.024) were associated to a reduced survival free of relapse. 64 patients died (median overall survival – 112 months). At univariate analysis, an association was found between reduced overall survival and age >62 years, clinical tumor size >4cm, clinical TNM stage >IB, clinical N0, pathological TNM stage >IB, pathological T2, pathological N0, vascular invasion and poor differentiation of tumor. At multivariate analysis, only pathological TNM stage >IB (p=0.024) remained a poorer overall survival factor.

Conclusion: Besides TNM staging, other factors are important on relapse and survival and should be considered for adjuvant therapy.

P4200 Effect of statin therapy in patients with lung cancer on mortality, incidence of infections and pulmonary embolism

Stefan Krüger1, Annika Vehl, Angelika Haselhuhn, Dirk Frechen. Medical Clinic I, University Clinic RWTH, Aachen, Germany.

Background: Statins (S) have antiproliferative effects. Aim of this study was to assess whether S users with lung cancer (LC) had reduced risk of mortality, infections and pulmonary embolism.

Methods: We studied the association of S use in a retrospective study in 465 pts with first diagnosis of LC. The primary variables were stage and type of LC and S use at time of LC diagnosis and thereafter. During follow-up occurrence of death, infections and pulmonary embolism were recorded.

Results: 91 pts (19.6%) had S, 371 pts not. LC stages were I-IIIA 201 pts (43.2%), IB-IV 264 pts (56.8%). Pts with S were older (67.8±10.8 vs. 64.5±9.8 yrs, p < 0.005), had higher BMI, more often diabetes, myocardial infarction and coronary heart failure. Charlson comorbidity index was not different (5.2±2.2 vs. 5.7±2.4, p = 0.08). During follow-up 43% of the pts died. In Kaplan Meier analysis stage I-IIIA pts with S had lower survival compared with pts without S (log rank test, p=0.001). However there was no significant difference in pts stage IB-IV. In pts < 65 yrs. survival was longer in pts with vs. without S (1062 (95%CI 588-3977) vs. 604 (95%CI 513-806) days, p<0.05). In pts ≥ 65 yrs. there was no difference in survival (493 (95%CI 308-776) vs. 693 (95%CI 555-917) days, p=n.s.). Incidence of severe infections and pulmonary embolism were not different in pts with and without S.

Conclusions: Long-term S therapy seems to reduce mortality in younger LC pts < 65 yrs, but not in pts ≥65 yrs. In stage I-IIIA pts S are associated with worse survival, whereas there is no difference in stage IB-IV. S do not reduce the incidence of severe infections and pulmonary embolism at follow-up.

P4201 Anaerobic exercise decreases the progression of lung cancer in experimental mice

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Introduction: Lung cancer is one of the most incident neoplasms in the world rep- resenting the main cause of mortality for cancer. Studies have suggested evaluate the effectiveness of the use of the physical activity in the suppression, remission and reduction of the recurrence of tumors.

Objective: To evaluate the effects of aerobic and anaerobic physical activity in the development and the progression of lung cancer.

Material and methods: Lung tumors were induced with a dose of 3mg of Ure- thane/kg, in 67 male Balb -C type mice, divided in three groups: Group 1 - 24 mice treated with Urethane and without physical activity; Group 2 - 25 mice with Urethane and subjected to aerobic swimming free exercise; Group 3 - 18 mice with Urethane, subjected to anaerobic swimming exercise with gradual loading 5 to 20% of body weight. All the animals were sacrificed after 20 weeks.

Results: The median number of lesions (nodules and hyperplasia) was 3.0 for group 1, 2.0 for group 2 and 1.5 to 3 (p = 0.052). When compared only the presence or absence of lesion, there was a decrease in the number of lesions in group 3 compared with group 1 (p = 0.03) but not in relation to group 2. There were no metastases or other changes in other organs.

Conclusions: In this study, the anaerobic physical activity but not aerobic, diminish the incidence of experimental lung tumors.

P4202 Splenectomy inhibits tumor development and metastases in murine lung cancer models

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Introduction & Aims: It has been shown that inhibitors of the immune system (e.g. myeloid derived suppressor cells) reside in the spleen and inhibit the endogenous anti-tumor effects of the immune system. We hypothesized that excision of the spleen (splenectomy) can inhibit growth of relatively big tumors, and reduce metastases by modulating systemic inhibition of the immune system. Our long-term goal is to implement mechanisms elucidated in these studies into future clinical trials.

Methods: The clinical effect of splenectomy was evaluated in several murine lung cancer models. We compared immunological properties of blood and tumor after splenectomy or sham operation in tumor-bearing mice, using FACS analysis, RT-PCR and specific depletion studies.

Results: We found that splenectomy reduces tumor growth, can induce their regression, and decreases metastases. These effects disappeared in NOD/SCID mice. No significant changes in cell types were found in the blood. Splenec- tomy increased the percentage out of total tumor cells of neutrophils (2.4% vs. 4.9%, p=0.012), and macrophages (10.9% vs. 14.4%, p=0.014), which tended
to be less immunoinhibitory (non-M2/M2 macrophages ratio increased from 3.4 to 12.1, p=0.04). We further noted a tendency to increased activation of CD8+ CTL (19.2% vs. 30%, p=0.09). Tumor microenvironment was found to be more pro-inflammatory following splenectomy (e.g. upregulation of M1, TNF-α and IFN-γ). Using specific depletion of cells we evaluated the role of each cell in the effect of splenectomy.

**Conclusions:** Splenectomy inhibits the development of tumors and metastases in murine models of lung cancer, by changing the amount and characteristics of myeloid cells.

**P4203**

**Direct medical costs of lung cancer in Oran hospital**

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**Objective:** To analyse epidemiological profile of lung cancer and to evaluate expenses inherent in its diagnostic and therapeutic management.

**Methods:** Retrospective study of all cases of lung cancer notified during the period 2004-2008 in our chest clinic. Data concerning epidemiological characters and expenses which take into account, hospitalisation, diagnostic tests and treatment, were kept in an Epi-Info software package (Epi-info, version 6.0).

**Results:** Among 130 cases, 127 were studied. The mean age of our population was 66 years, age more than 50 years represented 80% of cases, 66.7% were male and 33.3% were female. Tobacco smoking concerned 91% of our patients. Thoracic pain represented 20.6% of cases and cough 13% of cases. Frequent localisation of lung cancer was right upper lobar 68% and tumboral extension represented 80% of cases. Histological predominant lung cancer was epidermoid carcinoma with 35% of case followed by adenocarcinoma with 15% of cases. Global cost of hospitalisation was of £157086.86 with a mean cost per patient of £1208.36.

**Conclusion:** Lung cancer management in hospital level remain problematic taken into account tobacco smoking threat and the higher expenses inherent in hospitalisation, diagnosis and treatment of the disease. The interest of a national plan against lung cancer is necessary to improve its management and to rationalize expenses.

**418. New biomarkers for lung cancer**

**P4204**

**Volatile organic compounds (VOC) in exhaled breath in patients with lung cancer, using the analytical technique thermal desorber-gas chromatography-spectrometer masses**

Javier Jareno Fernández,1 María Ángeles Muñoz Lucas,1 Belén Carrillo Aranda1, Jose Angel Maldonado Sana1, Concepcion Civera Tejada, Aníbal Aguilar Ros2, Gema Rodriguez Trigo3, Carlos Gutiérrez Ortega4, Jose Luis Alvarez Sala5, Luis Calló Sanchez5, 1Unidad Multidisciplinar de Investigación en Diagnóstico Precoz de Cáncer de Pulmón, Hospital Central del Defensor, Madrid, Spain; 2Química Física II, Facultad de Farmacia. Universidad Complutense de Madrid, Madrid, Spain; 3Farmacocinetica, Facultad de Farmacia. Universidad San Pablo CEU, Madrid, Spain; 4Neumología, Hospital Clínico San Carlos, Madrid, Spain

**Aim:** Oxidative stress is increased in lung cancer (LC) and generated volatile organic compounds (VOC). We can detect VOC in exhaled breath using the analytical technique TD/GC/MS. The determination of VOC, may be useful as a noninvasive screening in LC.

**Objective:** To determine differences in VOC present in the exhaled breath in 3 groups: LC group, COPD group and clinically healthy volunteers.

**Methods:** Case-control study with 81 patients with LC, 40 patients with COPD and 89 healthy volunteers (without respiratory disease). Informed consent accepted. Collection of exhaled breath by means BioVOC® to functional residual capacity

**Analytical technique:** TD/GC/MS (Markes-Agilent Tech.)

**Statistical analysis:** SPSS® v-15 for Windows.

**Results:** Description of the sample. Quantitative study and qualitative study of VOC

**Conclusions:** 1. Nonanoic acid is the only VOC with statistical significance between study groups: and it is independent of age and smoke custom. 2. The frequency probability to find nonanoic acid in LC group is higher than control and COPD groups 3. Nonanoic acid and beptanal could be useful to discriminate between LC + COPD patients versus LC without COPD patients.

**In our sample, nonanoic acid could be useful like a LC tumoulike marker. Supported by FIS: PI07/1116; Neumomadril 2008 and SEPAR 2010: PI-881.

**P4205**

**Retrospective study of treatment outcomes according to exon difference with EGFR mutations in non-small cell lung cancer patient in Korea**

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**Background/Aims:** EGFR mutations in NSCLCs are most important biomarker for EGFR-TKI treatment. About 90% of EGFR mutations are clustered in exons 19 (deletion) and 21 (point mutation at codon 858) and patients with these mutations have great response to EGFR-TKIs. However, the response rates of NSCLC to EGFR-TKIs according to types of EGFR mutation in Korea are still not cleared. This study aimed to evaluate the genomic types of EGFR mutation and compare the influence of each genomic types on the response to EGFR-TKIs and clinical outcomes in patients with NSCLC.

**Methods:** We reviewed medical records from January 2007 to August 2011, and classified genotypes of EGFR mutations which were done by direct sequencing methods. Mutation status was compared with clinicopathological features. Clinical outcomes were assessed based on EGFR genotypes.

**Results:** EGFR gene mutations were identified in 43(20.2%) out of 211 NSCLC patients. EGFR mutations were significantly more frequent in females than in males (37.1% vs. 13.4%, p < 0.001), but not correlated with smoking status (22.9% vs. 18.4%, p = 0.311). There are no significant differences between exon 19 deletion and exon 21 point mutation at cordon 858 in progression-free survival (10.9 vs. 9.1 months; p = 0.554), nor in overall survival (21.8 vs. 18.2 months; p = 0.142) and disease control rate (90% vs 85.7%; p = 0.669) with EGFR-TKI treatment.

**Conclusion:** PFS and overall survival were not significantly different between exon 19 deletions and Exon 21 L858R mutations, these results are similar to those of previous studies.

**P4206**

**Clinical significance and functional roles of FoxM1 in non-small cell lung cancer**

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**Purpose:** To test the role of FoxM1 in the metastasis of non-small cell lung cancer.

**Experimental design:** FoxM1 expression was examined in 175 NSCLC patients with or without nodal metastasis by immunohistochemistry. By lentivirus transduction, the role of FoxM1 in metastasis was also tested by in vitro methods using different NSCLC cell lines.

**Results:** In this study, the FoxM1 expression was found to be significantly associated with nodal metastasis and the cumulative 5-year survival rate. Thus, an increased expression of FoxM1 is the indicator of shortened survival and high risk of metastasis of NSCLC patients. Furthermore, we also found that increased FoxM1 expression could enhance the migratory and invasive abilities of lung cancer cells, while inhibition of FoxM1 expression could reduce the migratory and invasive properties of lung cancer cells, which are the two important parameters of metastasis biology. In addition, cells with high FoxM1 expression were presented with phenotypic changes reminiscent of EMT, which was further proved by the results of immunohotting with down-regulation of E-cadherin and ZO-1 uptake regulation of N-cadherin and Vimentin.

**Conclusion:** These results suggested that FoxM1 plays an important role in lung cancer metastasis and elevated FoxM1 expression could be used as an indicator of poor prognosis and high risk of metastasis of NSCLC patients.

781s
Alterations of serum inflammatory biomarkers in the healthy and lung cancer patients before and post chemotherapy

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Introduction: Only 20% of lung cancer patients could be early diagnosed with surgical treatment. Due to the high cost, it is not practical to apply CT scan and pathological biopsy for lung cancer as regular screening tools even in high-risk population. A simple but sensitive and specific assay used for lung cancer diagnosis and prognosis is warranted.

Methods: Serum samples from 55 subjects including healthy people and patients with NSCLC (30 with adenocarcinoma and 13 with squamous cell carcinoma) were collected to measure 40 inflammatory mediators by multiplexed cytokine immunosassays. All patients have completed follow up for up to two years. A series of systematical computational analysis was applied.

Results: The set of 17 cytokines (such as IL-9, CXCL10, CXCL10, etc.) prefers to recognize adenocarcinoma samples from pool of the population, while the set of 2 cytokines (MSFp and IL-29) prefers to recognize squamous cell carcinoma samples. The decision trees based on these two kinds of biomarkers can both achieve about 80% accuracy in leave-one-out cross-validation. Cytokines like CXCL5, CXCL10 and CXCL16 were also found to play important roles in cancer survival.

Conclusions: This pattern of inflammatory mediators might be useful for cancer diagnosis, prognosis and evaluation of chemotherapy effects. The results of clustering of five CEPINs supported the adopted chemotherapy is effective for NSCLC patients.

This study was supported by National Basic Research Program of China (973 Program) No. 2012CB933300.

Anti-tumorigenic effect of age-diabetes-related advanced glycation end-products in lung carcinoma

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Background: Clinopathological studies indicated that lung carcinoma progression is impaired by advanced age and diabetes, which are either characterized by an excess accumulation of advanced glycation end-products (AGEs). AGEs result from the non-enzymatic reaction of sugars with proteins in the body and in foods. Therefore, our study aimed at the effect of AGEs on the non-small cell lung carcinoma (NSCLC) progression.

Methods: AGEs were quantified by detecting the AGE fluorescence in plasma samples of NSCLC patients prior to surgery. Experimentally, the tumor effect of circulating AGEs were quantified by detecting the AGE fluorescence in plasma samples from NSCLC patients of whom elevated AGEs were found to be associated with higher serum OPN levels compared to patients with low levels (25% vs. 47% 5-year-survival, P=0.011). In this regard, in vitro studies showed a lower sphereoid formation of NSCLC cells in the presence of AGE-modified plasma than non-modified plasma. 

Conclusion: The plasma AGE level has prognostic relevance for NSCLC patients, in which the tumor growth-inhibiting effect of circulating AGEs might play a critical role.

Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer

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Introduction: Previous studies that were based primarily on small numbers of patients suggested that certain circulating proinflammatory cytokines may be associated with lung cancer; however, large independent studies are lacking.

Methods: Associations between serum interleukin 6 (IL-6) and interleukin 8 (IL-8) levels and lung cancer were analyzed among 123 case patients. Associations between biomarkers and lung cancer were estimated using logistic regression models adjusted for smoking, stage, histology, age, and sex. The 10-year standardized absolute risks of lung cancer were estimated using a weighted Cox regression model.

Results: Serum IL-6 and IL-8 levels in the highest quartile were associated with lung cancer (IL-6, odds ratio [OR] = 2.89, 95% confidence interval [CI] = 1.28 to 6.23; IL-8, OR = 2.46, 95% CI = 1.02 to 4.12) and with lung cancer risk (IL-6, OR = 1.93, 95% CI = 0.87 to 2.36; IL-8, OR = 1.62, 95% CI = 1.36 to 2.48), compared with the lowest quartile. Increased IL-6 levels were only associated with lung cancer diagnosed within 2 years of blood collection, whereas increased IL-8 levels were associated with lung cancer diagnosed more than 2 years after blood collection (OR = 2.03, 95% CI = 1.05 to 2.73). The 10-year standardized absolute risks of lung cancer were highest among current smokers with high IL-8 and CRP levels (absolute risk = 7.46%, 95% CI = 4.52% to 10.25%).

Conclusions: Although increased levels of both serum IL-6 and IL-8 are associated with lung cancer, only IL-8 levels are associated with lung cancer risk several years before diagnosis.

Clinical significance of serum osteopontin levels in lung cancer

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Background: Osteopontin (OPN) is a multifunctional glycoprotein associated with lung cancer (LC) via several pathways including tumour angiogenesis.

Aims and objectives: The aim of our study was to investigate possible associations between serum levels of OPN in patients with LC and clinicopathological variables, VEGF and MMP-9 levels and overall survival.

Methods: We enrolled 51 patients (mean age 66.8±8.8 years) with primary LC and 10 healthy control subjects. 43 patients were ever smokers and 8 non-smokers. 12 patients had SCLC and 39 NSCLC (18 squamous, 16 adenocarcinoma and 5 NSCLC-NOS) with stage I-II/III/IV. 19/29 patients. Serum levels of OPN, VEGF and MMP-9 were measured by ELISA.

Results: Patients with LC had statistically significantly higher serum OPN levels than controls (45.9[10.5-266.8] vs 16.6[8.29.8] ng/ml, p<0.0001). ROC analysis showed that for OPN levels >25.8 ng/ml, sensitivity for detection of LC was 88.5% and specificity was 86.7%. OPN levels were also found to be significantly lower in non-smokers (p=0.019) and in older patients (p=0.026). Moreover, patients with squamous LC had statistically significantly higher OPN levels compared to patients with adenocarcinoma. Additionally, patients with serum OPN levels lower than median value (<45.9 ng/ml) had significantly better overall survival than those with higher levels (524 days vs. 306 days, p=0.01) and a 1-year survival rate of 80% vs. 37%. Finally, OPN levels were positively associated with VEGF levels (p=0.44, p=0.001).

Conclusions: OPN levels were increased in patients with LC, and higher levels were correlated with worse survival, thus suggesting a possible diagnostic and prognostic value of OPN in patients with LC.

Investigation of survivin gene polymorphism in non-small cell lung cancer patients (NSCLC)

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Introduction and aim: Survivin gene is one of the first reported inhibitors of apoptosis proteins (IAPs), which is an important family of proteins that regulate apoptosis. A common polymorphism at the survivin gene promoter (-31 GC) has been shown to influence survivin expression and the risk for cancer development.

Purpose of this study reports, relation between Turkish population who have survivin polymorphism and NSCLC also; its relevant with diseases’s development and prognosis.

Methods: 146 NSCLC cases and 98 healthy control cases who were diagnosed at Yedikule Chest Diseases and Chest Surgery, Training and Research Clinical third center were included in this study. Pulmonary function test and routine bio-chemical analysis were done for all voluntaries. PCR-RFLP technique was used for genotyping.

Results: Genotype distribution of Survivin gene’s -31GC region were detected (n=146) %77.4 GC (n=113), % 18.5 GC (n=27), %4 CC (n=6); at patient group and (n=98) % 6.1 GC (n=56), %47.5 GC (n=34), %46.4 CC (n=8); % (p=0.003), at control group: -464 TC region were detected (n=146) %40.4 TT (n=59), %48.6 TC (n=71), %11.0 CC (n=16); at patient group and (n=98) %55.1 TT (n=54), %40.8 TC (n=40), %41.1 CC (n=4) (p<0.031), at control group; -644T/C region were detected (n=146) %40.4 TT (n=59), %.48.6 CC (n=71), %11.0 CC (n=16); at patient group and (n=98) %55.1 TT (n=54), %40.8 TC (n=40), %41.1 CC (n=4) (p<0.031), at control group; -844 T/C region were detected (n=146) %40.7 TT (n=58), %45.9 TC (n=71), %11.0 CC (n=16); at patient group and (n=98) %57.1 GC (n=56), %32.7 GC (n=32), %10.2 CC (n=10) (p=0.484) at control group.

Conclusion: These results show that Survivin gene’s -31 GC polymorphism causes predisposition to lung cancer development in Turkish population.
Cox regression analyses (tumor size (P<0.01)). Higher pre-surgery serum PlGF levels were significantly associated with larger tumors (P<0.001). Within lung cancer patients compared to COPD patients and healthy controls, 0.645, 1.192 and 1.628 respectively. There was a negative correlation between stage and HO-1 activity.

Conclusions: HO-1 activity is reduced in patients with lung cancer and correlates with disease severity, suggesting its protective effect as an antioxidant enzyme. These findings may propose a role of agents stimulating HO-1 as a novel therapeutic approach in lung cancer.

P4213
Increased serum placenta growth factor level is significantly associated with progression, recurrence and poor prognosis of lung cancer
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We recently expressed the presence of placenta growth factor (PlGF) in lung cancer specimens is correlated with the progression and prognosis. In this study, serum samples were obtained from 72 patients with lung cancer and from 30 normal control cancer specimens is correlated with the progression and prognosis. In this study, serum samples were obtained from 72 patients with lung cancer and from 30 normal control group.

Results: Serum PlGF levels were significantly higher in lung cancer patients than in normal controls (9.1±10.7 vs. 10.1±4.5, P<0.001). Serum PlGF levels dropped to near the normal control levels after surgical cancer removal. Higher pre-surgery serum PlGF levels were significantly associated with larger tumors (P<0.014). Overall response rate was 85.7% in EGFR mutation positive, 32.9% in EGFR mutation negative and 31.5% in patients with COPD and healthy nonsmokers controls.

Methods: IS was conducted according to a standard protocol. HO-1 levels were measured in IS supernatant by a bilirubin reduce-dependant reaction using bilirubin as end product.

Results: Subjects (31 with lung cancer, 29 with COPD and 30 healthy non-smokers) underwent IS and HO-1 level measurements. Mean HO-1 levels were significantly (p<0.001) lower in lung cancer patients compared to COPD patients and healthy controls.

Conclusion: Our study demonstrates that higher serum PlGF levels are associated with larger lung cancers.

P4214
Epidermal growth factor receptor mutation status in advanced non-small cell lung cancer: A single institution experience
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Background: Lung cancer is a leading cause of morbidity and mortality worldwide, resulting in substantial economic and social burdens that are constantly increasing. There is a strong correlation between inflammation and oxidative stress and malignant transformation. Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that plays a central role in the defense against oxidative stress. HO-1 has anti-inflammatory, anti-proliferative and anti-apoptotic properties and is involved in the regulation of immunological balance in a wide range of lung diseases, including lung cancer.

Conclusions: HO-1 activity is reduced in patients with lung cancer and correlated with disease severity, suggesting its protective effect as an antioxidant enzyme. These findings may propose a role of agents stimulating HO-1 as a novel therapeutic approach in lung cancer.

P4215
Role of progestrin releasing peptide (ProGRP), a serum based biomarker in early diagnosis of SCLC in cohort of high-risk patient presenting with symptoms related to lung cancer
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Lung cancer has become the top killer among malignant tumors in China during past three decades. Mortality rate of lung cancer are about 23 times and 13 times higher in current male and female smokers compared to lifelong nonsmokers. An estimated 350 million people smoke in China. Early diagnosis of lung cancer and more significantly Small Cell Lung Cancer (SCLC) is a major challenge.

In the present study we analyzed serum samples of 144 high-risk patients using a serum based biomarker panel comprising of CEA, CYFRA 21-1, SCC, and ProGRP. These patients visited our service, during June 2011 to January 2012 with symptoms related to lung cancer. The average age of patients was 64.14±8.59 years. Total 92 patients were diagnosed with lung cancer (73 NSCLC, 16 SCLC, 3 unknown), 44 patients were diagnosed of non-malignant tumors while 8 patients had unknown clinical diagnosis of the lesion. The final diagnosis was based on pathology results.

Conclusion: Increased serum ProGRP in patients diagnosed with SCLC. The mean ProGRP conc. in patients with SCLC was 3731 pg/mL compared to the mean value of 33 pg/mL for patients with NSCLC and 54 pg/mL for patients with non-malignant tumors. The results showed that ProGRP can be used to identify patients that may have SCLC with a simple blood test on the same day which can lead to early diagnosis of SCLC by histological method and hopefully better prognosis. This test may also improve the differential diagnosis and selection of therapeutic approach for the patient.

This study was supported by National Basic Research Program of China (973 Program) No. 2012CB933300.

P4216
Investigation of a relationship between NF-KBIA gene polymorphism and non small cell lung cancer (NSCLC)
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Nuclear factor kappa b (NF-κB) is defined as a protein family. NF-κB (IkBα) is inhibitory of NF-κB transcription factor. It binds NF-κB transcription factor and blocks carrying NF-κB factor to nucleus and binding to DNA. NF-κB (IkBα) is a gene that contains six exons and locates in q413 chromosomal region. Purpose of study reports relation between Turkish people who have NF-κBIA gene polymorphism and NSCLC.

Method: 99 lung cancer cases and 99 healthy control cases who were diagnosed in our hospital included in the study. PCR-RFLP technique was used for genotyping.

Results: Genotype distribution of NF-κBIA gene’s relevant region were detected (n=99) 17.2% AA (n=17), 48.5% AG (n=48), 34.3% GG (n=34) at patient group and (n=99) 21.2% AA (n=21), 45.5% AG (n=45), 33.3% GG (n=33) at control group.

783s
Lung cancer (LC) has high morbidity and mortality rates. Today, research in biomarkers is a hot topic, and among these, the least frequently studied, are those of the metabolomics field.

Our aims are to present preliminary data using metabolomics techniques for the detection of differentiated patterns between patients with LC and non-lung cancer (NLC) patients, to obtain an effective screening method.

We obtained blood, urine, and bronchoalveolar lavage (BLA) samples from a group of patients who underwent bronchoscopy, for further analysis through mass spectrometry methods. These techniques provide us with metabolic fingerprinting, allowing the study of the metabolites involved in the process.

Identification of the resultant metabolites was performed through mass-mass fragmentation procedures. Guided by mass spectrum, the results where processed by Partial Least Squares Discriminant Analysis. We compared the results from both groups.

Initially, 7 LC patients and 7 NLC subjects' samples were included. We found differences in metabolite profiles among these groups, allowing us to differentiate between LC and NLC cases. Including the blood and urine samples, we were able to identify potential overexpressed markers, such as choline, phosphocholine, and propionylcarnitine, leaving analysis of BLA samples results pending.

In conclusion, both groups showed different metabolomics profiles in the analyzed samples, this allows for its statistical discrimination.

The preliminary data raises the possibility of further studies that will allow the development of early screening techniques.

Increased levels of plasmatic dopamine in human small cell lung cancer

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Dopamine (DA) is a monoamine neurotransmitter with pleiotropic effects that exerts an immunomodulatory action. Inhibition of proliferation and cytotoxicity of CD4+ and CD8+ T cell. In human malignancies increased plasmatic DA levels are documented. In addiction recent reports also indicate an active production of DA by some human tumor cell lines. Small cell lung cancer (SCLC) is a very aggressive neuroendocrine human tumor able to produce several molecules with neuroendocrine effect. Actually no data are available about DA plasmatic levels in patient affected by SCLC.

Aim of this study is to assess plasmatic DA levels in SCLC patients in comparison with non-small cell lung cancer (NSCLC) and healthy subjects and to correlate this data with the plasmatic levels of neuron specific enolase (NSE).

Before treatment whole blood was collected from patients affected by lung cancer (n=50; SCLC n=15; NSCLC n=35), healthy subjects (n=10), and plasma was separated to assess its DA content by High Performance Liquid Chromatography (HPLC).

DA levels are significantly increased in patients affected by SCLC comparing with NSCLC [102.5 ± 18.3(SEM) vs 52.3 ± 5.8(SEM); p < 0.05] and with healthy subjects [102.5 ± 18.3(SEM) vs 38.9 ± 13.5(SEM); p < 0.05]. In SCLC patients these increased levels are inversely correlated with the NSE plasmatic values (r = -0.5; p < 0.05).

The data here presented show increased plasmatic DA levels in SCLC patients comparing with NSCLC and healthy subjects. Further studies are needed to assess if this increased plasmatic levels represent an active ectopic secretion of DA by SCLC and if this may exerts a possible role in the tumor growth.

Potential angiogenic biomarkers in patients with non small cell lung cancer: Possible implications

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To date, no single agent has gained a sufficient prognostic significance for NSCLC patients. So, there is an urgent need for new innovative biomarkers in NSCLC. The present study was designed to: 1) Evaluate the role of Nitric Oxide (NO), Sialic Acid (SA) and Glutathione S-Transferase (GST) as prognostic indicators in NSCLC. 2) Correlate the above parameters levels with the clinicopathological status of the patients.

The study included 30 patients with newly diagnosed histopathologically confirmed NSCLC, as well as 10 healthy volunteers with matched age and sex as controls. Blood samples and lung tissue biopsies were taken from all subjects on admission and after chemotherapy with and without Nimesulide (Cox-2 inhibitor).

Results: Serum and tissue levels of NO, SA and GST activities were significantly higher in NSCLC patients compared to controls. These levels decreased significantly after chemotherapy (specialy if Cox-2 inhibitors were added). The serum and tissue levels of the studied parameters decreased significantly in the responders compared to resistant cases.

In conclusion, NO, SA, besides GST correlated significantly with the clinicopathological status of NSCLC patients and are considered cheap sensitive prognostic biochemical indices.
Ki67 expression was studied by immunohistochemistry techniques. We used the Chi square test to analyze the differences in the Ki67 expression between the squamous cell carcinoma and adenocarcinoma and a bivariate analysis to study the prognostic significance of Ki67 expression according to the 5 years survival using the Wilcoxon-Gehan (W-G) test and the log rank (L-R).

Results: We included 146 patients, 91% were men with a median age of 67 yo. 99 were squamous cell carcinoma, 37 adenocarcinoma and 10 large cell carcinoma. The Ki67 expression was positive in 56% cases, negative in 42% and no valid in 2%. The Ki67 positive expression found in the different types of NSCLC is shown in Table 1 and the prognostic significance of Ki67 expression, in NSCLC and its different types, is shown in Table 2.

Conclusion: In the population studied, the Ki67 expression was higher in the squamous cell carcinoma and was associated with a bad prognosis.

P4223

Increased activity of Lyn tyrosine kinase causes multiple chronic obstructive pulmonary disease-like changes in mouse

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Lyn is a member of the Src family of tyrosine kinases and it was first discovered to be an key regulator of B cell activation. There are many studies now showing that Lyn also plays a role in the progression of myelodysplastic syndromes and several types of epithelial cancer. The Lyn gain-of-function ( Lyn up/up) mutant mouse was created to investigate putative proto-oncogenic roles of Lyn. Lyn up/up mice develop chronic lung inflammation and emphysema at young age. The extent of alveolar airspace enlargement in the Lynup/up model mouse is more severe than any other gene-targeted or smoke-induced mouse model of emphysema to date. Chronic lung inflammation, characterised by increase in macrophages, neutrophils and T cells and reduced number of alveolar wall macrophages and osteopetrosis in COPD patients were also observed in Lynup/up mice. Lung tumors have also been found in some aged animals although penetrance is low. Histological assessment of lungs in the Lyn up/up mice suggest that alveolar epithelial cells are hyperplastic and there were a lack of blood vessels formation around the alveoli. There is also reduced numbers of apoptotic cells in the lung as detected by TUNEL assay. This suggests that alveolar airspace enlargement is not a result of emphysematous destruction caused by chronic inflammation but a possible attribute of perturbed signaling in endothelial and epithelial cells that needs further investigation. The complex process that leads to the occurrence of emphysema together with lung cancer is still not understood. The Lyn up/up mouse will be an excellent model to investigate the underlying co-determinant of the two seemingly opposite outcome of lung disease.

P4224

Genetic polymorphisms of k-ras gene in smoking related diseases

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Ras is a family of genes that have many biological functions but mainly control cell growth and development. Chemicals in cigarette smoke cause mutation in ras gene. Smoking causes lung cancer because the carcinogen bind strongly to the precise site in k-ras gene. Our aim of the study is to detect genetic polymorphism of k-ras gene in smoking related disease.

The study included 50 patients, 20 with chronic obstructive pulmonary disease (COPD), 20 with lung cancer and 10 normal subjects. All patients and normal subjects were smokers. Serum samples were evaluated. DNA was extracted and mutational analyses performed using a PCR assay. Two (10%) out of 20 COPD patients and four (20%) out of 20 lung cancer patients had mutated k-ras gene, while there was no mutation in the control group. The mutation of k-ras gene was associated with smoking history, severity of COPD and cell type of lung cancer. Mutations were observed in heavy smokers in COPD (13.3%) and lung cancer (22.2%) patients. Moderate (14.3%) and severe (12.5%) obstruction in COPD patients were associated with mutations. All k-ras mutations were observed in non small cell lung cancer (NSCLC (95%)).

In conclusion, k-ras mutation is detected in the lung cancer and COPD patients suggesting that COPD patients were in the early stages of developing cancer. For COPD patients the ras gene might be a biomarker for cancer as a screening of DNA in serum using a noninvasive technique.
Poor treatment outcomes have been reported for tuberculosis (TB) patients harbouring strains resistant to isoniazid and rifampicin (multidrug resistance or MDR-TB), fluoroquinolones and/or second-line injectable drugs. We undertook a meta-analysis for response to treatment using individual data for MDR-TB patients whose strains had additional resistance to fluoroquinolones (MDR-TB+FQ), second-line injectables (MDR-TB+Inj) or both (extensive drug resistance; XDR-TB) including demographic and clinical details, treatment regimens, and outcomes. 26 centres provided data for 424 MDR-TB+Inj, 1192 MDR-TB+Inj, 405 XDR-TB, and 4776 other MDR-TB patients susceptible to FQ and Inj. Success was lower in MDR-TB+FQ (adjusted OR=0.6 [95%CI 0.5-0.7]) and XDR-TB patients (0.4 [0.3-0.6]) than in those with MDR-TB+Inj (0.8 [0.7-0.9]) and those with MDR-TB and no additional resistance (reference). No single drug was significantly associated with treatment success in MDR-TB+FQ and XDR-TB patients. In XDR-TB patients, success was highest if at least 6 drugs were used in the intensive phase (4.9 [1.4-16.6]) and 4 in the continuation phase (6.1 [1.4-26.3]). Study results suggest that regimens of a similar duration to those recommended in MDR-TB patients but containing more drugs achieve better results in XDR-TB patients. As all data in the analysis were from observational studies, bias may be substantial and better quality evidence will be needed to guide the optimization of regimens.

### Conclusion

Algorithms are needed for identifying patients suitable for treatment of MDR-TB. DOTS PLUS ensures both correct regimens with access to all active second line drugs; fluoroquinolones and/or second-line injectable drugs present a serious challenge to TB treatment programmes. In 2006, the World Health Organization (WHO) started DOTS PLUS in 20 countries, with 1-3 cases. In countries with more than half the cases in 2006, the World Health Organization (WHO) started DOTS PLUS in 20 countries, with 1-3 cases. In countries with more than half the cases in 2006, the World Health Organization (WHO) started DOTS PLUS in 20 countries, with 1-3 cases.

### References

- **Introduction:** The MDR programme to the West Coast Winelands area consists of impatient treatment centres and an outreach programme, for treatment of patients in the community.
- **Objective:** To compare baseline demographic and culture conversion rates among patients initiating MDR-TB treatment in the community versus those initiated as inpatients.
- **Methods:** We retrospectively reviewed clinical records at the impatient Centre of patients diagnosed between 2000 – 2006 with a first episode of MDR-TB. Patients were included if started on a regimen with 3 or more second-line anti-TB drugs (SLD), came from this area and had a bacteriological confirmed diagnosis. From diagnosis to treatment initiation and from initiation to culture conversion were determined, and demographic and clinical indicators at baseline.
- **Results:** 502 patients were diagnosed with new MDR-TB, among which 324 (64.5%) started on SLD. Median age was 34, with 105 females (32%). 45/342 (45%) started in the community vs. 179 (55%) as inpatients. Inpatients and community-based were similar in baseline age and AFB result; but inpatients were more likely to be female (40% v. 23%; p<0.01), and had lower weights (47.3 kg v. 53.3 kg; p<0.01). Inpatients had a longer time to treatment initiation (76 v. 64 days; p<0.01). Of 172/545 (31%) who converted, 96 (54%) were inpatients and 76(145/52%) community-based. Days to conversion were also similar between the two groups: community 121 (Q1 61-206.5) and inpatient 105 (Q1 64.5-164).
- **Conclusion:** Algorithms are needed for identifying patients suitable for treatment of MDR-TB.

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**DOTS PLUS versus non DOTS PLUS outcomes in MDR-TB patients**

Aim: To assess the impact of DOTS PLUS strategy on cases registered in Iasi, Romania in 2007-2010.

Method: Comparative analysis of MDR-TB characteristics, treatment regimens and outcomes.

Conclusions: Treatment outcomes in DOTS PLUS group were significantly better.

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**Aminoglycoside ototoxicity monitoring in multidrug resistant tuberculosis:**

**How much is enough?**

Aim: To evaluate the use of frequent audiometric assessments in MDR-TB patients receiving extended-duration aminoglycosides and to describe their influence on hearing.


Conclusions: DOTS PLUS ensures both correct regimens with access to all active second line drugs and regular drug supply; it is an opportunity for proper management of MDR-TB cases.
4281 Adverse effects of moxifloxacin during tuberculosis treatment

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Aim: Prolonged use of moxifloxacin in tuberculosis (TB) may have adverse effects, particularly prolongation of the QT interval and arrhythmias.

Methods: All TB patients treated with moxifloxacin from 2003-2011 were identified. Concurrent medication and history of drug abuse were noted. Charts noted adverse effects. ECGs were obtained on and off treatment and the longest QTc was used for the study.

Results: 93 patients treated with moxifloxacin for at least one month were identified. Adverse effects included: nausea (2), palpitations (1) and photosensitivity (1); itching, arthralgia, flushing and depression were probably due to concurrent medication. 60 patients had ECGs, mostly taken during treatment and none had a QTc >500 ms. Variability in QTc was high (standard deviation 31 ms). One male had a QTc >450 ms and 3 females >470 ms but none had arrhythmias; one patient developed right bundle branch block during treatment, but this persisted when not taking moxifloxacin. All 4 used opiates.

Code Sex Pre-treatment QTc's (ms) QTc's during treatment (ms)
8.078 M 441, 424, 444, 476 430, 472, 479
6.104 F 421, 446, 451, 456, 460, 471, 455, 476, 484, 476
9.045 F 415, 419, 460, 482 456
9.129 F 404, 409, 439, 480, 480, 490, 492

28 patients had paired ECGs on and off treatment showing a QTc interval increase of 6.4 msec (95% CI -4.2 to 17.0 msec). Five increased by 69, 51, 48, 44 and 28 patients had paired ECGs on and off treatment showing a QTc interval increase of 9.129 F 404, 409, 438, 450, 480, 373, 426, 429, 439, 480, 490, 492.

Conclusions: Moxifloxacin is well tolerated in treating TB. ECGs should be obtained at baseline and periodically, with particular attention to the QT interval.

4293 Short term glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: "REDUCE", a non-inferiority multicenter trial

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Background: The optimal dose and duration of systemic glucocorticoid therapy for acute exacerbations of COPD (AECOPD) is unknown. In this trial, we aimed to demonstrate non-inferiority of 5 days vs 14 days of systemic glucocorticoids with respect to COPD exacerbation.

Methods: Patients admitted to hospital with AECOPD were randomized to receive prednisolone-equivalent daily for either 5 or 14 days in a placebo-controlled fashion. Follow-up was 180 days. The primary endpoint was time to exacerbation.

Results: Of 721 evaluated patients, 327 underwent randomization, and 304 completed the study. Mean age was 63.9±23.2 years; mean FEV1%predicted 51.5±14.3% and 60.8% were male. Exacerbations occurred in 36.8% and 38.4% of patients in the 5 day and 14 day treatment arms, respectively (p=0.81). Time to exacerbation did not differ between groups in the intention-to-treat and per-protocol analyses (hazard ratios for the short treatment arm, 0.92 (95% CI, 0.64 to 1.34; p=0.67) and 0.91 (95% CI, 0.63 to 1.32; p=0.62); respectively); nor did time to death or the combined endpoint of exacerbation and/or death, with both hazard ratios for the short treatment arm being <1 as well. With respect to the primary outcome, short treatment was not inferior to conventional treatment, since the 95%-confidence intervals did not include the predefined non-inferiority threshold of 1.515.

Conclusion: In AECOPD, 5-day treatment with systemic glucocorticoids is non-inferior to 14-day treatment with regard to re-exacerbation during 6 months of follow-up.

4292 Adverse reactions during treatment of multidrug-resistant and extensively drug-resistant tuberculosis

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Introduction: Treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is often complicated by adverse reactions.

Objectives: To describe the adverse reactions, time of occurrence, attitudes and risk factors among MDR/XDR-TB patients.

Methods: Retrospective cohort of all patients with MDR/XDR-TB evaluated at the Regional Referral Center for MDR/XDR-TB in northern Portugal from July 2009 until January 2012.

Results: We analyzed 29 patients, 19 (65.5%) men, mean age 48 years. Eighteen (62.1%) had co-morbidities of which HIV infection was the most frequent (8 patients). Twenty-two patients (75.9%) had adverse reactions and 17 (77.3%) had to suspend the drug involved. Median time to occurrence of adverse reactions was 94 days (min=2, max=619). Toxicity related to the injectable drug was the most frequent - 9 (31%) with ototoxicity, and 7 (24.1%) with renal insufficiency. Hypothyroidism was present in 6 (20.7%) of the patients. Psychiatric disorders, associated to Cicloserine occurred in 6 (20.7%) patients. Multivariate analysis could not identify independent risk factors in relation to adverse reactions. The occurrence of adverse reactions was not associated with a higher risk of death or a worse outcome.

Conclusions: The occurrence of adverse reactions more often correlated with the injectable drug and occurred around the third month. We could not identify independent risk factors for adverse reactions and they did not affect the outcome.

4294 Relationship between exacerbation frequency and survival post MI in COPD patients

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COPD patients are at increased risk of myocardial infarction (MI).1 Particularly after an exacerbation. 2 COPD patients have shorter survival post MI compared with patients with infrequent exacerbations (IE).

All COPD patients with a first MI between 1/1/03 and 31/12/08 as recorded in the MINAP, who had no previous evidence of MI in GPRD or MINAP were included. Patients under 35, not registered with GPRD at the time of MI, or with less than 1 year of follow-up before their MI were excluded. Exacerbations were defined using pre-defined READ codes and prescription of pre-specified antibiotics and/or steroids. FEV1 had ≥ 2 exacerbations in the year preceding MI and IE <2. Data were provided by the CALIBER group at UCL. The primary outcome was death after MI. Cox proportional hazards models were used to adjust for potential confounders. 1063 patients were identified with a first STEMI or NSTEMI. 111 (10.4%) FE and 952 (89.6%) IE. The unadjusted mortality rate in MI was 285.7 deaths (95% CI 222.3-367.2) per 1000 person years and in IE 152.4 deaths (95% CI 138.1-168.1) per 1000 person years. Adjusting for confounding by smoking and gender and stratifying by age, mortality was greater in FE compared to IE; HR 1.61 (95% CI 1.23-2.11); p<0.001. Mortality was greater in patients who exacerbated in the 2 months preceding the MI; HR 3.88 (720-76 550); p<0.001.

Conclusions: FE have shorter survival after a first MI than IE. There appears to be an association between timing of exacerbations, exacerbation frequency and survival after 1st MI.
References:

4295 The impact of airway infection on cardiovascular risk during COPD exacerbations
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Arterial stiffness, a validated measure of cardiovascular risk, increases from stable COPD to exacerbation (Patel et al, ERS 2011). We hypothesised this increased cardiovascular risk was mediated by airway infection.

We measured aortic pulse wave velocity (aPWV) in the stable state, at exacerbation and during recovery at 3,7,14 and 35 days thereafter. Infective exacerbations were defined by a potentially pathogenic microbe (PPM) in exacerbation sputum by culture or positive PCR for *H. influenzae, S. pneumoniae, M. catarrhalis*, or human rhinovirus.

Differences in the area under the curve (AUC) adjusted for stable aPWV level between groups were compared by unpaired t-test.

55 COPD patients (32 male, 11 current smokers) had a mean±SD FEV1 of 1.14±1.4L (46.7±18.5% predicted) and FEV1/FVC ratio 0.46±0.14. Two-thirds of them (36/55, 65%) produced a sputum sample at exacerbation. Two-thirds of these events (24/36, 67%) had an identifiable PPM. Patients with an infective exacerbation had a greater rise in arterial stiffness from stable state to exacerbation (1.4±1.7ms-1 vs 0.4±1.0ms-1, p=0.050).

Arterial stiffness was also higher during the recovery period in those with an infective exacerbation (AUC 37.4±8v 37.1±9.5ms-1days, p=0.036).

The increase in arterial stiffness during COPD exacerbations appears to be driven by airway infection and may explain the association between these infective events and increased cardiovascular risk.

4296 Evaluation of multiple admissions of COPD patients: European COPD audit
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Background: Patients with multiple admissions represent an especially at risk population with therapeutic and prognostic implications. The European COPD Audit is a clinical audit to evaluate clinical practice variability, clinical and organisational factors related to outcomes for COPD admissions across Europe (422 hospitals from 15 European countries). The current presentation aimed at evaluating multiple admission patients and their clinical features and outcomes.

Methods: The study comprised a first 8-week phase during which all consecutive cases admitted to hospital due to an exacerbation of COPD were identified and information on clinical practice and outcomes was gathered. During the 90-day follow-up second phase mortality and readmissions were sought. Multivariate odds ratios (OR) were calculated to evaluate factors associated with multiple admissions.

Results: Data on 14,456 cases are reported, of which 6,821 (47.2%) were the first admission (countries range 29.3-74.5%). Patients characteristics associated with multiple previous admissions were current smoker (OR 0.69), FEV1 value (OR 0.99), and PO2 value (OR 1.003). Health care proved to multiple admission patients was different in terms of chest x-ray not done (OR 2.03), methylxanthines use (OR 1.2), antibiotic use (OR 0.78), diuretics use (OR 1.16) and use of NIV (OR 1.11). Reports at discharge tended to have a higher use of theophylline (OR 1.23), oxygen (OR 1.8) and mechanical ventilation (OR 1.5). We also found an impact on readmission rate (OR 0.4).

Conclusions: Multiple admission patients represent a different type of COPD patient admitted to hospital, with a more severe disease requiring more resources.

4297 Emergency oxygen use and monitoring in the pre-hospital and acute hospital setting – The significance of a common problem
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Introduction: Evidence shows that oxygen (O2) can cause decompensated type 2 respiratory failure (T2RF) increasing morbidity and mortality in COPD patients.

Aim: To review pre-hospital and emergency hospital use of O2 in COPD patients.

Methods: All COPD admissions in January 2011 to Worcester Royal Hospital were audited against BTS guidelines.

Results: Ambulance documentation showed no record of previous NIV or O2 alert card. There is no box to record FiO2 on the ambulance data form. O2 dose (51.6%) and mask (48.4%) recordings were suboptimal. 60% of patients were given 28% venturi masks and 13.3% non-rebreather masks. 45.8% of patients were given O2 with adequate saturations (sats). 72% of patients given O2 had sats > 92%.

In hospital, 9.5% of clerking charts contained a history of prior NIV. 2/3 of patients with adequate sats were given O2. 80% of those on O2 had sats above 92. 36.7% of patients had O2 prescribed with 45% having correct sats ranges. 15 patients had T2RF: 5 with sats > 92%. 3 patients met the criteria of NIV: all had sats > 92%.

Mean length of stay (LOS) was 6 days longer in those who had NIV. 90.5% of discharge letters did not contain an ABG result.

Conclusions: There is still a major issue with O2 use and monitoring in COPD patients. Patients are being given too much oxygen, it is not reviewed and documented accurately. This causes increased morbidity and cost, evidenced by those with hyperoxia developing T2RF and longer LOS. We recommend the ambulance data form includes an FiO2 box, O2 prescription is mandatory, documentation is improved and discharge letters include an ABG. Doctors, nurses and paramedics should all be regularly educated in O2 therapy.

4298 An audit of inpatient mortality and readmission rates in acute exacerbation of COPD – Exploring the role of comorbidity and inflammatory markers
Aisha McClintock-Tiongco, Arjun Patel, Jindruni Chakravarty, Acute Medical Unit, St. George’s Hospital, London, United Kingdom

Acute exacerbations of COPD is the cause of rising admissions and burden on resources in spite of systems to minimise inpatient stay and facilitate discharge. The system of reimbursements in the UK NHS, penalises hospitals for readmission within 30 days. Understanding the factors leading to early readmission may help to focus resources.

We audited inpatient records of 577 (female = 260) episodes in 12-months till Dec’11. Age, co-morbidities, length of stay (LOS), readmission rate, time to readmission, white cell count and C reactive protein were collected. 218 episodes with >1 admission, 47% readmissions within 30 days; and 20 inpatient deaths. Age 69 (±11) yrs men & 72 (±12) yrs women, p=0.02. The LOS was 6(±2) days men & 7 (±3) days women. 34 patients had >1 associated co-morbidity. Standard mortality was 35/1000 admissions.

Patients who died were older than (76±8 vs 70±11 yrs, p = 0.03) had higher (WCC 26.2±26 vs 12.7±9.8, p <0.01), CRP 79±100 vs 44±57 g/l, p = 0.01). A higher LOs was predicted by (WCCmax Lin reg coef B 0.118, p=0.05) and age (Spearmans r 0.19, p<0.001). Time to readmission was not predicted by any of the above parameters.

Inpatient mortality and LOS were predictably correlated with age and raised inflammatory markers. Nearly half of the patients were readmitted within 30 days, which would lead to morbidity and a loss of revenue. Yet, none of the common factors were found to predict the ‘risk of’ or ‘time to’, readmission. Therefore, future prevention of admission strategies may need to include telemedicine, monitoring at home and frequent flyrer clinic visits.

4299 Differences between men and women COPD admissions: Evidence from the European COPD audit
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Introduction: Studies using administrative data from N America provide conflicting results for gender survival differences in COPD (Machado 2006, Gonzalez 2011). We used clinician collected data to look at Hospital and 90 day survival following admission with COPD exacerbation.

Method: The European audit programme collected retrospective data from clinical case notes and telephone enquiry from 15,821 patients admitted between October
Acute exacerbation of COPD is associated with three-fold elevation of cardiac troponin T. Machado Am J Respir Crit Care Med 2006;174:524. Gonzalez Thorax 2011;66:38. These data suggest women exhibit different COPD characteristics and have a higher mortality when admitted to hospital.

Determinants of exhaled NO in a population of subjects with different respiratory symptoms – Results from the Swedish GA2LEN survey

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The fraction of exhaled nitric oxide (FeNO) is a marker of steroid-sensitive airways inflammation and is used in asthma management. The Asthma Control Test (ACT) is one of the most used instruments to assess control in asthmatic subjects. The evidence for a relation between airways inflammation and asthma control is inconclusive so far. The aim of the present study was to assess the relation between FeNO and ACT score in treated, stable asthmatic children.

Within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS), measurements of FeNO and specific IgE against aerosol allergens or food allergen mix were done in 165 asthmatic children (101 boys aged 10-18 years). Among the children, 79% (79/101) were positive against aerosol allergens and 61 (40%) tested positive against food allergens. Uncontrolled asthma (ACT score <20) was confirmed in 53 children.

FeNO levels in subjects with uncontrolled asthma (n=53) were approximately 30% higher than in subjects with controlled asthma (n=112): 19.8 ppb (15.5, 25.3) vs 15.1 ppb (13.1, 17.4), p=0.04. FeNO was a determinant of asthma control in logistic regression models both before (p=0.01) and after adjustments for gender, age, BMI, FEV1, IgE sensitisation to Aero- or food allergens (p=0.04). Furthermore, a significant relation between asthma control and FeNO could be found when using absolute values of the ACT score (p=0.016, p=0.004). In conclusion, increased FeNO in treated, stable asthmatic children relate to uncontrolled asthma. It has to be further studied if intensified anti-inflammatory therapy in these subjects would lead to improved asthma control.

Exhaled biomarkers to assess airway inflammation

Modeling of exhaled nitric oxide in relation to smoking history – A population based study

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Smokers produce less NO in central airways compared to nonsmokers whereas the effect of smoking on NO concentration in the peripheral alveolar regions remains unclear, particularly if axial diffusion of NO is considered. It is also unclear to what extent exhaled NO recover among ex-smokers. We have measured exhaled NO (FeNO) at three flow rates in a population sample of 3968 subjects and the aim of the present analysis has been to try and clarify effects of current and previous smoking on exhaled NO and its central and alveolar origin and to provide reference equations for exhaled NO for healthy smokers.

The essential findings are 1) FeNO of ex-smokers and nonsmokers are indistinguishable, 2) the apparent association between FeNO and time since smoking is considerably lower than the corresponding limit of normal healthy nonsmokers. 3) The association is considerably lower than the corresponding limit of normal healthy nonsmokers.

Exhaled nitric oxide levels predict uncontrolled asthma in children – Results from the MIDAS-study

Increased exhaled nitric oxide levels predict uncontrolled asthma in children

FeNO is a common method to assess airways inflammation. Determinants of FeNO have neverthless mostly been studied in the healthy general population. Therefore, we studied determinants of FeNO in a large population of subjects with respiratory symptoms that may reflect the type of patients seen in clinical practice. FeNO was measured in 1018 subjects with asthma, sinusitis, asthma and sinusitis, or symptoms suggestive of asthma but without fulfilling the asthma diagnosis criteria, aged 17-76 years (median 45 yrs).

Female gender, current smoking and having both parents smoking during childhood were related to lower FeNO while increased height, age, atopy and asthma diagnosis were related to higher FeNO, both before and after adjustments for variables given in Table.

In conclusion, constitutional factors, such as male gender, increased height and age, are related to increased FeNO in subjects with respiratory symptoms. They should be accounted for in clinical practice as their effect size is comparable to the effect of diagnosed asthma. Parental smoking during childhood was related to decreased FeNO and this warrants further studies.

Modeling of exhaled nitric oxide in relation to smoking history – A population based study

Smokers produce less NO in central airways compared to nonsmokers whereas the effect of smoking on NO concentration in the peripheral alveolar regions remains unclear, particularly if axial diffusion of NO is considered. It is also unclear to what extent exhaled NO recover among ex-smokers. We have measured exhaled NO (FeNO) at three flow rates in a population sample of 3968 subjects and the aim of the present analysis has been to try and clarify effects of current and previous smoking on exhaled NO and its central and alveolar origin and to provide reference equations for exhaled NO for healthy smokers.

The essential findings are 1) FeNO of ex-smokers and nonsmokers are indistinguishable, 2) the apparent association between FeNO and time since smoking is considerably lower than the corresponding limit of normal healthy nonsmokers. 3) The association is considerably lower than the corresponding limit of normal healthy nonsmokers.
Tanya Kralimarkova

Acute effect of inhaled corticosteroid on exhaled breath temperature in asthmatic patients

The first author is receiving an ERS Long Term Fellowship.

Conclusions: Both nNO and FENO are useful screening tests for PCD: using the composite score nNO * FENO < 7.1 ppb had a sensitivity of 92.6% and a specificity of 93.1% for a sensitivity of 92.0% from nNO measurement alone.

Figure 1. Normalized data from 5 eNoses based on different concentrations of ethanol.

Rationale: Breath analysis by electronic nose (eNose) technology represents a promising diagnostic tool in lung disease. A critical step in making this technology suitable for multi-centre trials, such as the U-BIOPRED Study, is to facilitate centralized measurements on multiple eNoses simultaneously. This can be accomplished with a (semi)-automatic measurement and control platform.

Methods: Ethanol was chosen as one of the calibration gases. Different concentrations (500 ppb-8 ppm) were generated by a permeation system. Measurements at all concentrations were done in duplicate. Total number of sensors in the platform was 81. The obtained data were processed by averaging duplicate measurements after normalisation (scale 0-1).

Results: The platform (not all individual sensors) was sensitive to ethanol at used concentrations (Fig. 1). The difference in normalized sensor deflections between duplicate measurements at 2 ppm was (mean [SD], range): 0.09 [0.1], 0.55-0.0004.

Conclusion: The eNose platform is capable of detecting ethanol at concentrations from 500 ppb to 8 ppm level with acceptable repeatability.

Implication: This method of platform calibration with standard gases is feasible and mandatory for quality control of eNose assessments in a multi-centre setting.

Do volatile organic compounds discriminate between eosinophils and neutrophils in vitro?

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Inflammation associated oxidative stress leads to peroxidation of polysaturated fatty acids thereby generating volatile organic compounds (VOCs) excreted in exhaled air. The purpose of the present study is to examine whether specific VOCs are associated with eosinophilic and neutrophilic inflammation, and thus offers the possibility of noninvasive monitoring of both asthma inflammatory phenotypes.

Methods: Eosinophils and neutrophils were isolated from 27ml blood of 16 healthy non-smokers by gradient centrifugation using lymphoprep. Eosinophils were isolated from neutrophils by immunomagnetic cell separation (MACS) using anti-CD16. The average absolute number of eosinophils and neutrophils upon isolation was 3.5 x 10^6 and 19.4 x 10^6 respectively. Cells were incubated in RPMI at 37°C and activated with phorbol 12-myristate 13-acetate (100ng/ml). Headspace air was sampled at time 0', 30', 60' and 90' by introduction of ultra-pure nitrogen in closed flasks at a flow rate of 200 ml/min during 10 min. The air was pushed onto a cartridge and the total amount of trapped VOCs (volatile) was analysed by time-of-flight GC-MS.

Results: From the 2005 compounds present in the volatome, those present in at least 8% of the samples (1123 compounds) were used for further analysis. Discriminant analysis (SPSS statistics 19) showed that 5 VOCs were able to distinguish between both culturing types with 100% and 96% correct classification in original
and cross-validated set respectively. Chemical identification of the compounds is ongoing and these are potential candidates to check in asthmatic patients for their possible diagnostic value in asthma phenotyping.

442. Paediatrics and sleep apnoea/adults and upper airway stimulation

4309 Childhood obstructive sleep apnoea and elevated blood pressure: A longitudinal follow-up study
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Background and objective: Childhood obstructive sleep apnoea (OSA) is a prevalent condition, and is associated with raised blood pressure (BP) in cross-sectional studies. This study aimed to investigate if baseline or changes in OSA severity could predict BP changes over a 4-year period.

Methods and results: Children who participated in our previous OSA prevalence study were invited to undergo repeat overnight sleep study and ambulatory 24-hr BP monitoring at 4-year follow-up. One hundred and ninety-one (62% out of 306) subjects took part in this follow-up study. Children with baseline moderate-to-severe OSA (OAI>55) had significantly higher BP at follow-up than controls. The change in OAI was positively associated with the changes in wake and sleep systolic BP. Path analysis revealed a best-fit model in which log-transformed baseline OAI and change in OAI were both independent predictors for change in sleep systolic BP, after adjusting for baseline sleep systolic BP, gender, height and body mass index z score.

Conclusions: In the first longitudinal study that examined the relationship between OSA and BP in children, we found baseline OSA severity could predict systolic BP at 4-year follow-up. One hundred and ninety-one (62% out of 306) subjects took part in this follow-up study. Children with baseline moderate-to-severe OSA (OAI>55) had significantly higher BP at follow-up than controls. The change in OAI was positively associated with the changes in wake and sleep systolic BP. Path analysis revealed a best-fit model in which log-transformed baseline OAI and change in OAI were both independent predictors for change in sleep systolic BP, after adjusting for baseline sleep systolic BP, gender, height and body mass index z score. Early diagnosis and intervention should thus be advocated in the management of childhood OSA.

4310 Adipokines in obese children and adolescents with sleep-disordered breathing
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Background: Sleep-disordered breathing (SDB) is prevalent in obesity. It has been linked to the metabolic syndrome. Possible mechanism is intermittent hypoxia of the fat tissue and alterations of adipokine secretion.

Aim: This study looked into the effects of intermittent hypoxia on adipokine levels before and after weight loss treatment.

Methods: Obese children and adolescents between 10-18 years were included while entering an inpatient weight loss treatment program. All patients had 2 visits: baseline and after 4-6 months of treatment. Leptin, adiponectin, TNF-alpha and IL-6 were determined at both visits and a sleep screening was performed at baseline. Mean nocturnal saturation correlated with leptin (r=0.19; P=0.02) and adiponectin (r=0.17; P=0.04). IL-6 correlated with oxygen desaturation index (r=0.20; P<0.02). TNF-alpha levels were not linked to sleep parameters. After weight loss 19% of subjects with SDB at baseline that participated in the follow-up study had residual SDB. Average weight loss was 29%. Correlation analysis did not show associations between improvements in sleep parameters and improvements in adipokines. These were mostly linked to a lowering in BMI z-score.

Conclusion: In an obese pediatric population SDB was linked to changes in the fat tissue and alterations of adipokine secretion.

4311 Prevalence of obstructive sleep apnea syndrome in obese children (NANOS study)
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Introduction: The most common cause of Obstructive Sleep Apnea Syndrome (OSAS) in children is the adenotonsillar hypertrophy. The prevalence of OSAS in obese children is unknown.

Methods: Aim: To determine the prevalence of OSAS in pediatric obese population.

Methods: Cross-sectional, prospective, multicenter study. The children included in the study came from general population of Spain, randomly selected, of both sexes between 3 and 14 years and body mass index (BMI) greater than or equal to percentil 95 for age and sex. Medical history, snoring and Chervin questionnaires were performed in all children included, as well as, physical examination, nasopharyngoscopy, polysomnography (PSG) with Co2 recording and blood tests.

For the assessment of the sleep stages and respiratory events, the criteria of the AASM (2007), were used. The diagnosis of OSAS was made if the apnea hypopnea index per hour of sleep (AHI) was ≥ 3.

Results: 247 children were included: 135 males (54.7%), age from 4 to 14 with an age mean of 10.82 years (SD: 2.71). The mean BMI and the mean BMI Percentile were 28.01±4.72 and 96.82±0.59 respectively. Of the 247 children studied, 122 of them (50.4%), reported the presence of snoring. The mean AHI was 5.60±9.91. 99 children were diagnosed with OSAS, so the prevalence of OSAS was 40.1% (95% CI 33.8%-46.4%). The prevalence showed no statistically significant differences based on age or sex. The correlation between AHI and BMI was directly and significantly (r = 0.150, p = 0.018).

Conclusions: The prevalence of OSAS in obese children from general population is high 40.1%. Obese in children suggests a possible risk factor for developing OSAS.

Funded: SEPAR and Mutua Madrileña.

4312 Results of a new questionnaire to assess sleep problems in childhood
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Screening of sleep disorders in children is of high importance. In Hungary there is no standardized questionnaire for assessing sleep problems. We evaluated the results of sleep quality scales of our questionnaire and compared the data of healthy and clinical population. We analyzed the correlation between our questionnaire and validated tests and the severity of obstructive sleep apnea (OSA).

Our questionnaire is designed to estimate sleep hygiene and quality in two age groups (6-14 and 15-18 yrs.) by nighttime and daytime symptoms score. Two groups of children were analyzed: 1. healthy group (n=2020), 2. children with sleep problems (n=66). The second group filled out two validated tests, Modified Pediatric Epworth Sleepiness Scale (MP-ESS), Conner’s Rating Scales-Revised (CRS-R) and underwent polysomnography. Severity of OSAS was characterized by Apnea-Hypopnea Index (AHI) and Oxygen-Desaturation Index (ODI).

Children underwent polysomnography had significantly higher score both on nighttime and daytime symptoms scale than healthy children. Correlations were: score of nighttime symptoms scale and CRS-R score (r=0.441; p=0.001), score of daytime symptoms scale and MP-ESS score (r=0.389; p=0.001). Children in the highest quartile of nighttime symptoms scale had significantly higher AHI (mean±SD: 0.62±1.07 vs. 5.97±1.19; p=0.04) and ODI (mean±SD: 0.49±0.53 vs. 6.23±12.07; p=0.02) than children in the lowest quartile. The nighttime and daytime score index had higher sensitivity to predict OSA than other tests.

Our questionnaire can be potentially useful in evaluating sleep problems in children and give more information about sleep problems than other tests. However validation of the questionnaire is still needed.

4313 Long-term response of upper airway stimulation in obstructive sleep apnea
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Background: Previous studies identified patient selection criteria for therapy success in Upper Airway Stimulation (Inspire Medical Systems, USA) for treatment of moderate-to-severe OSA in patients intolerant to continuous positive airway pressure. The current study reported therapy response at 12-months post-implant in subjects who met selection criteria.

Methods: Among 34 implanted subjects, 18 met criteria for responder and 16 did not. AHI (Level 1 monitoring) were measured at 12 months. All patients were
monitored for device-related adverse events and patients met selection criteria for therapy response during over-night PSG.

**Results:** There were no device malfunctions or un-anticipated device-related adverse events from 6-12 months. Among patients who met selection criteria and for which data are available, the AHI reduction was maintained at 12-month. Improvement for ESS and FOSQ were also observed in these subjects from baseline to 6 months. One patient had an unusual long and thick uvula and the third one had no special features.

**Conclusion:** The current study has demonstrated that Upper Airway Stimulation to treat OSA has a sustained therapy efficacy at 12-month post-implant in a selected group of moderate-to-severe OSA subjects.

**4314 Targeted hypoglossal neurostimulation (THIN) to treat obstructive sleep apnea (OSA): A one year safety and efficacy trial**

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Patients with severe OSA non-compliant to CPAP need an alternative treatment. We performed a one-year safety and efficacy study of a new therapy using unilateral stimulation (THIN).

The system was implanted in 13 (12 males) out of 14 patients aged 50±10 years, with an average AHI of 20 and one patient an AHI of 22 at one year. Three patients were considered as failures: one patient had predominantly central apnea and an implanted morphine pump, one patient had an unusual long and thick uvula and the third one had no special features.

There were no serious adverse events. Three electrodes failures in two subjects led to treatment interruptions. One patient had his IPG replaced due to malfunction, and there was one twiddler phenomenon.

We performed a one-year safety and efficacy study of THIN, using unilateral stimulation.

The main efficacy outcomes were the apnea-hypopnea index (AHI), the 4% oxygen desaturation index (ODI) and the movement arousal index (MAI). Diagnostic data showed AHI 45±19, ODI 29±20 and MAI 37±13. The Total Sleep Time (TST) was 414±85 min. After one year, AHI was 2±16, ODI 15±16, and MAI 25±14, all p<0.001, with unchanged TST (406±60 min). Nine patients reached AHI < 20 and one patient an AHI of 22 at one year. Three patients were considered as failures: one patient had predominantly central apnea and an implanted morphine pump, one patient had an unusual long and thick uvula and the third one had no special features.

**Conclusion:** THIN is safe and efficient in most OSA patients.

**4315 Analysis of arousability of upper airway stimulation in obstructive sleep apnea**

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**Background:** Previous studies showed that electrical stimulation of the hypoglossal nerve (N XII) can improve obstructive sleep apnea (OSA). In this study we looked to the effect on the different arousals indices in both responders and non-responders.

**Methods:** Upper Airway Stimulation (Inspire Medical Systems, Inc) systems were implanted in moderate-to-severe OSA patients who failed, or were intolerant of CPAP. The system is intended to reduce sleep apnea by stimulating the N XII to advance the tongue-base. AHI (events/hr), Micro Arousal Index (MAI, events/hr), total number of arousals and respiratory arousals were collected using lab-based PSG in 7 patients including comparison of responders (n=4) vs. non-responders (n=3) at baseline (pre-implant) and 6-M post-implant. All arousal indices decreased statistically significantly in responders and there was no stimulation disturbance seen in the non-responder group.

**Conclusion:** Upper Airway Stimulation to treat OSA has a clear therapy efficacy at 6-M post-implant in a selected group of moderate-to-severe OSA subjects and that there is no arousal effect of the stimulation itself. It confirms the non-arousal effect of N XII stimulation as shown in our earlier pilot study (Arch Otalaryngol Head Neck Surg 2001;127:1216-23).

**4316 Regional differences in characteristics of patients referred to European sleep centers. Results from the European Sleep Apnea Database (ESADA)**

Teresa Sagarese1, Marisa Bonsignore, Ludger Grote, Jan Hedner, Walter McNicholas, Josep Montserrat, Thomas Penzel, Renata Raha, Pawel Slominski, Jan Zielinski, Dept. of Pulmonary Diseases, Turku University Hospital, Turku, Finland

The ESADA contains multiple information from patients with suspected OSA at 22 European sleep centers. We analyzed regional differences in characteristics of 551 OSA patients. Centers were grouped into the following regions: NORTH (Friede, NOR – Gothenburg, SWE – Turku, FIN), SOUTH (Barcelona, Càceres, Lleida, ESP – Milan, Palermo, ITA – Haifa, ISR), EAST (Klaipeda, LTU – Kosice, SVK – Prague, CZE – Riga, LAT – Warsaw, POL – WEST (Dublin, IRL – Edinburgh, GBR) and CENTRAL (Antwerp, Brussels, BEL – Berlin, Giessen, GER – Paris, FRA).

Mean age was 51.8 (12.6) years in the cohort and females were slightly older than males. The highest and lowest prevalence of obesity (BMI>30) was found in the WEST and NORTH regions, respectively. The sleep study technique varied between regions, with the NORTH reporting more than 99% cardiorespiratory polygraphy compared with only 34% in the EAST. Sleep apnea severity varied between regions and the proportion of male patients with severe sleep apnea (AHI>30) was 23% in the NORTH compared with >40% in all other regions. Less than 50% of all patients reported severe daytime sleepiness (ESS>10), the highest ESS was found in patients in the WEST, the lowest scores in men in NORTH and women from EAST centers. Sleep length was 7.0 (1.8) hrs in women and 6.8 (1.6) hrs in men, and was shorter in the SOUTH compared with all other regions. No systematic regional differences were detected in frequency of comorbidities.

The data shows considerable regional differences between patients referred to European sleep centers, suggesting an influence of local referral patterns and/or phenotypic traits in Europe.

**443 Novel mechanisms of acute lung injury**

**4317 On the effectiveness of steroids in acute lung injury: Experimental separation of inflammation and hypoxemia**

Lucy Kathleen Reiss, Stefan Uhlig, Institute of Pharmacology and Toxicology, Medical Faculty of RWTH Aachen University, Aachen, Germany

Acute lung injury (ALI) is defined by hypoxemia in the presence of excessive inflammation. Despite of a multitude of clinical trials the role of glucocorticoids in the treatment of ALI is under constant debate. The present study was designed to investigate the effectiveness of dexamethasone in dependence on the type and severity of lung injury and the fraction of inspired oxygen (FiO2).

C57Bl/6 mice were instilled intratracheally with 50 μL HCl at pH 1.5 or 1.8 and were then ventilated with recruitment manoeuvres (RM) and FiO2=0.3 or 1.0. Another group was ventilated without acid instillation and without RM to induce atelectasis. Dexamethasone [1mg/kg] was injected intravenously at the beginning of ventilation. Lung mechanics were followed by the forced oscillation technique. Cardiovascular parameters, oxygen saturation and body temperature were monitored. Blood gases, cytokines, neutrophil recruitment, microvascular permeability and lung histology were examined.

Dexamethasone attenuated acid-induced lung injury (neutrophil recruitment, edema formation, cytokine liberation) in all models. Hypoxemia and lung mechanics were improved in the groups instilled with acid pH 1.8 (moderate injury), but in the groups instilled with acid pH 1.5 (severe injury) or in those with atelectasis. A high FiO2=1.0 augmented acid-induced lung injury, but did not affect the effectiveness of dexamethasone.

The present study starkly were highly effective in preventing inflammation under all conditions, whereas they improved the clinical outcome in moderate, but
not in severe lung injury or in cases of derecruitment, suggesting that steroids are effective only in a subclass of patients with ALI.

Alastair Proudfoot1,2, Charlotte Summers1, Timothy Jackson1, Matthew Hind1,2, Mark Griffiths1,2, 3 Adult Intensive Care Unit, Royal Brompton Hospital, London, United Kingdom; 2Critical Care, National Heart and Lung Institute, Imperial College, London, United Kingdom; 3Respiratory Medicine, University of Cambridge, Cambridge, United Kingdom

Activation and migration of neutrophils into the lung is a central factor in both the onset and progression of acute lung injury (ALI). The assessment of neutrophil biology and trafficking in the lung is fraught with methodological pitfalls. Human ex vivo ALI models could provide a tractable platform with which to investigate neutrophil trafficking in the lung. Human lungs from brain dead donors (N=3) were cold preserved and transferred for leukocyte quantification by flow cytometry. Lung tissue was harvested for wet:dry ratio or processed to a single cell suspension for leukocyte recruitment (cells/g dry lung mass) also tended to be reduced.

Figure 1. CT image of LPS injured lung at 4 hours.

Figure 2

Further characterisation of this novel model allied with established methodology in pulmonary neutrophil trafficking will provide a powerful tool to investigate neutrophil biology in human ALI.

4319 Sphingosine kinase-1 and sphingosine-1-phosphate promote the development of acute lung injury in pneumococcal pneumonia
Bjoern Gutbier1, Stefanie M. Schönrock1, Rainer Haberberger2, Andreas C. Hocke1, Stefan Schröder1, Anja Luth1, Burkhard Kleuser1, Wilhelm G. Bertrams1, Kolja Szymanski1, Katrin Reppe1, Holger C. Müller-Redetzky1, Bernd Schmoeck1, Manfred Andratsch1, Timothy J. Mitchell1, Hartwig Schünke1, Konstantin Mayer1, Norbert Suttorp1, Martin Wittenrauth1, Capneth Study Group2, 3, Dept. of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin, Berlin, Germany; 1Institute of Anatomy and Histology, University of Innsbruck, Austria; 4Molecular Pneumology, Philipps University, Marburg, Germany; 5Dept. of Physiology, University of Innbruck, Austria; 6Glasgow Biomedical Research Centre, University of Glasgow, United Kingdom; 7Medical Clinic II, University of Giessen and Marburg Lung Center, Giessen, Germany; 8Capneth, Stiftung, Hannover, Germany

Pneumonia may evoke acute lung injury. Basal plasma levels of sphingosine-1-phosphate (S1P) contribute to vascular integrity. Pulmonary S1P, mainly synthesized by sphingosine kinase-1 (SphK1), regulates inflammatory mechanisms. We have therefore investigated the impact of high fat diet-induced obesity on VILI in mice. Male C57BL/6 mice were fed high fat diet for a minimum of 13 weeks, resulting in a mean body weight 30% greater than lean age-matched controls. Animals were anaesthetised and ventilated with high-stretch, standardised as plateau pressure (Pplat) 35-37cmH2O. Tidal volumes were similar between groups (mean ±SD; n=5 per group; *p<0.05 by ANOVA).

<table>
<thead>
<tr>
<th>Pplat increase (cmH2O)</th>
<th>pO2 decrease (mmHg)</th>
<th>Wet dry ratio</th>
<th>Neutrophils (&gt; 107)</th>
<th>Monocytes (&gt; 106)</th>
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<td>Lean</td>
<td>6.0±0.4</td>
<td>111±39</td>
<td>6.5±0.74</td>
<td>120±6.4</td>
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<tr>
<td>Obese</td>
<td>–1.4±1.7</td>
<td>37±29</td>
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Mean±SD; n=5 per group; *p<0.05 by ANOVA.

Conclusion: High fat feeding attenuates pneumonia oedema and lung dysfunction

4320 Z antitrypsin polymerization is associated with enhanced pulmonary inflammation
Sum Alam1, Zhenjun Li1, Sabina Jancauskiene2, Ravi Mahadeva1, 3Department of Medicine, University of Cambridge, United Kingdom; 3Department of Pulmonology, Hannover Medical School, Hannover, Germany

Severe antitrypsin (AT) deficiency due to polymerization of the Z variant is the commonest genetic cause of emphysema. There is variability in the development and progression of emphysema even in Z-AT homozygotes. We postulated that episodes of pulmonary inflammation could induce polymerization of AT protein thereby further reducing the anti-protease protection. 8 Transgenic mice for human Z-AT (Z-mice) and M-AT (M-mice) received 10μg of intrapulmonary LPS. BALF and lung homogenates (LH) were assessed for lung injury and inflammation. Z-mice had more pulmonary PMNs (d1, BALF 71±3x104 cells (mean(SEM)) vs. 52±4, p<0.004; d3, 6±1.5x104 vs. 4.5±0.24, p<0.001; d7, 7.1±0.51 vs. 5.7±0.29, p=0.03). Z-mice had more pulmonary PMNs-d1, BALF 71±3x104 (cells) vs. 52±4, p<0.001; BALF 490±391 ng/ml vs. 261(285-220), p<0.001. Z-mice had a higher concentration of 8-isoprostane (8-IP) and free NE in BALF compared with M-mice; 8-IP (Z vs. M), d1, 6.5±0.4 vs. 4.5±0.24, p<0.001; d3, 7±0.51 vs. 5.7±0.29, p=0.03. Z-mice had more pulmonary PMNs-d1, BALF 71±3x104 cells (mean(SEM)) vs. 52±4, p<0.004; d3, 6±1.5x104 vs. 4.5±0.24, p<0.001; BALF free NE, d1 (Z vs. M), median(IQR) 436(436-316)ng/ml vs. 213(245-113), p=0.001. ELISA and immunoblot revealed that LPS instillation in Z-AT mice led to the development of oxidized-polyamers of Z-AT, which further reduces the anti-elasticity protection and nullifies the anti-inflammatory effect of AT. This data suggests a molecular mechanism whereby infective excursions could further inactivate Z-AT and contribute to the faster decline in lung function in PZ ZZ individuals. This may explain some of the heterogeneity of the lung disease in these individuals.

4321 Obesity induced by high fat feeding attenuates ventilator-induced lung injury in mice
Joanne Pétrie1, Michael Wilson, Brijesh Patel, Kieran O’Dea, Masao Takata.
Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College, London, United Kingdom

Background: Retrospective analysis of Intensive Care data suggests that obesity may confer a survival advantage in Acute Lung Injury (ALI). Development of ventilator-induced lung injury (VILI) is a major determinant of ALI mortality. We have therefore investigated the impact of high fat diet-induced obesity on VILI in mice. Methods: Male C57BL/6 mice were fed high fat diet for a minimum of 13 weeks, in a mean body weight 30% greater than lean age-matched controls. Animals were anaesthetised and ventilated with high-stretch, standardised as plateau pressure (Pplat) 35-37cmH2O. Tidal volumes were similar between groups (mean ±SD; n=5 per group; *p<0.05 by ANOVA).

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Mean±SD; n=5 per group; *p<0.05 by ANOVA.
4324
Resident alveolar macrophages mediate early alveolar epithelial death signaling and dysfunction
Brijesh Patel, Michael Wilson, Masao Takata. Anesthesiology, Pain Medicine, and Intensive Care, Chelsea and Westminster Hospital, Imperial College London, United Kingdom

Acute lung injury (ALI) is characterized by alveolar epithelial dysfunction. We previously showed that early epithelial dysfunction was specifically mediated through tumor necrosis factor (TNF) p55 receptor signaling [1]. This study examined the contribution of resident alveolar macrophages (AM) to this phenomenon following acid aspiration.
C57Bl6 mice were treated intratracheally with liposomes containing either clofibrate or PBS. After 48 hours, they underwent intratracheal instillation of hydrochloric acid followed by mechanical ventilation to assess respiratory parameters. Oxygenation, respiratory elastance, alveolar TNF concentration, lung capsaicin-8 activity and alveolar fluid clearance (AFC) were measured at 90 minutes after acid instillation. Clofibrate liposomes induced an 80% depletion of AMs. AM depletion significantly improved the deterioration in respiratory elastance (cM2O/s: PBS=0.06±0.008; CLOD=0.05±0.004; p<0.05) and PaO2:FiO2 ( PBS=304±372; P=0.05), along with attenuated lung capsaicin-8 activity (arbitrary units: PBS=1476±5466; CLOD=7135±372; P<0.01), and improved AFC (%/30min: PBS=3.8±2.6; CLOD=7.1±2.4; P<0.05). Caspase-8 activity showed an inverse correlation to AFC (Pearson r=−0.766; P<0.0001) implying epithelial death receptor activation. These data suggest that during ALI induced by acid aspiration, epithelial dys- function and hypoxemia are a result of epithelial cell death receptor activation by alveolar macrophage-derived TNF. Supported by Wellcome Trust.

Reference:

445. “Life’s a gas”: aspects of respiratory gas exchange

4329
The influence of carboxyhemoglobin (COHb) generation on measured total lung diffusion capacity
Evgeny Babarskov1, Evgeny Stepnov2, Yury Shulagin3, Alexander Cherniak1, Zaubeck Aisanov1, Alexander Chuchalin1. Respiratory Physiology, Pulmonology Research Institute, Moscow, Russian Federation; 2 Quantum Electronics, General Physics Institute, Moscow, Russian Federation; 3 Respiratory Physiology, Institute of Biomedical Problems, Moscow, Russian Federation

Background: We found earlier that as a result of single breath diffusion capacity test for CO and NO mean relative current COHb concentration in lung capillary volume (Vc) reaches to 10% [Babarskov E. et al. ERZ 2009. v.34 suppl.5:39].

Methods: Dynamic balance equations of CO and COHb in alveolar and capillary volumes were solved by numerical method.

Results: The dependence of average relative COHb concentration on breathholding time and initial CO alveolar concentration was determined, as well as relationships between measured DLco and COHb concentration. It was demonstrated, that using of gas mixtures with usually recommended CO content (0.28%) results in COHb concentration increase to about 10%, that in turn leads to reducing of DLco about by 5% and Vc by 10%. If initial CO content in gas mixture is increased three fold (0.84%), then COHb concentration reaches to about 30%, that in turn leads to reducing of DLco about by 15% and Vc by 30%.

Conclusion: Our findings confirm possibility of experimental measurement of the difference between DLco values, which may be used for noninvasive investigating of lung hemodynamics. Particularly this allows to determine important diagnostic parameter - capillar blood flow rate across ventilated alveoli and correctly to calculate Vc.

4330
How long does it take for supine TLNO & TLCO to become stable after sitting upright?
Liam O’Reilly, Helen Ward, Martin Miller, Brendan Cooper. Lung Function and Sleep, NHS, Birmingham, United Kingdom

Introduction: We previously investigated (ERS Congress, 2011) the change in gas transfer for carbon monoxide (TLCO) from sitting to supine in healthy subjects, but were unable to find published studies showing how long subjects should be supine before a stable TLNO measurement could be made.
Method: We measured single breath TLCO & TLNO in 13 healthy subjects (5F:8M; ages 23-57 years; mean height (SD) 1.77 m (0.10)) using a Master Screen lung function system (Jaeger Ltd, Hoechberg, Germany), twice sitting at rest and then after 10, 15, 20, 25 & 30 mins respectively lying supine.

Results: Table 1 shows mean (SD) for TLCO and TLNO.

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Sitting</th>
<th>Supine +10</th>
<th>Supine +15</th>
<th>Supine -10</th>
<th>Supine -15</th>
</tr>
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<tbody>
<tr>
<td>TLCO</td>
<td>106 (2.4)</td>
<td>0.55*</td>
<td>0.58*</td>
<td>0.23</td>
<td>0.18</td>
</tr>
<tr>
<td>%Change</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
<td>2%</td>
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<td>TLNO</td>
<td>40.0 (8.8)</td>
<td>0.46</td>
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<td>0.04</td>
</tr>
<tr>
<td>%Change</td>
<td>5%</td>
<td>-4%</td>
<td>-1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>VA Eff (%)</td>
<td>6.43 (0.39)</td>
<td>-0.23*</td>
<td>-0.22*</td>
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Values shown as Mean (SD) TLCO in mmol/kPa/min; TLNO in mmol/kPa/min/L; V A eff in L/mins.

Discussion: We have shown that when supine for 30 mins TLCO changes but TLNO remains stable. We confirm TLCO increases from sitting to supine but that TLNO, which reflects membrane function, remains unchanged. TLNO/TLCO demonstrates a small decrease followed by an accommodation in pulmonary capillary blood volume.

Conclusion: Supine gas transfer using TLNO + TLCO show physiological changes consistent with changes in pulmonary capillary blood volume when subjects lie supine. Measurements before 20 mins are transients and suggest care should be taken when making supine gas transfer estimations.

4331

Fraction of exhaled nitric oxide in children aged 4 to 11 years
Jana Kivastik1, Tiina Rebane2, Maire Vasar2,3. Department of Physiology, University of Tartu, Estonia; 2Children's Clinic, Tartu University Hospital, Tartu, Estonia; 3Department of Pediatrics, University of Tartu, Estonia

Introduction: Fraction of exhaled nitric oxide (FENO) is a useful marker of allergic airway inflammation and can measure the response to anti-inflammatory therapy. Availability of commercial portable FENO analyzers has made the measurement more widespread in clinical care.

Aim: To study FENO in relation to current respiratory symptoms and medication in patients of Tartu Children's Clinic and in healthy children.

Methods: We measured fraction of exhaled NO with the hand-held device (NIOX MINO; Aerocrine AB, Sweden) in 242 children aged 4-11 years. Children were classified as wheezers (wheeze during the last 12 months), coughers or healthy (groups W, C and H, resp) according to the questionnaires about respiratory and atopic problems. 79 out of 207 symptomatic children had been treated with inhaled corticosteroids (ICS) during the last month. We defined FENO values >20 ppb as abnormal, the limit suggested for children aged 12 or less by Taylor.

Results: Table 1 shows mean (SD) for TLCO and TLNO.

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Conclusion: Supine gas transfer using TLNO + TLCO show physiological changes consistent with changes in pulmonary capillary blood volume when subjects lie supine. Measurements before 20 mins are transients and suggest care should be taken when making supine gas transfer estimations.

4333

Correlation between gas-exchange dynamics in recovery of exercise tests and cardiovascular parameters in pulmonary hypertension
Patrick Jaka, Harri-Jan Boogaard, Anton Vanh-Neerdegraege, Dept. of Pulmonary Medicine, VUMC Medical Center, Amsterdam, Netherlands

Introduction: In pulmonary hypertension (PH), cardiac dysfunction and gas-exchange abnormalities within the lung may both delay the rate of recovery in O2-uptake ($V'O_2$) and CO2-release ($V'CO_2$) after a cardiopulmonary exercise test (CPET).

Aim: Determine the correlation between recovery rates of $V'O_2$,$V'CO_2$ after CPET with pulmonary vascular resistance (PVR) and right ventricular ejection fraction (RVEF).

Methods: In this retrospective study measurements on 12 PH-patients were used. 1-4 CPETs and heart catherisations (for PVR measurement) per patient were done. Sometimes also a cardiac MRI was performed, rendering RVEF.

Results: Changes in $V'O_2$, $V'CO_2$ strongly correlated with PVR and RVEF.

Conclusion: Diffusing capacity can predict hypoxemia during sub maximal exercise in patients with ILD.

Our data suggest that supplemental oxygen during exercise in ILD patients with a TLCO (%pred) >61% is not necessary.

4334

Diffusing capacity > 61% (predicted) predicts absence of hypoxemia during 6-Minute Walk test in patients with interstitial lung disease
H.T. de Raaf1, M. Wapenaar1, Y.M. de Feijter1, H. Groepenhoff2, M.S. Wijnen3, B. Blink van den1, H.C. Hoogsteden1, H. Stam1, 1Department of Pulmonary Diseases, Erasmus Medical Center, Rotterdam, Netherlands; 2Department of Pulmonology, VU University Medical Center, Amsterdam, Netherlands

Introduction and aim: In patients with interstitial lung disease (ILD) the 6-minute walk test (6MWT) can be used to assess the need for supplemental oxygen during physical training and in-test hypoxemia is an indicator of poor survival. We investigated if TLCO (%pred) is a predictor for hypoxemia during 6MWT.

Methods: We analysed data of 66 consecutive ILD patients who performed spirometry, TLCO-measurement and 6MWT at the same day between March 2011 and February 2012. We excluded patients with pulmonary hypertension, musculoskeletal impairment, oxygen dependence and incomplete 6MWT.

Conclusion: In PH-patients, slow recovery-rates of VO2 and VCO2 are associated with a high PVR and low RVEF.
4334 BTS recommendations for referral for hypoxic flight assessment are not appropriate in paediatrics
Patrick Jamieson, Colleen Carden. Respiratory Function Laboratory, Royal Hospital for Sick Children, Yorkhill, Glasgow, United Kingdom

Introduction: The assessment of paediatric hypoxia during commercial flight is not as well understood as the equivalent area in adults. The BTS recommends that patients with a baseline greater than 95% do not need a hypoxic flight assessment. This study examined the BTS criteria for referral for hypoxic flight assessment with respect to prevalence of hypoxia during this assessment, in a paediatric sample.

Methods: This was a retrospective audit of patients referred to a paediatric respiratory function laboratory. The test protocol used 100% nitrogen to dilute the contents of a body plethysmograph to a FiO2 of 15%, before assessing the SpO2 profile for 20 minutes. Failure of hypoxic challenge, according to BTS criteria, constituted a mean SpO2 of less than 90% when breathing FiO2 15%.

Results: 107 children (58% female) age 0.1-19.2 years (mean 7.0, SD 5.4) were tested. They were referred for a variety of conditions including muscular dystrophy, cystic fibrosis, severe asthma, long term ventilation, long term oxygen therapy and sleep breathing disorders. 83% of patients referred had a baseline SpO2 in FiO2 21% of greater than 95%. 29% of these patients were determined to be hypoxic in FiO2 15%.

Conclusions: If BTS criteria for referral were applied to this patient sample, only 6% would be detected as hypoxic in FiO2 15%. When these criteria are not used then a total of 35% of these patients are found to be hypoxic. Either the BTS criteria for detecting hypoxia are too sensitive, or the BTS indications for hypoxic flight assessments are not specific enough. This study highlights the problems associated with predicting a patient’s response to hypoxia using baseline measures.

4335 Are 6MWD and FEV1 the most clinically relevant measures? Matthews A, Rutter1, Jennifer A. Colbourne, Jonathan P. Field1, Karl P. Sylvester2. 1Tang Function Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; 2Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Six minute walk tests (6MWT) are used to assess exercise tolerance and widely used to assess the response to interventions. The six minute walk distance (6MWD) is used clinically to describe the patients’ ability to tolerate exercise and is often used in comparison to FEV1. Although FEV1 and 6MWD performed concomitantly correlate, FEV1 in certain patient populations can remain stable over time while 6MWD changes over 5% (e.g. curves 7, 16). These test-curves have non-physiological flow spikes (e.g. curves 3, 17, 19), while those curves that end suddenly had small effects (e.g. curves 1, 15). The 2005 ATS/ERS guidelines on spirometry recommend validating the quality of a spirometer by simulating forced expirations with computerized syringes. It was recently shown, that these test-curves have non-physiological flow spikes of approximately 150 mL/s instead of a slow drop towards the end of the expiration(1).

Spirometers vary in their minimal detectable flow, especially turbine type spirometers. Due to the spiky flow, such difference might not be detected by the current ATS/ERS waveform tests. We used the interpolated form of the ATS curves(3) to calculate the effect on the measured FVC of the curves with varying lowest detectable flows. We evaluated flow cut-offs of 10–150 mL/s in 10 mL/s increments. Only flows that were above the cut-off were integrated for volume.

The effect on FVC was high for those ATS curves that have a low tapering end (e.g. curves 3, 17, 19), while those curves that end suddenly had small effects (e.g. curves 7, 16). The deviations in FVC become larger than the ATS/ERS repeatability criterion even with lowest detectable flows of 50–100 mL/sec. But those failures would be missed by the currently used ATS/ERS waveforms. We recommend to un-gently adapting the test curves to the interpolated version to avoid missing poor performing spirometers in the future.


446. Effectiveness of respiratory disease management in primary care

4337 Can the organisation of COPD care in primary health care centres help preventing exacerbations in COPD patients? Josefina Sundh1, Scott Montgomery2, Christer Janson3, Eva Osterlund4, Efremsson5, Bjorn Stalberg6, Karin Lisspers7. 1Department of Respiratory Medicine, Orebro University Hospital, Orebro, Sweden; 2Clinical Epidemiology and Biostatistics Unit, Orebro University Hospital, School of Health and Medical Science, Orebro University, Orebro, Sweden; 3Department of Medical Sciences, Respiratory Medicine and Allergology, Upplanda University, Uppsala, Sweden; 4School of Health and Social Studies, Dalarna University, Falun, Sweden; 5Department of Public Health and Caring Science, Family Medicine and Clinical Epidemiology, Uppsala University, Uppsala, Sweden

Introduction: COPD exacerbations are associated with lung function decline, lower quality of life and increased mortality, and can be prevented by pharmacological treatment and rehabilitation. The aim of this study was to explore if the organization of the COPD care in primary health care centres influences the risk for new exacerbations.

Methods: A clinical population of 735 COPD patients was randomly selected from 70 Swedish primary health care centres (PHCCs). Data on COPD exacerbations and following preventive measures were obtained from medical record review. Cox regression analyses were used to estimate the risk of a new exacerbation with adjustment for age and sex.

Results: During a study period of four years 458 patients had an exacerbation, and of these 278 patients (61%) had a second exacerbation during the follow-up period. Patients with a scheduled extra visit to an asthma/COPD nurse following an exacerbation had a decreased risk of a new exacerbation compared to patients with no extra follow-up besides regularly scheduled visits (adjusted hazard ratio (95% CI) 0.54 (0.32 to 0.93), p=0.026).

Conclusion: Scheduling an extra visit to an asthma/COPD nurse following a COPD exacerbation decreased the risk of reexacerbations in primary care patients. We conclude that a close cooperation between professional categories is important in the prevention of COPD exacerbations in primary care.

4338 Are disease management programs for COPD cost-effective? Melinde Boland1, Apostolos Tsiafristhas2, Annmarie Kruis2, Niels Chavannes3, Maureen Rutten-van Molken4. 1Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands; 2Public Health and Primary Care, Leiden University Medical Center, Leiden, Netherlands

Background: There is insufficient evidence of cost-effectiveness of COPD disease management (COPD-DM) programs. Aim: The aim of this study is to review the impact of COPD-DM on healthcare costs and outcomes. We also investigated the impact of disease-, intervention-, and study-characteristics.

Methods: We conducted a systematic review to identify cost-effectiveness of
COPD-DM. The data, results, and characteristics of the studies were grouped and, if feasible, included in a random-effects meta-analysis.

**Results:** We included 16 papers describing 11 studies. The meta-analysis showed that DM decrease hospitalizations (RR: 0.76 [95CI: 0.63-0.93]), and let to a significant reduction of hospitalization costs ($1196 [95CI: $722 - $1670]) per patient per year (PPP). Average healthcare savings were $1914 [95CI: $1464-$2367] PPP. These savings have to be weighed against the costs of developing, implementing and managing the DM program. Our results showed great variability in study-, intervention-, and disease-characteristics. There are indications that studies with greater savings in hospital costs in studies with: severe COPD patients (GOLD stage 3+), patients with exacerbations, smokers, non-RCT design, short intervention duration, low methodological quality, 1-2 Chronic Care Model components and non-EU origin.

**Conclusion:** DM decreased the risk of hospitalization and healthcare costs (excluding program costs). Furthermore, cost-effectiveness was influenced by heterogeneity in study-, intervention-, and disease-characteristics. Although favourable results on healthcare costs and effects have been demonstrated, more studies are needed to draw conclusions on the impact of DM on total costs and cost-effectiveness of DM in different settings.

**4339 COPD in primary care in Sweden – An 11 years epidemiological register study**

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**Background:** Analysis of longitudinal clinical practice data yields important information about disease characteristics, natural course and disease management.

**Objectives:** To describe chronic obstructive pulmonary disease (COPD) in primary care in Sweden with special reference to management, co-morbidity, and life expectancy (NCT01146392).

**Methods:** Primary care medical records’ data on COPD patients ≥ 18 years was linked to national hospital, drug, and cause of death register data for 1999 – 2009. Index date was first COPD diagnosis. Exacerbation defined as hospitalisations, emergency room visits, prescription of oral steroids, or antibiotics for COPD.

**Results:** Study population, 21,361 patients (47% males; 68.0 years). During the two years before the index date, 77% had exhaled nitric oxide (FENO) measurements; 62% had inhalers (ICS); 26% had inhalers (ICS); During the 11-year period, COPD was associated with asthma (odds ratio 2.71, 95% CI: 2.59-2.83), COPD was associated with asthma (odds ratio 2.71, 95% CI: 2.59-2.83), and mean age at diagnosis decreased by 7 years (73 to 66 years). Prescriptions of tiotropium and fixed ICS/LABA (long-acting β2-agonist) combinations increased to 25% and 37%, respectively; while ipratropium, LABA and ICS showed decreased to stable/decreasing trends. Exacerbations simultaneously decreased from 3.0 to 1.3 exacerbations/patient/year. Diagnosis of co-morbidities increased from index to 8 years after; diabetes from 12 to 19%; heart failure 16 to 26%; and lung cancer 0.94 to 1.47%. Mean life expectancy improved 8 months shorter than for the general population.

**Conclusion:** Management of COPD improved during the study period, with earlier diagnosis, primary care focus, changes in treatment options and decrease of exacerbations.

**Study sponsor:** AstraZeneca.

**4340 Adherence to a maintenance exercise programme 1 year after pulmonary rehabilitation: What are the predictors of drop-out?**

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Centre for Rehabilitation, University Medical Center, Groningen, Netherlands.

**Objective:** To study adherence to a maintenance exercise programme in patients with COPD, who had been following a pulmonary rehabilitation programme.

**Methods:** 70 patients with COPD were included in the study after completing the rehabilitation programme. All were referred to an community-based maintenance exercise programme. Adherence was assessed by open questionnaire after 6 and 12 months and lung function, exercise capacity, exercise self-efficacy, illness perceptions, health related quality of life, levels of anxiety and depression, duration of rehabilitation and number of exacerbations were studied as possible predictors of non-adherence.

**Results:** Ten patients died or were lost to follow up. Of the remaining 60 patients, 73.3% and 63.3% were adherent to the exercise programme after 6 and 12 months, respectively. FEV1 (p=0.021), HADS depression score (p=0.025) and duration of rehabilitation (p=0.018) were statistically significant predictors of adherence.

**Conclusions:** Adherence to a maintenance exercise programme, after having followed a pulmonary rehabilitation programme, is quite reasonable for patients with COPD: about one third drops out during the first year. A poorer lung function, a longer rehabilitation course, and higher level of depressive symptoms are predictive for drop-out.

**Practice implications:** To improve adherence to a maintenance programme, special attention should be paid to patients with lower FEV1, those with signs of depression or in need of a longer rehabilitation.

**4341 Lower incidence of asthma exacerbations with FENO-guided anti-inflammatory treatment: A randomised controlled trial**

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We examined the effects of anti-inflammatory treatment guided by fractional exhaled nitric oxide (FENO) on asthma outcomes in adult patients with allergic asthma.

This was a primary health care multicentre study (17 sites). 181 non-smoking participants (18-64 years) with perennial allergy and regular inhaled corticosteroid (ICS) treatment were randomly assigned to two treatment arms: a control group (n=88), where FENO was not measured and an anti-inflammatory treatment (ICS and leukotriene receptor antagonists) adjusted according to routine clinical practice, and an active group (n=93) where the anti-inflammatory treatment was adjusted according to FENO. Participants were followed for one year (5 visits). FENO was measured and questionnaires on asthma-related quality of life (mini-AQLQ) and asthma control (6-item ACQ) were completed. Health care contacts and asthma events were noted at every visit. The primary endpoint mini-AQLQ overall score over one year did not differ between the groups at last visit (p=0.20), whereas the mini-AQLQ symptom domain score (p=0.041) and the ACQ score (p=0.045) improved significantly more in the FENO-guided group than in the control group. Furthermore, a significantly lower cumulative incidence of exacerbations was found in the FENO-guided group vs. control group (p=0.029). This was dependent on a reduction in moderate (p=0.006) but not severe (p=0.73) exacerbations. Mean use of ICS over the study period was similar in the two groups (p=0.95).

Using FENO to guide anti-inflammatory treatment reduced exacerbation frequency and improved asthma control in adults with atopic asthma without increasing overall ICS use.

**4342 Reducing asthma admission: Impact of the Easy Asthma Clinic Network**

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**Introduction:** Easy Asthma Clinic Network has been developed as a model to enhance the implementation of GINA guidelines in Thailand. We set up Easy Asthma Clinic in the hospitals throughout Thailand. The 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. This study aim to study the effect of the Easy Asthma Clinic Network on asthma admissions.

**Method:** All asthmatics under the universal health care scheme registered in the Easy Asthma Clinic Network during October 2007 to September 2009 were ana-lyzed for hospitalization rate and hospital days due to asthma. The hospitalization rate and hospital days due to asthma during one year before and after registration were compared.

**Results:** There were 22,564 asthmatics registered from 360 hospitals. There were 6,449 admissions, which were associated with 36,589 hospital days during one year before registration. The rate of hospitalization was 0.2585 admissions/patient/year. There were 4,071 admissions, which were associated with with 11,608 hospital days during one year period after registration. The rate of hospitalization was 0.1804 admissions/patient/year. Registration to the Easy Asthma Clinic Network lower the risk of hospitalization (incidence rate ratio 0.39, confidence interval (CI) 0.38 to 0.41).

**Conclusions:** The Easy Asthma Clinic Network is effective in reducing hospitalization due to asthma.

**4343 More than 50% of patients visit a general practitioner (GP), general physician (Gen P) or a pediatrician (P) in India for respiratory symptoms:**

Results of a one-day-point-prevalence study in 2,048,912 patients across 22 states and 5 union territories in India

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A better understanding of the disease pattern and symptoms for which a patient visits a doctor will help design appropriate health care management strategies. This study was aimed to investigate the symptoms for which a patient visits a general healthcare provider in India using a 1-day-point-prevalence cross-sectional study design.
Method: 13,225 practicing GPs, Gen Ps and Ps, randomly selected from 880 cities and towns in India based on a proportionate random sampling strategy were invited to participate in this study. On 1st February 2011, all participating doctors completed a questionnaire based on the validated FEED-10 classification, wherein they captured age, gender and symptoms of all patients who visited their clinic. Data was collected, cleaned and entered in Epi Info software and simple descriptive analysis was performed.

Results: A total of 2,04,912 patients visited 7400 doctors who consented and gave clean data. Amongst these, 50.6% presented with respiratory symptoms (31.8% cough, 15.8% rhinitis, 9.4% sore throat, 8.4% wheeze and 6.9% breathlessness), 25% presented with gastrointestinal symptoms, 18% cardiovascular, 5% dermatology and 3% for endocrine related symptoms/diagnosis. These observations were generally uniform across 22 states and 5 union territories in India with no hot spot regions.

Conclusion: Respiratory symptoms account for over 50% of symptoms for which a patient visits a doctor in India, which extrapolates to at least 20 million patient visits for respiratory symptoms every day in India.

4344 Comparative study of respiratory symptoms, lung function, BMI and exercise capacity in patients with COPD associated with tobacco smoke (TS) and biomass smoke (BS) exposure
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Background: COPD is the 4th leading cause of death and is expected to be 3rd by 2030. Tobacco smoke and indoor air pollution are the major risk factors for COPD. While there are large number of studies on tobacco smoke and COPD, there is paucity of data on biomass smoke and COPD. It is not clear whether this phenotype of COPD is different or similar to COPD caused by tobacco smoke.

Aim: To compare the clinical symptoms, lung function, BMI and 6MWD (exercise capacity) in TS-COPD and BS-COPD.

Method: We prospectively evaluated 103 stable COPD patients from the out-patient clinic. COPD was diagnosed by GOLD guidelines (post bronchodilator FEV1/FVC <70%), respiratory questionnaire captured symptoms and six minute walk test (6MWT) was done as per ATS guidelines.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TS-COPD (%)</th>
<th>BS-COPD (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean SD</td>
<td>63.39(8.87)</td>
<td>60.04(7.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Cough</td>
<td>70.7%</td>
<td>71%</td>
<td>NS</td>
</tr>
<tr>
<td>Wheeze</td>
<td>24%</td>
<td>3.6%</td>
<td>p&lt;0.017</td>
</tr>
<tr>
<td>BMI</td>
<td>19.83(3.90)</td>
<td>18.46(3.81)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 Post</td>
<td>47.87(14.98)</td>
<td>44.95(14.49)</td>
<td>NS</td>
</tr>
<tr>
<td>6MWT</td>
<td>379.88(84.84)</td>
<td>344.12(88.31)</td>
<td>NS</td>
</tr>
</tbody>
</table>

There were 75(TS-COPD) and 28(BS-COPD) patients with mean age of 63.39(8.87) and 60.04(7.57) respectively. Females (92.85%) dominated the biomass group while 97.3% males were in the tobacco smoking group TS-COPD presented with wheeze(24%) as compared to 3.6% in BS COPD(p<0.017). There was no difference in clinical symptoms of cough and dyspnea in both groups. Severity of disease, BMI and exercise capacity showed no statistical difference in both groups.

Conclusions: Our results confirmed that BS-COPD and TS-COPD have similar clinical characteristics.

447. Respiratory diseases at at work: epidemiology, inflammation and challenge studies

P4345 Increased markers of oxidative stress in workers exposed to nanoparticles
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Introduction: Possible adverse health effects of nanoparticles are little understood. Pilot study was performed in workers exposed to TiO2 aerosol.

Methods: Dynamics of aerosol number size distributions at the workplaces was monitored by SMPS and APS spectrometers in size range 15 nm-10 μm. Spatial distributions of total concentrations were determined using monitors of particle number (P-TRAK) and mass concentrations (DustTRAK DRX). Pre-shift and post-shift FeNO and markers in exhaled breath condensate (EBC) were measured in 20 workers, and 17 controls. Malondialdehyde (MDA), 4-hydroxy-2-trans-nonenal (HNE), 4-hydroxy-trans-hexenal (HHE), 8-isoprostaglandin F2α (8-iso-PGF2α), 8-hydroxy-2-deoxyguanosine (8-OHG), 8-hydroxyguanosine (8- OHG), hydroxymethyl uracil (HMeU), c-trosine (c-Tyr), 3-chloro-trosine (3-Cl-Tyr), nitrotyrosine (NO-Tyr), C6-C13, and leukotrienes (LTs) were analyzed by LC/MS. Pre-shift and post-shift electrospray ionization-mass spectrometry.

Results: Total aerosol concentrations in the production plant varied in space and time; number concentrations 1x104-2x105 particles/cm3, mass concentrations 0.1-30 mg/m3. In the workshops, 90% of particles were under 100 nm in diameter. All pre-shift markers, except LTB4 and FeNO, were increased in workers. Markers of lipid oxidation were elevated (p<0.01): MDA, HNE, HHE, 8-iso-prostaglandin, and C6-C13. Markers of oxidation of nucleic acids and proteins were higher (p<0.001): 8-OHG, HMeU, 3-Cl-Tyr and NO-Tyr. Elevated was also c-Tyr, LTB4, LTETC and LTE4. No difference was noted for post-shift EBC and FeNO.

Conclusion: This first study of EBC in workers suggests deleterious effects of exposure to aerosols with particle sizes.

P4346 Cytokines and MMP 9 level in serum and induced sputum of patients with suspicion of occupational COPD
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Background: Chronic obstructive pulmonary disease (COPD) may be work-related. It is estimated that working in exposure to dust and irritant gases is responsible for 10 to 20% cases of COPD.

Aim: The study was aimed to evaluate the usefulness of determination of cytokines and MMP 9 in occupational COPD.

Material and methods: The study group included 36 patients (10 with suspicion of occupational COPD, 14 with occupational asthma and 12 healthy subjects). They underwent clinical examination, spirometry, methacholine challenge test, gasometry, induced sputum. Determination of IL-1, IL-6, TNF α, MMP 9, fibrinogen and C-reactive protein were performed in all the patients. Results: Analysis of acute-phase proteins concentration and cells proportion in induced sputum did not reveal significant differences. The determinations of cytokines and MMP 9 showed higher concentrations in induced sputum compared to serum tests. Among patients with suspicion of COPD, the significantly higher concentrations of IL-1, IL-6, TNF α and MMP 9 were detected in control group.

Conclusions: The obtained results revealed the increased concentrations of IL-1, IL-6, TNF α and MMP 9 in induced sputum among COPD subjects compared to control group. The determination of cytokines and MMP 9 in induced sputum was more useful method in comparison to serum analysis. There was no relationship found between acute-phase proteins concentration and cells proportion in induced sputum in the study groups, however further investigations are required.

P4347 Imputed classical HLA II alleles, occupational allergen exposure and adult-onset asthma
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Background: HLA is a principal candidate gene region for occupational asthma, and HLA-DQ was the only significant locus in the GABRIEL genome-wide association study (GWAS) of late-onset adult-onset asthma. Aim: To elucidate the role of HLA-II in adult-onset asthma, we imputed classical HLA-II alleles from 7579 single nucleotide polymorphisms. We explored associations between 25 alleles with frequency >5% and adult-onset asthma, and we did separate analyses in subjects exposed to occupational allergens.

Methods: We studied 607 subjects with adult-onset asthma and 2104 adults without asthma from three European cohorts (ESE Consortium: ECRHS, SAPALDIA, and IGEA. According to a job exposure matrix, 44 subjects (13% with adult-onset asthma) were exposed to high molecular weight (HMW) agents, with 74% exposed...
to latex. In addition, we studied 946 HMW-exposed workers (392 with asthma) from Dutch and Danish surveys of bakers and farmers.

**Results:** In the ESE cohorts, DPB1*0301 (OR 0.76, 95%CI 0.60-0.97) and DQA1*0301 (OR 1.22, 95%CI 1.02-1.44) were associated with adult-onset asthma. DQA1*0103 was associated with asthma, but only in HMW-exposed ESE subjects (OR 0.54, 95%CI 0.29-0.98). In the HMW-exposed bakers and farmers, six other HLA-II alleles were associated with asthma (p<0.05). None of the associations in ESE subjects or workers remained statistically significant after correction for multiple testing.

**Conclusions:** Imputation allows a complete evaluation of HLA alleles following GWAS. In a general population and among populations exposed to a variety of occupational allergens, analyses did not reveal a clear association between common classical HLA-II alleles and adult-onset asthma.

**Funding:** ANR-PRSP10 Iago.

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**P4348**

**Work-related asthma among a general asthma population: A cross sectional survey**

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To find the impact of occupational exposure to irritants or sensitizers on the occurrence, recrudescence and worsening of asthma and to identify unrecognized cases of work related asthma (WRA) in a general asthma clinic population sample, we studied 893 subjects from 15 to 46 yrs with diagnosis of asthma identified from the Medical Reimbursement Register of the National Health Service. All subjects were classified in different categories of occupational risk exposures (Low, Low or High: 58.9, 27.9, 13.2% respectively) according to the italian standard classification for industries and job titles, associated with the judgment of occupational hygiene-experts. Subjects with higher occupational risk had a lower lung function (p=0.02) and asthma severity (<0.01). Prevalence of WRA (47%), including occupational asthma (OA: 7%) and work exacerbated asthma (WEA: 40%), was significantly associated with higher occupational risk exposed (OR: 6.8, p=0.001). Subjects with WRA had a lower lung function (<0.01) and asthma severity (p=0.01) with respect to subjects without WRA. Two-thirds of OA and half of WEA caused loss of work. In conclusion our study shows a high prevalence of WRA (especially WEA) associated with employment in industries and job titles at risk for airways sensitizers and/or irritants. Control of exposure, an appropriate medical surveillance and an accurate therapeutic management can avoid the loss of job and its socioeconomic consequences in asthmatic subjects.

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**P4349**

**Shield 1992-2012: 20 years of a reporting scheme for occupational asthma**

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SHIELD is the Midland Thoracic Society’s rare surveillance scheme for occupational asthma in the West Midlands, England, UK (working population 2.2 million). The database is a useful tool to locate outbreaks within a particular field of work and discover causative agents. There have been 1644 notifications of occupational asthma since January 1992.

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**P4350**

**The effect of work on asthma in middle-aged men having asthma from youth**

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**Aims:** We studied the effect of current workplace exposure on current asthma severity, asthma control and occurrence of exacerbations in a population of approximately 40-year old men having asthma since their youth.

**Methods:** We used Finnish Defence Force registers, 1986-1990, to select: (1) conscripts with asthma to represent a mild/moderate asthma group (n=485), (2) asthmatics who were exempted from military service to represent a relatively severe asthma group (n=393) and (3) a control group (n=1500) without asthma. A questionnaire consisting of validated questions on asthma and occupations was sent out in 2009 and current occupational exposure was estimated with asthma Job Exposure Matrix (JEM). Asthma severity was evaluated with the modified GINA guidelines and control with the Asthma Control Test. Logistic regression was used in risk factor analyses. A total of 54% of the men in asthma group 1, 44% of those in asthma group 2 and 44% of the controls answered.

**Results:** A total of 17.5% of the men in asthma group 1 and 40.5% of the subjects in asthma group 2 had and currently moderate or severe persistent asthma. Asthma was more often uncontrolled in asthma group 2 (28.0% vs. 15.1%, p=0.002) and exacerbations during last 12 months were more frequent (19.3% vs. 11.6%, p=0.0363). Being currently not-employed (OR 2.0, 95%CI 1.0-4.0) and self-reported occupational exposure to abnormal temperatures (OR 2.0, 95%CI 1.0-4.0) were associated with asthma exacerbations, while occupational exposure based on JEM was not related to current asthma status.

**Conclusion:** Current workplace exposure seems to have only minor effect on asthma severity, control and exacerbations in 40-year old men having asthma since their youth.
Occupational asthma and rhinitis in champagne vineyard workers

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Background: Vineyard workers (VW) are exposed to various inhaled respiratory allergens. However, the prevalence and risk factors of occupational asthma (OA) and rhinitis (OR) in Champagne VW have not been studied.

Aims: The objectives of this cross-sectional study were to determine the prevalence of OA and OR in Champagne VW and to analyze the relationships between occupational exposures (OS), occupational exposure and sensitization profile.

Methods: Champagne VW were recruited from the Department of Occupational Medicine in May and June 2010. Demographic and occupational characteristics were recorded. Nasal and respiratory symptoms were scored for each month of the past year. OS were defined by symptoms related to work exposure. Diagnosis of asthma was based on symptoms (SS) and occupational exposure mon respiratory allergens, grape mould (botrytis) and grape pollen. FEV1/FEV6 ratio was measured.

Results: Sixty-six patients were included. The prevalence of rhinitis and asthma was 38% and 13% respectively. The prevalence of OR and OA was 21% and 3% respectively. SPT showed sensitization for gramineae (18%), D. pteronyssinus (12%), D. farinae (11%), vine pollen (11%), botrytis (5%). Compared to VW without OS, VW with OS were more frequently sensitized to betulacaeae (20% vs 2% respectively, p=0.03) and were involved in the activities of disbudding, straightening and/or hooking (35% vs 6% respectively, p=0.04). OS were present in May and June for 67% of patients, corresponding to disbudding, straightening and hooking.

Conclusion: The prevalence of OR in Champagne VW is high, whereas OA is relatively rare. OA and OR are associated with a sensitization to betulacaeae and with direct exposure to vine.

Quartz exposure and lung function

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Occupational exposure to quartz not only leads to silicosis but also to chronic bronchitis and obstructive lung disease. In Austria more stringent occupational limit values for dusts have been introduced in 2007. We assumed that (a) workers exposed to mineral dusts (quartz) have a poorer lung function (LF) than other workers that do not use such dusts or that cause (b) other occupational exposures (dusts and fumes), (b) LF decline is fastest in the quartz-group, and (c) the decline slowed down after the introduction of stricter limit values.

We examined repeated LF data (FVC, FEV1, MEF50) from the routine examination (usually every 2 years) performed by one occupational health centre from the years 2002 through 2010. Three main linear regression models were analysed on each LF parameter. (a) The effect of quartz exposure on the raw parameter after controlling for age, weight, height, gender, and smoking. (b) The effect of quartz exposure on the difference between actual value and the age-sex-height-dependent Austrian norm value. This approach allowed us to additionally control for the impact of duration of exposure. (c) The impact of quartz exposure on the intra-individual decrease in LF parameters per year. In this analysis we could also check for differences in the slope before and after the introduction of new limit values.

We analysed 7315 data-sets (on average 5 per person, mostly males). Nearly 40% of these were from workers exposed to quartz dusts. The remaining workers were welders or were exposed aluminium or other dusts. Both smoking and quartz exposure lead to lower LF values. Duration of quartz exposure also was a significant predictor of LF decline. The decline slowed after the introduction of stricter limit values.

Conclusion: Specific inhalation challenge tests to MWF did not produce non-specific reactions. A number of the MWF can be the cause of occupational asthma even with a negative challenge to used MWF.
negative in 6 control patients with work-related asthma due to another cause and exposed to QACs.

Conclusions: Our study demonstrated the usefulness of BCT to confirm an occupational asthma to QACs. As compared to previous publication from our group, bronchial response occurred more rapidly suggesting a sensitisation to DDAc.

P4357 Persistence of the asthmatic response after exposure to ammonium persulfate in an animal model

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Introduction: The aim of the study is to evaluate the persistence of respiratory symptoms after the end of exposure to ammonium persulfate (AP) in a validated model of occupational asthma (OA).1

Material and methods: BAL/Bc mice received dermal applications of AP or dimethylsulfoxide (DMSO) (control) on days 1 and 8. On day 15, they received a single nasal instillation of AP or saline. The ventilatory function (Penh) was monitored by whole body plethysmography for 40 minutes after the nasal instillation. Bronchial hyperreactivity was assessed using methacholine provocation, while pulmonary inflammation was evaluated in BAL and total serum IgE was measured in blood. 1 day (day 16), 2 days (day 17), 3 days (day 18), 4 days (day 19), 1 week (day 23) or 2 weeks (day 30) after the single challenge on day 15.

Results: There was a significant increase in bronchial hyperreactiveness and the percentage of neutrophils (12%) 24h after the challenge with AP in AP-sensitized mice. The peak response in AHR and neutrophil inflammation was found 48h post-challenge. From then onwards, both the bronchial hyperreactiveness and the percentage of neutrophils decrease gradually. Levels of total serum IgE increased significantly, reaching a peak three days after challenge, after which the levels return to baseline 23 days post-challenge.

Conclusions: Overall, after two dermal sensitizations, followed by a single challenge, the asthmatic response decreases, with initially only decreases in respiratory and inflammatory responses, but later also in the immunological responses.

Study funded by FIS PPI080730.

Reference:

P4358 Metalworking fluids, machine operator’s lung and serological diagnosis evolution

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Machine operator’s lung (MOL) has been related to Mycobacterium immunogenum (MI) growing in metalworking fluids (MWF). Our contribution to the serological evolution of MOL diagnosis is a 3 step story:

1. Sera from 13 MOL cases from the same plant, and 30 controls were tested against MI antigen (Ag). MI was identified in 40% of used MWF (n=831 plant).
2. The threshold for differentiating MOL cases from controls was 5 arcs (sensitivity (Se) 77% and specificity (Sp) 92%), as determined by electrosyneresis (ES). Using ELISA a threshold leading to 92% Se and 100% Sp was established (Tillie-Leblond, 2011. 1, et al. ERJ 2011; 37:640-7).
3. Immunogenic proteins were identified by two-dimensional Western blot and mass spectrometry. Recombinant antigens (rAg) were expressed in Escherichia coli and tested by ELISA. From the 350 spots visualized, 6 immunogenic proteins were selected to be expressed as rAg. Acyl-CoA dehydrogenase (Acyl-CoA DH) allowed for the best discrimination (Se 100%; Sp 83%) (Rousset, S. et al. Int J Med Microbiol 2011; 301:150-6.).
4. Serological diagnosis of 10 new German suspected cases was made by ES and ELISA. Independence from the strain isolated from the first cluster cases was obtained by using rAg. But whereas other strains was isolated in Germany from 3 new plants, ES made with French MI strain Ag demonstrated a similar threshold (4 arcs) to discriminate MOL from exposed subjects. Dihydrolipoamide dehydrogenase and Acyl-CoA DH results were useful together to make the diagnostic true regardless to the clinical and radiological data (Se 100%; Sp 100%), when used isolated Se reduced to 78 to 88% with Sp 100%. Uses of a panel of rAg seem the best way to serological diagnosis of MOL.

P4359 Persistence of functional and inflammatory response in mice dermally sensitized to persulfate salts

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Introduction: Years after removal from exposure, patients with occupational asthma (OA) still can show respiratory symptoms and bronchial hyperresponsiveness on re-exposure to the causal agent. The aim of the study was to assess the persistence of respiratory symptoms in an animal model of occupational asthma due to persulfate salts.

Material and methods: BAL/Bc mice received dermal applications of ammonium persulfate (AP) or dimethylsulfoxide (DMSO) (control) on days 1 and 8. They then received a single nasal instillation of AP or saline on day 15, 22, 29, 36, 45 or 60. The ventilatory parameters were evaluated by spirometry after the challenge in a whole body plethysmography (40 min.). Bronchial hyperreactivity was measured 24 hours afterwards using a non-specific methacholine provocation test. Pulmonary inflammation was assessed by analysis of bronchoalveolar lavage (BAL).

Results: Mice dermally sensitized and intranasally challenged with AP showed bronchial hyperreactivity to methacholine and increased percentage of neutrophil in BAL as long as 45 days after initial sensitization, compared with the control group. At day 60, mice were still bronchially hypersensitive, while the percentage of neutrophils fell to levels similar to those in the control groups.

Conclusions: Pulmonary inflammation decreased with increasing intervals between dermal sensitization and the challenge with AP, despite the persistence of hyperresponsiveness.

Study funded by FIS PPI080730.

P4360 Prevalence and factors associated with COPD in dairy farmers

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Several studies have suggested an increased risk of chronic obstructive pulmonary disease (COPD) among dairy farmers despite a lower prevalence of smoking compared with general populations. The prevalence of COPD among farmers, and the occupational factors associated with COPD are however unknown.

We therefore retrospectively analyzed the medical records of 590 dairy farmers (mean age 44.4 yrs; 75% males) and 69 control patients (mean age 43.5 yrs; 75% males), using respiratory medical questionnaires in 3 cohorts of dairy farmers. All studied subjects (n=590) were males without asthma and/or hypersensitivity pneumonia previous.

Criteria of COPD (i.e., a FEV1/FVC ratio < 70%) were found in 12% of all subjects (69/590, including 38 patients in GOLD stage 1 and 28 in stage 2). Symptoms of chronic bronchitis and wheezing were more frequent in patients with COPD (15.9 vs. 7.9%, p=0.03 and 30.3% vs. 10.6%, p<0.001, respectively). On multivariate analysis, the three independent factors associated with COPD were an older age (adjusted odds ratio [95% confidence interval]: 1.04 [1.02-1.07]), tobacco smoking (2.83 [1.29-6.19]) and low modernity of farms (2.89 [1.48-5.63]). Moreover, the association between tobacco smoking and working in traditional farms seemed to be synergistically linked with COPD in this population.

The finding that an occupational factor (i.e., working in traditional farms) is independently associated with COPD in dairy farmers suggests that prospective studies should be conducted in this population in order (1) to identify etiologic factors of COPD and (2) to characterize the COPD patients in terms of distension, exercise capacity and cardiovascular comorbidities.

P4361 Prevalence of chronic respiratory symptoms, ventilatory capacity and bronchial responsiveness in welders

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Objective: To evaluate the prevalence of chronic respiratory symptoms, ventilatory capacity abnormalities and bronchial hyperresponsiveness in welders and to clarify the role of workplace exposure.

Methods: A cross sectional study was performed including 40 males working as stainless steel welders (mean age=43.9±7.4; duration of exposure 15.2±6.8 yrs) and 40 male office workers as a control group (mean age=42.8±7.1) matched for age, duration of employment, smoking habits and socioeconomic status. Evaluation of examined subjects included completion of a questionnaire on respiratory symptoms in the last 12 months (cough, phlegm, dyspnea, wheezing, and chest tightness), spirometry and histamine challenge (PC20=8 mg/mL).

Results: We found non-significantly higher prevalence of respiratory symptoms in the last 12 months in welders with significant difference for cough (P=0.036)
P4362 The effect of radiographic abnormalities on mental health of former workers and residents of Wittenoom in Western Australia

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Introduction: Exposure to asbestos causes radiographic abnormalities such as pleural plaque (PP), diffuse pleural thickening (DPT) and asbestosis. Knowledge of presence of these radiographic abnormalities may affect individuals’ mental health (MH).

Aims: The aim of this study is to examine the effect radiographic abnormalities on the MH of people exposed to crocidolite.

Method: Subjects were former workers and residents of Wittenoom, a crocidolite mining town in Western Australia, who had participated in an Asbestos Review Program. The diagnosis of PP, DPT or asbestosis was determined from plain chest x-rays. In 2007, participant had completed a questionnaire that included questions on mental health status (SF-12) and sense of personal control (SOPC). Generalised linear modelling was used to relate the presence of PP, DPT and asbestosis to MH scores and SOPC scores controlling for asbestos exposure measurements, smoking status, other cancers, general physical health and demographic variables.

Results: A diagnosis of asbestosis was significantly associated with worse MH status (β = −0.04; 95% CI −0.079 to −0.004; p=0.031) but not SOPC. The presence of PP and DPT were not related to either poor mental health or reduced SOPC.

Conclusion: The presence of PP or DPT in the absence of other disease, do not seem to affect the mental health of crocidolite exposed subjects from Wittenoom compared to exposed persons without radiographic abnormalities. However, patients with asbestosis have evidence of worse MH compared to other asbestos exposed individuals.

448. Anti-infective treatment and resistance in respiratory infections

P4363 Therapeutic efficacy of macrolides, minocycline and tosufloxacin against macrolide-resistant Mycoplasma pneumoniae pneumonia in pediatric patients

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Background and objective: Since 2000 the prevalence of macrolide-resistant (MR) Mycoplasma pneumoniae in pediatric patients has increased in Japan. The purpose of our study was to investigate differences in the clinical course, bacteriological effect and therapeutic efficacy against MR M. pneumoniae among macrolides, minocycline and tosufloxacin.

Methods: We performed a multicenter prospective epidemiological study of MR M. pneumoniae for the first time. A total of 152 children with M. pneumoniae pneumonia confirmed by polymerase chain reaction (PCR) were analyzed. A search for mutations at sites 2063, 2064, and 2617 in the M. pneumoniae 23S rRNA domain V gene region was performed.

Results: One hundred nine patients of 152 children with M. pneumoniae pneumonia were determined to have a MR gene. Fever disappeared within 48 hours after antibiotics administration in the MR patients was seen in 25% of the macrolides group, 83% in the minocycline group, and 81% in the tosufloxacin group. The DNA copy numbers in the MR patients showed little decrease after macrolide administration, but rapid decrease after administration of minocycline or tosufloxacin.

Conclusions: The number of M. pneumoniae in the MR patients decreased promptly after 48 hours minocycline and tosufloxacin treatment and had a close relationship with clinical outcome. In contrast, we found that the clinical and bacteriological efficacy of macrolides for treating cases of MR patients was low. Our results might be indicate that minocycline and tosufloxacin considered as the first choice drugs for treatment of M. pneumoniae pneumonia in Japanese situation.

P4364 Clarithromycin inhibits pandemic A/H1N1/2009 influenza virus infection in human airway epithelial cells

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Rationale: We reported previously that clarithromycin (CAM), a macrolide antibiotic, inhibits seasonal type A influenza virus (H3N2) infection in human airways. However, the effects of CAM on infection by the pandemic A/H1N1/2009 influenza virus (A/H1N1 pdm) have not been studied.

Methods: Human tracheal epithelial cells (n=3) were pretreated with CAM (10 μM) and then infected with the A/H1N1 pdm in 24-well plates.

Results: The viral titer and the amount of interleukin (IL)-6, a pro-inflammatory cytokine, in the supernatant increased with time after A/H1N1 pdm infection. CAM reduced the viral titer (6.7±0.4 log TCID 50 units/ml/24 h for virus alone vs. 4.9±0.2 log TCID 50 units/ml/24 h for virus plus CAM; p<0.05, mean ± 5E) and IL-6 (211±8 pg/ml/24 h for virus alone vs. 149±7 pg/ml/24 h for virus plus CAM; p<0.05) 3 days after infection. CAM also reduced the number of epithelial cells detached from culture vessels 7 days after infection (32±2 x 10³/well in virus alone vs. 12 ±2 x 10³/well in virus plus CAM; p<0.05). In addition, we compared the viral titer and the numbers of detached cells after infection between the A/H1 pdm and the A/H3N2 virus. The viral titer and the number of the detached cells after infection with the A/H1 pdm were higher than those after infection with the A/H3N2 virus (4.1±0.4 log TCID 50 units/ml/24 h and 5±1 x 10³/well for A/H1N1 pdm vs. p<0.05).

Conclusions: Clarithromycin may inhibit A/H1N1 pdm infection and may modulate airway inflammation and epithelial damage during the infection. The A/H1 pdm may release higher levels of virus and may be more cytotoxic than seasonal influenza virus (H3N2).

P4365 Community-acquired pneumonia in five European countries: Usage patterns and real-life effectiveness of antibiotics (REACH study)

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Background: Comprehensive, current data on the burden of hospitalized community-acquired pneumonia (CAP) in Europe are scarce. Aim: To describe the hospitalized CAP population in Europe and to review current clinical practice and its impact.

Methods: REACH (NCT01293435) was a retrospective (2010–2011), observational study in ten EU countries. Patients were ≥ 18 years old, hospitalized with community-acquired pneumonia and treated with antibiotics for the treatment of CAP, were included.

Results: A total of 12,663 CAP patients were included. The mean age of the patients was 68 years (range 18 to 104 years) and 5,448 patients (42.9% of the total study population) were men. Microorganisms were identified in 11,281 cases (89.2%). The most common pathogen was Streptococcus pneumoniae (14.3%), followed by Haemophilus influenzae (11.5%) and Staphylococcus aureus (11.3%). The most commonly used antimicrobial agents were amoxicillin (48.7%), followed by ceftriaxone (35.9%) and azithromycin (15.5%). The resistance rates for the three most frequently used antibiotics were 10.6% for macrolides (amoxicillin), 9.1% for beta-lactams (ceftriaxone) and 1.2% for macrolides (azithromycin). The most common side effects were diarrhea (5.6%) and nausea (4.8%). The mortality rate was 7.0% and the median length of stay was 7 days (range 1–59 days).

Conclusions: The REACH study provides valuable data on the burden of community-acquired pneumonia in Europe and the real-life effectiveness of antibiotics. Further research is needed to improve the quality of care for these patients.
CAP and requiring IV antibiotics. Data were collected via an electronic Case Report Form. We present data from five countries selected as representative of the full sample: Italy (IT), the Netherlands (NL), Spain (ES), Turkey (TR) and the UK.

**Results:** Patient characteristics were similar in the five countries. Rates of initial treatment modification (due to treatment failure or other reasons) were 33.0% (TR), 36.7% (IT), 42.5% (ES), 50.0% (UK) and 51.7% (NL) (overall population 37.1%).

**Conclusions:** Antibiotic use differed somewhat between countries. Modification of initial treatment was common with many frequently used therapies, with variability among countries, suggesting that initial treatment choices may not always be optimal.

**P4366**

**Caspofungin to treat invasive pulmonary aspergillosis in sarcoidosis**

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**Rationale:** Invasive pulmonary aspergillosis is a potentially life-threatening complication of sarcoidosis, with destructive fibrotic lung disease and immunosuppressive therapy contributing to its development. Optimal therapy is not known. We report a successful treatment protocol using cyclical intravenous caspofungin infusions.

**Methods:** Consecutive patients with sarcoidosis and invasive pulmonary aspergillosis treated with caspofungin were identified from our pharmacy prescribing database. Clinical and radiological data were collected retrospectively prior to caspofungin treatment, and during follow-up.

**Results:** Nine patients (5 men), with a mean age of 44±11.13 years, and a median duration of sarcoidosis of 10 years (range 2-12), were treated with caspofungin. All patients had fibrotic pulmonary sarcoidosis (stage IV) on chest radiograph. Eight patients also received prednisolone. Six patients received prior oral antifungal therapy (voriconazole or itraconazole), and were converted to caspofungin due to lack of efficacy or side-effects.

Median follow-up was 12.5 months (4-32) after the commencement of caspofungin. In eight patients, symptoms and inflammatory markers improved rapidly after the first dose of caspofungin, with a decrease in median CRP from 31 (3.94) to 15 (3.23) (p<0.02) within 3 months. In the 6 patients for whom a minimum of 6 months follow-up was available, chest radiographs improved in 4 (67%), and median BMI improved from 23.2 (17.0-31.0) to 25.2 (21.5-36.0) (p<0.04).

**Conclusion:** Invasive pulmonary aspergillosis associated with sarcoidosis may be refractory to conventional antifungal therapy, and caspofungin appears to be a safe and effective therapeutic alternative in these patients.

**P4367**

**Macrolides vs quinolones in Legionella pneumonia treatment: CAPAVANT group. Valencia, Spain**

Sussana Herrera, Estrella Fernandez, Angel Cervera, A. Carmen Aguar2

**Methods:** Aims: To compare of community-acquired pneumonia between diabetic and non-diabetic patients with hyperglycemia status (HG) at hospital admission. We performed a prospective, observational study of patients admitted to the Pneumology department consecutively with a diagnosis of CAP. The plasma glucose levels were measured on admission and patients were divided into two groups: diabetic patients and non-diabetic with HG. We consider HG when plasma glucose level >=99mg/dl. We studied different variables, included severe clinical course (mortality and/or septic shock and/or invasive mechanical ventilation (IMV) during hospital stay.

**Results:** We studied 1389 patients, 274 were known diabetic and 53 (3,8%) were non-diabetic with HG.

**Table 1**

<table>
<thead>
<tr>
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<th>Diabetic N=274 (19,7%)</th>
<th>Non-DM with hyperGlc N=53 (3,8%)</th>
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<tr>
<td><strong>Means</strong></td>
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<tr>
<td>Age (years)</td>
<td>69.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Respiratory frequency (bpm)</td>
<td>21.7</td>
<td>24.0</td>
</tr>
<tr>
<td>Clinical stability (days)</td>
<td>4.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6.7</td>
<td>12.1</td>
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<tr>
<td><strong>Percentages</strong></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory morbidities</td>
<td>33.3</td>
<td>52.5</td>
</tr>
<tr>
<td>Dyspnoea</td>
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<td>77.4</td>
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<tr>
<td>Altered mental status</td>
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<td>Typical auscultation</td>
<td>59.4</td>
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<tr>
<td>Plural effusion</td>
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<td>ICU admission</td>
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<td>16.9</td>
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<tr>
<td>IMV</td>
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<td>FINE score &gt;4</td>
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</tr>
<tr>
<td>Mortality</td>
<td>6.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Severe clinical course</td>
<td>9.9</td>
<td>20.8</td>
</tr>
</tbody>
</table>

**Table 1**

**Conclusions:** 1. Non-diabetic patients with HG had a more severe clinical course comparing to known-diabetic, although mortality was similar. 2. Non-diabetic patients with HG had more respiratory morbidities, reached clinical stability later, had a higher admission to ICU and needed more IMV, with a longer hospital stay. 3. 4% of patients admitted with a CAP had a not-known HG.
P4370
Factors associated with compliance with palivizumab treatment in the Canadian rSV evaluation study for synagis (CARESS) registry (32005-2011)  
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Objective: Determine factors affecting compliance in palivizumab use. 
Methods: Registry of infants who received ≥1 dose of palivizumab during 6 RSV seasons. Demographic data collected at enrolment. Data on palivizumab utilization, compliance, and outcomes (respiratory illness - RI) collected monthly. Compliant interval between doses, and percentage of expected injections received. 
Results: 10,452 infants enrolled, 7492 (71.7%) complied with timing of doses. 91.9%≥2.7% of expected injections received. Greater proportion of non-compliant infants were hospitalized for RI (7.5% versus 6.0%, p=0.005), compliance did not affect RSV-positive hospitalizations (1.79% versus 1.53%, p=0.177). Compliant infants (all >0.05): were younger at enrolment (5.4±5.9 versus 5.9±6.1 months), had siblings (61.3% versus 58.5%), were a multiple (29.7% versus 27.2%), and had >5 household individuals (23.9% versus 21.7%). More non-compliant infants had smoke exposure (30.5% versus 28.4%, p=0.033). Six factors influenced compliance in regression analysis: age (HR=0.989, 95%CI 0.982-0.996, p=0.002), siblings (HR=1.104, 95%CI 1.007-1.211, p=0.034), ≥5 household individuals (HR=1.114, 95%CI 1.001-1.241, p=0.047), smoke exposure (HR=0.891, 95%CI 0.811-0.980, p=0.018) and CHD (HR=0.805, 95%CI 0.700-0.927, p=0.002), and RI-related hospitalization (HR=0.837, 95%CI 0.705-0.930, p=0.043).

Conclusions: Siblings ≥5 household individuals is associated with increased treatment compliance; being older, smoke exposure, having CHD and being hospitalized with decreased compliance.

P4371
Therapeutic outcomes for cavitary Mycobacterium avium complex (MAC) lung disease  
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Beginning in 1992, patients were enrolled in a series of prospective clinical trials investigating the safety and efficacy of 3 or 4 drug macrolide-containing regimens for treating cavitary MAC lung disease. Based on these studies subsequent MAC lung disease patients received similar regimens. All patients were diagnosed according to contemporary nontuberculous mycobacterial (NTM) diagnostic guidelines. Patients are included in this analysis only if they had a macrolide susceptible MAC isolate prior to initiation of therapy and subsequently tolerated a 3 to 4 drug regimen consisting of macrolide, ethambutol, and a rifamycin (rifampin or rifabutin) ± injectable agent (streptomycin or amikacin) administered daily or three times weekly. There were 240 patients in the intent to treat analysis with a mean age 63.2±12.4 years (range 35-90 years) who were 76% male, 80% white and 75% current or ex-smokers (>10 pack years smoking). 134 patients had adequate records available for treatment outcome evaluation. 86/134 (64%) had sputum AFB culture conversion while on therapy. Over the study period, the all cause mortality was 57% for the intent to treat cohort and 41% for patients with sputum AFB culture conversion on therapy. We conclude that cavitary MAC lung disease can be effectively treated with macrolide-based regimens but is associated with high all cause mortality regardless of MAC treatment response.

Funded in part by the Amon Carter Foundation, Ft. Worth, TX and W.A. and E.B. Moncrief Distinguished Professorship UTHSC.

P4372
Invasive pulmonary aspergillosis: What is the role of surgery in the voriconazole era?  
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Invasive pulmonary aspergillosis (IPA) is one of the most severe infections in immunocompromised patients. In the 90’s, surgery was considered a potentially curative treatment. Since voriconazole has become the first line treatment, the role of surgery has not been evaluated. Thirty immunocompromised patients who underwent surgery for a suspected IPA were retrospectively reviewed and separated into two groups: the group A (n=20) who received amphotericin B or itraconazole before the surgery, and the group B (n=10) treated by voriconazole.

The diagnosis of IPA before surgery was certain or probable for 44% of the patients. The main indications for surgery were: the resection of a persistent pulmonary lesion prior to subsequent immunosuppressive treatments (50%), incomplete control of the infection (43%), and risk of haemoptysis (10%). The median duration of antifungal treatment before surgery was 3 months in the group A, and 2.5 months in the group B (p=0.02). Persisting aspergillosis was confirmed for 85% among the patients from the group A, and only 20% of the group B (p=0.001). Anatomopathological study provided an alternative diagnosis for 4 patients, all in the group B: 2 mucormycosis, 1 mycobacterial infection, 1 specific lesion of the leukemia. Perioperative mortality was low (3%).

Surgery is a therapeutic option for IPA with low mortality in a well trained surgical team. In the voriconazole era, the proportion of resected pulmonary lesions containing Aspergillus appears to be decreasing, whereas other fungal infections are detected. The role of surgery has to be defined in patients previously treated with voriconazole, particularly for remaining pulmonary lesions.

P4373
Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia.  
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Background: Health care-associated pneumonia (HCAP) includes a broad range of patients having frequent or chronic contact with health care systems. However, the relationship between current defining criteria for HCAP and the risk of potentially drug-resistant (PDR) pathogens is controversial.

Methods: We retrospectively evaluated patients admitted to Severance Hospital in South Korea with culture-positive pneumonia from January 2008 to December 2009. We analyzed the associations between risk factors for HCAP and infection with PDR pathogens.

Results: Among 339 patients, PDR pathogens were observed in 122 (36.6%) and non-PDR pathogens in 217 (64.4%). PDR pathogens were more common in HCAP than community-acquired pneumonia (CAP) (48.5% vs 23.8%, P < 0.001), but 51.5% of HCAP showed non-PDR pathogens. In a logistic regression, prior hospitalization within 90 days of pneumonia (OR = 2.52, P = 0.003), recent treatment with antimicrobials (OR = 2.35, P = 0.039) and nasogastric tube feeding (OR = 13.94, P = 0.001) were independently associated with PDR pathogens.

Conclusions: The current criteria for HCAP are poor predictors of PDR pathogens and all patients with HCAP should not be empirically treated for these pathogens. To avoid excessive antibiotic use, individual risk stratification approaches should be considered.

P4374
Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia.  
Seon Cheol Park1, Bosco Paes2, Abby Li1, Krista Lanctot1. 1Pulmonology, University of Calgary, AB, Canada; 2Pulmonology, McMaster University, Hamilton, ON, Canada

Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia.  
Seon Cheol Park1, Bosco Paes2, Abby Li1, Krista Lanctot1. 1Pulmonology, University of Calgary, AB, Canada; 2Pulmonology, McMaster University, Hamilton, ON, Canada

Background: Health care-associated pneumonia (HCAP) includes a broad range of patients having frequent or chronic contact with health care systems. However, the relationship between current defining criteria for HCAP and the risk of potentially drug-resistant (PDR) pathogens is controversial.

Methods: We retrospectively evaluated patients admitted to Severance Hospital in South Korea with culture-positive pneumonia from January 2008 to December 2009. We analyzed the associations between risk factors for HCAP and infection with PDR pathogens.

Results: Among 339 patients, PDR pathogens were observed in 122 (36.6%) and non-PDR pathogens in 217 (64.4%). PDR pathogens were more common in HCAP than community-acquired pneumonia (CAP) (48.5% vs 23.8%, P < 0.001), but 51.5% of HCAP showed non-PDR pathogens. In a logistic regression, prior hospitalization within 90 days of pneumonia (OR = 2.52, P = 0.003), recent treatment with antimicrobials (OR = 2.35, P = 0.039) and nasogastric tube feeding (OR = 13.94, P = 0.001) were independently associated with PDR pathogens.

Conclusions: The current criteria for HCAP are poor predictors of PDR pathogens and all patients with HCAP should not be empirically treated for these pathogens. To avoid excessive antibiotic use, individual risk stratification approaches should be considered.

P4375
Rates of ophthalmic complications due to ethambutol in patients with non-tuberculous mycobacteria  
Andrew Malem1, Helen Barker2, Nadia Shafi1, Dennis Wat1, Charles Hawthor1, R. Andres Plaza2. 1Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, United Kingdom; 2Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom

Infection with Non-Tuberculous Mycobacteria (NTM) is a growing clinical problem particularly in patients with inflammatory lung disease. For many NTM infections, treatment involves at least 12 months of combination antibiotic therapy including Ethambutol. While ophthalmic complications are extremely rare in patients taking ethambutol as part of standard quadruple therapy for Mycobacterium avium complex (MTB) infection, they may be higher during treatment for extended periods. We therefore carried out a retrospective analysis of patients treated with ethambutol for NTM infection at the Cambridge Centre for Lung Infection between 2006 and 2011. We identified 46 patients with confirmed NTM infection who received ethambutol. 4 individuals were excluded from further analysis because of incomplete/missing notes. We identified 5 out of 43 patients (11.9%) with documented changes in visual acuity and colour vision diagnosed by an ophthalmologist as probable ethambutol toxicity. There was no significant difference between those with ophthalmic com-
plications and those without in the following parameters: age, dose of ethambutol per kilogram, serum creatinine levels and treatment duration. Where measured, low serum zinc levels were found in individuals who developed ophthalmic complications but these were not significantly lower than those of unaffected patients.

Our data suggests that ethambutol toxicity is a relative common problem in patients with NTM infection requiring extended treatment with ethambutol despite appropriate dosing and regular ophthalmology review. Further studies will be needed to define how best to minimize this potentially devastating complication.

**P4376**

**Evaluation of moxifloxacin (MXF) as empiric antibiotic therapy of CAP outpatients: A multicenter prospective study**

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Antoni Peces5,1 Servicio de Neumología, Hospital Clinínic IDIBAPS CIBERSERES, Barcelona, Spain; 2 Respiratory Disease Department, University of Bochum, Germany; 3 Respiratory Disease Department, University of Hannover, Hannover, Germany; 4 Servicio de Neumología, Hospital La Princesa, Madrid, Spain; 5 Servicio de Neumología, Hospital de Galdakao, Spain; 6 Servicio de Neumología, Hospital del Mar, Mesures, Spain

**Objectives:** To compare clinical characteristics and outcomes of CAP outpatients receiving MXF with standard therapies (levofloxacin [LFX] or amoxicillin-clavulanic acid plus azithromycin [AMC/AT]).

**Methods:** A retrospective analysis was conducted on 300 patients prospectively recorded in 4 Spanish and 2 German hospitals (174 LVF, 75 MXF, and 51 AMC/AT). Demographic, clinical characteristics and outcomes (mortality, hospitalization) were recorded. Since demographic and clinical data did not differ between LXF and AMC/AT patients we analysed them together.

**Results:**

**MXF vs LXF vs AMC/AT (p<0.05)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MXF (n=75)</th>
<th>LXF (n=425)</th>
<th>AMC/AT (n=225)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>73±17</td>
<td>64±17</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Males, %</td>
<td>54</td>
<td>54</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccine, %</td>
<td>20</td>
<td>6</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine, %</td>
<td>40</td>
<td>23</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure, %</td>
<td>7</td>
<td>2</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>15</td>
<td>8</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease, %</td>
<td>36</td>
<td>24</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>Previous antibiotic (2 months), %</td>
<td>23</td>
<td>25</td>
<td>0.495</td>
<td></td>
</tr>
<tr>
<td>PSI classes I-III, %</td>
<td>90</td>
<td>97</td>
<td>0.086</td>
<td></td>
</tr>
<tr>
<td>PSI class IV, %</td>
<td>5</td>
<td>3</td>
<td>0.304</td>
<td></td>
</tr>
<tr>
<td>CURB-65 classes 0-1, %</td>
<td>94</td>
<td>95</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>CURB-65 class 2, %</td>
<td>5</td>
<td>5</td>
<td>0.599</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure, %</td>
<td>18±5</td>
<td>22±5</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>CIM (mg/dl), mean±SD</td>
<td>7±11±3</td>
<td>14±4±10</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Leukocytes, mean±SD</td>
<td>10067±4910</td>
<td>1250±7691</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>SatO2%, mean±SD</td>
<td>96±12</td>
<td>95±8</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion, %</td>
<td>1.3</td>
<td>7</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Multilobar infiltrate, %</td>
<td>0</td>
<td>10</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

No microbiological differences were observed (S. pneumoniae in 20% [MXF], 18% [LXF+AMC/AT]). There were no fatality cases. Five hospitalizations were recorded. Since demographic and clinical data did not differ between MXF and AMC/AT patients we analysed them together.

**Conclusions:** MXF was prescribed in older patients with more comorbidities and therefore, is a valuable option for outpatient treatment of CAP.
P4380 Pulmonary nocardiosis in a teaching hospital in the Central Anatolia of Turkey: Clinical experience in 26 patients
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Pulmonary nocardiosis (PN) is an uncommon but severe infection caused by Nocardia spp., which can behave either as opportunistic or primary pathogens. The diagnosis of PN can easily be missed. The purpose of this retrospective study is to review the predisposing factors, clinical symptoms, microbiologic, radiographic characteristics, diagnostic procedures, treatment and outcome of the patients with PN confirmed positive culture, diagnosed in a teaching hospital over the last 11 years. Twenty-six (20 men and 6 women) adult patients with a mean age at time of 49 years (range: 21 to 72 years) were identified with PN. Half of the patients had disseminated nocardiosis (8 with dissemination to central nervous system, 5 with soft tissue and cutaneous abscesses). The predisposing conditions were treatment of steroids (88%), chronic lung diseases (31%), transplantation (19%) and malignancy (19%). Mean time to diagnosis was 31 days. In 21 patients (80%), the infection occurred outside the hospital setting. Respiratory tract sampling using noninvasive techniques had a diagnostic yield of 81%, while specimens from invasive methods had a yield of 37%. The radiological changes were diverse and non-specific. Nocardia asteroides-type V (N. caryophyllaceae) and N. farcinica were the most common species. Treatment was started empirically, modified according to the antimicrobial susceptibility pattern, and then continued for 6–12 months. Overall mortality was 58%, with death being caused by the Nocardia infection in 7 patients (27%). PN is a rare infection and mainly affects immunocompromised patients. Higher index of suspicion is needed for earlier diagnosis and treatment to improve prognosis.

449. Outcomes and assessment methods in physiotherapy and rehabilitation

P4381 Predicting the risk of falls in patients with COPD: Does age matter?
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Introduction: The extrapolationary manifestations of COPD have been associated with deficits in mobility and balance, which potentiate the risk of falls. This is more evident in advanced COPD. However, research in the risk of falling in this population is scarce, as deterioration of balance increases with age, it is important to understand how age influences the fall risk in these patients.

Aim: To assess the risk of falls in different age groups of patients with advanced COPD.

Methods: Fifty-five outpatients with COPD (GOLD III and IV) were recruited. The risk of falling was assessed using the Timed Up & Go (TUG) test. Two TUG tests were performed and the best performance was considered. Participants (9 males) were divided into 4 groups according to their age: <50 (n=11; G1), 50-69 (n=11; G2), 70-79 (n=20; G3) and 80-99 years old (n=13; G4).

Results: The mean TUG time for each group was G1 11.03±3.11, G2 10.73±1.36, G3 11.22±4.35, G4 14.34±4.87 seconds. No statistical significant differences between groups were found. However, all groups presented worse values than the average performance of their age-matched healthy peers.

Conclusion: Patients with advanced COPD exhibit changes in balance and are at risk of falling, regardless of their age. The results suggest that pulmonary rehabilitation, a recommended standard of care for patients with COPD aimed to optimize functional status and increase participation, should include a specific component of balance training and strategies to prevent falls, to restore the highest possible level of independent function in this population.


P4382 Does the incremental shuttle walking test (ISWT) require maximal effort in healthy subjects of different ages?
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Background: It is unknown whether the ISWT requires maximal effort in subjects of different ages.

Objective: To evaluate if the ISWT requires maximal effort in healthy subjects of different ages.

Methods: 331 individuals (158 men) performed two ISWT, allowing more than 12 levels of the test, if necessary. The participants were separated into six groups according to their age (G1: 18-28, G2: 29-39, G3: 40-50, G4: 51-61, G5: 62-72 and G6: 73-83 years). Heart rate (HR) and symptoms of dyspnea and fatigue were recorded. HR achieved at the end of the test was expressed as a percentage of the maximum heart rate (HRmax).

Results: 31% of the subjects achieved more than 12 speed levels. The majority of the subjects reached HR values below 85% of HRmax at the end of the test with a median [interquartile range] of: G1: 100[95-104]; G2: 100[96-105]; G3: 102[97-107]; G4: 99[91-105]; G5: 95[87-106] and G6: 95[90-109]%HRmax. Regarding symptoms, all groups showed higher values of dyspnea and fatigue at the end of the test (p < 0.05). A multivariate analysis (logistic regression) identified that female gender (odds ratio: 3.3 [95% confidence interval: 1.4-8.1], worse performance in the ISWT (low: 4.2 [1.7;10.0], normal: 2.6 [1.3-5.4] versus high) and age (4.7 [1.7;12.9]) increased the chance for not achieving 90% of HRmax at the end of the ISWT.

Conclusion: The Incremental Shuttle Walking Test is a field test that requires between individuals, and for that it is necessary to test the end beyond twelve speed levels. Female gender, older age and worse performance in the test are the determinants for not reaching maximal effort during the ISWT.

P4383 Are 30 minutes of rest between two incremental shuttle walking tests enough for cardiovascular variables and symptoms to return to baseline values?
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Background: The Incremental Shuttle Walking Test (ISWT) is commonly performed twice for purposes of reproducibility, in general, 30 minutes of rest between the tests. However, it is unknown if the 30 minutes’ rest is sufficient for stabilization of cardiovascular and symptomatological variables.

Aim: To investigate if 30 minutes of rest between two ISWTs are enough for cardiovascular and symptomatological variables to return to baseline values in healthy subjects of different ages.

Methods: 457 healthy subjects (154 men, 63[45-70] years, 27[24-30] kgm²) were assessed and separated into quartiles according to their age: Q1 (18 to 45 years, n=117), Q2 (46 to 63 years, n=116), Q3 (64 to 70 years, n=121) and Q4 (71 to 83 years, n=103). Two ISWTs were performed with at least 30 minutes of rest in between, and heart rate (HR), blood pressure (BP) and symptoms of dyspnea and fatigue were assessed before and after the tests.

Results: The HR before the ISWT was higher in the second test compared to the first one in the whole group and in all subgroups (p<0.001 for all). The systolic BP was higher before the second test only in the whole group (p=0.04). Regarding symptoms, fatigue showed statistical significance only in Q1 (p=0.02), being higher before the second test compared to the first. Diastolic BP and symptoms of dyspnea were similar before the two ISWTs in the whole group and in all subgroups.

Conclusions: 30 minutes of rest between two ISWTs are not enough for the cardiovascular system to return to baseline values in healthy subjects, regardless of age. For perceived symptoms of dyspnea, this amount of rest seems to be enough.

P4384 Predictors for longitudinal change in 6-minute walk distance in COPD patients
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Introduction: The 6-min walk distance (6MWD) is widely used to evaluate exercise capacity in patients with Chronic Obstructive Pulmonary Disease (COPD), and is predictive of mortality and exacerbations.

Aim: To examine the change in 6MWD over 3 yrs in COPD patients and elucidate factors at baseline that may predict that change.

806s
Methods: This prospective observational study included 389 patients aged 40-75 yrs, with clinically stable COPD in GOLD stage II-IV. Measurements at baseline and after 1 and 3 yrs included 6MWD, spirometry, body mass index (BMI), and assessment of smoking habits and exacerbations by questionnaires. Adjusted generalized estimating equations (GEE) regression analyses were used to analyze predictors for change in 6MWD.

Results: There was no significant change in 6MWD from baseline to 1 yr for any GOLD stage, or from baseline to 3 yrs for patients in GOLD II. For GOLD III (β= -36 m, 95% CI=-55, -17) and IV (β=86 m, 95% CI= -138, -33) 6MWD decreased (p<0.001). In the multivariate GEE forced expiratory volume in one second (FEV1) (p<0.001), forced vital capacity (p<0.001), age (p<0.001), exacerbations (p=0.018), BMI (p=0.001) and pack years (p=0.003) were predictors for 6MWD, though only FEV1 predicted change over time (p=0.003).

Conclusion: Patients in GOLD stage II maintained 6MWD at 3 yrs, while patients in GOLD III and IV reduced 6MWD significantly. FEV1 was a strong predictor for longitudinal change in 6MWD.

P4385

Twelve-minute walking distance predicts COPD mortality
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1Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 2School of Health Sciences, University of Akureyri, Iceland; 1Rehabilitation Unit, Akureyri Hospital, Akureyri, Iceland

Background: Patients in pulmonary rehabilitation (PR) suffer from poor lung function, exercise capacity and health-related quality of life (HRQoL). Some of these factors have been shown to relate to mortality in COPD. Drop-out from clinical PR-studies is often high and might indicate worse prognosis in that group.

Aims: To measure the five-year survival of 89 COPD-patients enrolled in a four-month PR at Uppsala University Hospital and investigate if the 12 min walking distance (12MWD), peak exercise capacity (Wpeak), HRQoL and being able to fulfill the training period had prognostic value for survival.

Methods: Long function (FEV1, VC), 12MWD. Wpeak and HRQoL (SF-36) were measured at baseline. Of 89 included patients, 53 fulfilled the PR-program.

Results: Mean baseline FEV1 was 34±1 L, 95% CI=31.4, 36.5). The desaturation was significantly lower for CE compared to ISIT-1 or ISIT-2 (r=0.72, r=0.21, respectively) and for heart rate expressed as a percentage of the predicted rate (89±12, 90±13, 88±11, respectively). The desaturation was significantly lower for CE compared to ISIT-1 or ISIT-2 (r=0.72, r=0.21, respectively). The desaturation was significantly lower for CE compared to ISIT-1 or ISIT-2 (r=0.72, r=0.21, respectively). The desaturation was significantly lower for CE compared to ISIT-1 or ISIT-2 (r=0.72, r=0.21, respectively).

Conclusion: A symptom-limited incremental step test, externally paced, elicits maximal cardiopulmonary and metabolic responses, and is well tolerated and reproducible in patients with COPD.

P4387

The impact of MRC classification on daily physical activity and physical health-related quality of life in mild to moderate COPD
Hans, Van Remenste1,2, Michele Hornok1,2, Hellen Deneyer1,2, Kristien De Bent1, Erica Ballingard1, Laurence Vrancken1,2, Chris Buttin1,2, Daniel Langer1,2, Marc Decramer1,2, Rikk Gosselink1,2, Wim Janssens1,2, Thierry Troosters1,2
1Rehabilitation Sciences, Katholieke Universiteit Leuven, Faculty of Kinesiology and Rehabilitation Sciences, Leuven, Belgium; 2Respiratory Division and Pulmonary Rehabilitation, University Hospital K.U. Leuven, Belgium; 3Clinical Trial Unit, Department of Pneumology, University Hospital K.U. Leuven, Belgium

Dyspnea, reduced physical activity (PA) and impaired health-related quality of life (HRQoL) are common features in COPD. This study aimed to investigate the impact of dyspnea on PA and HRQoL in mild/moderate COPD.

Fifty-three subjects with COPD and 60 smoking controls were recruited. Medical Research Council (MRC) classified patients by symptoms of dyspnea. The SenseWear Armband was worn for 7 days and time spent in at least moderate intensity PA and amount of steps served as PA estimates. HRQL was assessed by the SF-36 physical functioning score and the EQ5D general health VAS score.

Conclusion: A symptom-limited incremental step test, externally paced, elicits maximal cardiopulmonary and metabolic responses, and is well tolerated and reproducible in patients with COPD.

P4388

Does the energy expenditure of patients with COPD reflect their time spent walking and intensity of walking in daily life?
Thais Sant’Anna, Carlos Augusto Camillo, Renato Vitorasso, Anaisa Cortez Vercese, Victoria Cristina Escobar, Nidia Aparecida Hernandez, Fabio Pitta. Laboratory of Research in Respiratory Physiotherapy (LHRP), Department of Physiotherapy, State University of Londrina, Londrina, Brazil

Introduction: The level of physical activity in daily life (PADL) is frequently assessed by energy expenditure (EE) measurement. However, patients with chronic obstructive pulmonary disease (COPD) often present high EE due to increased work of breathing, systemic inflammation and other factors. Thus, EE might not be a good outcome to characterize PADL in this population.

Aim: To verify the influence of time spent walking, movement intensity and other PADL variables on EE of patients with moderate to severe COPD.

Methods: The PADL of 53 patients (51m, 66±9 yrs, FEV1 38±15 (predicted) was evaluated by two activity monitors (DynaPort MiniMod and SenseWear). The DynaPort mainly registers time spent walking (TW), standing, sitting, lying (TL), and the other PADL variables on EE of patients with moderate to severe COPD.

Conclusion: Moderate intense PA was significantly reduced in MRC1 COPD compared to MRC1 smokers and tended to be lower versus MRC0 COPD (p<0.10). A trend for reduced daily steps in MRC1 COPD was observed versus MRC3 smokers and MRC0 COPD (p<0.09). MRC1 COPD reported reduced physical functioning and PA scores versus MRC0 COPD (70±19 vs 81±13 vs 84±17, respectively) for physical functioning, p<0.01 and 71±12 vs 77±14 vs 81±10 for VAS score, p<0.05.

PA levels are reduced in symptomatic patients with mild to moderate COPD. MRC classification, as proposed by the new GOLD guidelines, is useful in identifying reductions in PA and (physical) HRQoL, even in the early stages of COPD.

P4389

The impact of age on physical activity and health-related quality of life in COPD
Thais Sant’Anna, Carlos Augusto Camillo, Renato Vitorasso, Anaisa Cortez Vercese, Victoria Cristina Escobar, Nidia Aparecida Hernandez, Fabio Pitta. Laboratory of Research in Respiratory Physiotherapy (LHRP), Department of Physiotherapy, State University of Londrina, Londrina, Brazil

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Methods: The PADL of 53 patients (51m, 66±9 yrs, FEV1 38±15 (predicted) was evaluated by two activity monitors (DynaPort MiniMod and SenseWear). The DynaPort mainly registers time spent walking (TW), standing, sitting, lying (TL), and movement intensity during walking (MI). The SenseWear mainly registers total energy expenditure (TEE) and active energy expenditure (AEE). Patients wore both motion sensors in daily life during two consecutive weekdays (12hs/day).

Conclusion: Moderate intense PA was significantly reduced in MRC1 COPD compared to MRC1 smokers and tended to be lower versus MRC0 COPD (p<0.10). A trend for reduced daily steps in MRC1 COPD was observed versus MRC3 smokers and MRC0 COPD (p<0.09). MRC1 COPD reported reduced physical functioning and PA scores versus MRC0 COPD (70±19 vs 81±13 vs 84±17, respectively) for physical functioning, p<0.01 and 71±12 vs 77±14 vs 81±10 for VAS score, p<0.05.

PA levels are reduced in symptomatic patients with mild to moderate COPD. MRC classification, as proposed by the new GOLD guidelines, is useful in identifying reductions in PA and (physical) HRQoL, even in the early stages of COPD.
P4389
Comparison of outcomes of the Actigraph and the Dynaport activity monitor in patients with COPD: results from PROactive
Juliana Maria Sousa Pinto,1 Thierry Troosters,2 Laurence Vranken1,2, Miek Hernikx1, Heleen Demeyer2, Wim Janssens1, Marc Decramer1, Judith Garcia-Aymerich1,2, 2Rehabilitation Sciences and Respiratory Division, KU Leuven and UZ Leuven, Leuven, Belgium; 2Center for Research in Environmental Epidemiology, CREAL, Barcelona, Spain

Activity monitors are increasingly used to assess physical activity. We aimed to compare wearing time and walking between two activity monitors in COPD. Fifty four patients (FEV1 62±22%pred; MFWD 459±138m) wore the Actigraph (AG) and Dynaport (DP) twice for 14 days with 14 days in between, in the frame of the PROactive project. Wearing time (h/d); walking time(min/d) of DP (DPWT) and step/day of AG (ASteps) were retrieved. Calculations were done on the mean wearing and walking variables obtained over 28 days (Inter-patient correlations).

Activity monitors were calculated over the 28 days obtained in each patient, as well as between mean weekly values of the 4 weeks (6 contrasts).

Results: Wearing time of the AG and DP were strongly related (R=0.80 p<0.001).

Intra-patient correlations were calculated over the 28 days obtained in each patient, as well as between mean weekly values of the 4 weeks (6 contrasts).

Conclusion: These data show that both monitors provide comparable outcomes and are capable of measuring differences between separate weeks of assessment. The difference in wearing time needs clarification.

P4390
Cell phone based physical activity monitoring: A validation study
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Background: Accelerometers are accurate and useful for monitoring Physical Activity (PA) in people with chronic lung disease (eg. COPD) and can help motivate clients to comply with rehabilitation. However, they are expensive and largely limited to research. Similar motion sensors are embedded within the majority of newer mobile phones, which are widely accessible.

Aim: This study investigated whether the built-in accelerometers within mobile phones may be valid and reliable for monitoring PA.

Method: A mobile phone application to record real time tri-axial accelerometer data (Actigraph GT3X). Wearing all 3 devices, 7 healthy adults performed 7 different activities, paced with a metronome, each repeated 7 times. Absolute values of 3D acceleration signals were summed and averaged over each time period. Reliability was evaluated using intra-class Correlation Coefficients (ICC). Concurrent validity was assessed using a general linear model for repeated measures (GLM) and Pearson correlation.

Results: The ICC for both phone devices ranged between 0.82 and 0.98. GLM and Pearson correlation results showed good agreement (R2 = 0.72, R2-chance = 0.11 for step 1, R2-chance = 0.06 for step 2 (p<0.001). **p<0.01, ***p<0.001.

Conclusion: Mobile phone accelerometers appear to be reliable and valid for measuring PA. Further research is needed to confirm these data in a patient population.
and upper limb exercise capacity in people with chronic obstructive pulmonary disease (COPD).

Methods: Repeated measures design. Participants were included if they had a diagnosis of COPD, FEV1/FVC ratio < 0.7. Exclusion criteria were an acute infection in the prior month, or neurological, musculoskeletal or cardiovascular conditions that limited upper limb exercise. Participants completed the following assessments: spirometry, incremental supported arm exercise (SAE) to peak work capacity on an arm ergometer, incremental unsupported arm exercise (UAEx) to peak capacity using an unsupported arm test (Takahashi, T. et al. ICRP 2003;23:24-30), isometric upper limb strength measurements using a hand held dynamometer. Dominant arm strength was calculated by the mean of the following strength measurements: shoulder flexion & extension, horizontal abduction & adduction, internal & external rotation and elbow flexion. SAE and UAEx were performed in random order based on concealed allocation sequence.

Results: 68 participants completed the study, mean (SD) age 65(8) yrs, FEV1 %pred 50 (17), FVC %pred 77 (17), FEV1/FVC 0.48 (0.1). Peak oxygen consumption (VO2peak) for SAE and UAEx was 8.00 (0.28) L/min and 0.71 (0.31) L/min respectively. Dominant arm strength was 103 (29) Newtons. Multiple regression on VO2 and VE/VCO2 using combined dominant arm strength and FEV1 %pred as predictors, accounted for 66% (p < 0.001) and 55% (p < 0.001) of the variance, respectively.

Conclusion: Upper limb strength combined with FEV1 %pred are significant predictors of both supported and unsupported upper limb exercise capacity in COPD.

P4394

Relationship between oxygen uptake kinetics and BODE index at the onset of high-intensity exercise in moderate-to-severe COPD patients

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Background: Patients with chronic obstructive pulmonary disease (COPD) present reduced exercise capacity due impaired oxygen delivery-utilization, caused primarily by pulmonary dysfunction and deleterious peripheral adaptations. Assuming that COPD patients present with slower VO2 and heart rate (HR) kinetics, we hypothesized that this finding is related to degree of severity in according to BODE index.

Aim: To evaluate the relationship between oxygen consumption (VO2) on-kinetics during high intensity exercise and the BODE index in patients with COPD.

Methods: Twenty males with moderate to severe stable COPD and thirteen healthy control subjects matched by age and gender were evaluated. Initially, COPD patients were screening by BODE index and then, all volunteers were submitted to an incremental cardiopulmonary exercise testing, and subsequently, a constant speed on a treadmill at 70%, for 6 minutes. The on-transient (first 360 seconds) response of VO2 and HR was modeled according to a monoexponential fit.

Results: VO2 and HR on-kinetics were slower in the COPD group than controls. Additionally, VO2 on-kinetic parameters revealed a strong correlation (p=0.77, p<0.05) between BODE scores and negative and moderate correlation between walking distance (r=0.45, p<0.05).

Conclusion: Our data show that moderate to severe COPD is related to impairment of oxygen delivery and utilization during the onset of intense exercise. In addition, there is a relationship between walking distance as well as BODE index with VO2 on-kinetic behavior. Thus, the severity of COPD is reflected by progressive slowing of VO2 on-kinetics.

Financial support: FAPESP.

P4395 Quantifying the variability of physical activity in daily life caused by seasonality in smokers

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Background: The level of physical activity in daily life (PADL) depends on many factors, such as social, economical, physiological and demographical aspects. Despite these many causes of variability, the influence of the seasons of the year on PADL is unknown in smokers.

Aims: To compare changes in the level of PADL in apparently healthy smokers who started in different climatic conditions a protocol aiming at improving PADL; and to quantify the proportion of subjects who achieved 8000 steps/day before and after the intervention.

Methods: 20 smokers with normal lung function were submitted to a 5-month protocol using booklets and pedometers (or step counters) in order to improve PADL by aiming to increase the number of steps/day. They had their baseline PADL assessed for 6 days with a pedometer during Spring/Summer (SS: n=10, 5 men, 51[39-59] years, BMI 26[23-29] kg/m2, 38[17-50] pack-years) or Autumn/Winter (AW: n=10, 5 men, 53[48-57] years, BMI 26[24-28] kg/m2, 38[17-50] pack-years). Reassessment was performed after the protocol, in the opposite climatic condition as compared to baseline.

Results: Both groups improved their PADL after the protocol (Δ steps/day = SS: 3191[1888-4461] and AW: 2903[517-5377]; p<0.002 for both). There were no between-groups statistical differences concerning baseline PADL changes after the protocol, and proportion of subjects who reach 8000 steps/day before and after the protocol (SS: from 46% to 86%; AW: from 36% to 76%).

Conclusions: These preliminary results showed that climatic variation does not incur in significant impact in the level of PADL in apparently healthy smokers, since the same benefits could be achieved regardless of the seasonality.

P4396

Chest wall motion and volume changes with and without non-invasive ventilation in patients with amyotrophic lateral sclerosis

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In Amyotrophic Lateral Sclerosis (ALS), inspiratory, expiratory, and bulbar muscles are altered, leading to chronic respiratory failure. Non-invasive ventilation (NIV) can be used to improve gas exchange in this patient population.

Aims: To analyze the chest wall motion and operational volume changes in patients with ALS with and without NIV in the supine position.

Method: Ten patients with ALS, aged 54±13 years were included. Optoelectronic plethysmography (BTS, Milan, Italy) was used to measure: tidal volume of the chest wall (VTe CW), tidal volume of the pulmonary rib cage (Vtrc), tidal volume of the abdominal rib cage (Vtrc), tidal volume of the abdomen (Vtba),
end-inspiratory (Veicw) and end-expiratory (Veecw) volumes of the chest wall, respiratory frequency (f) and minute ventilation (VE). All patients were evaluated in the supine position with and without NIV for five minutes (Triology 100, Respironics, USA) NIV was used in the spontaneous/timed mode, with inspiratory and expiratory pressures of 14 cmH2O and 4 cmH2O, respectively. Paired t-tests were used for statistical analyses (p<0.05).

Results: See Table 1.

Table 1: Chest wall motion and volume changes with and without NIV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine without NIV</th>
<th>Supine with NIV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veiw (L)</td>
<td>0.4 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.025</td>
</tr>
<tr>
<td>Vixi%</td>
<td>28.1 ± 15</td>
<td>32.15 ± 15</td>
<td>0.572</td>
</tr>
<tr>
<td>Vixi%</td>
<td>13.5 ±</td>
<td>11.6 ±</td>
<td>0.180</td>
</tr>
<tr>
<td>Vixi%</td>
<td>58.0 ± 15</td>
<td>57.2 ± 18</td>
<td>0.830</td>
</tr>
<tr>
<td>Vixi%</td>
<td>18.9 ± 4</td>
<td>19.4 ± 3.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Vixi%</td>
<td>18.5 ± 4</td>
<td>18.8 ± 4</td>
<td>0.019</td>
</tr>
<tr>
<td>f (ipms)</td>
<td>19.9 ±</td>
<td>21.1 ±</td>
<td>0.212</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>6.92 ± 2.5</td>
<td>10.7 ± 4</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Conclusion: NIV led to significant increases in tidal, end-inspiratory, and end-expiratory volumes, with no changes in the contributions of the three chest wall compartments. Partially supported by FAPEMIG and CNPq.

P4397

Can breathing pattern parameters be differentiated between healthy and severe asthma patients?

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Abnormal breathing patterns during acute episodes of asthma are common. However, little is known about breathing pattern parameters (BPP) in severe asthma (SA) patients during the asymptomatic phase, or how they relate to those in the healthy population.

Aim: To determine which BPP differentiate SA patients from healthy controls.

Method: Ten SA patients and 10 healthy controls were recruited. BPP were monitored over 30 minutes by a respiratory inductive plethysmography. Recorded BPP were: 1. Tidal volume (Vt); 2. Variability in tidal volume (VVi); 3. Expiration time (Te); 4. Symptoms of hyperventilation (SH); 5. End-tidal carbon dioxide (ETCO2); 6. Vt was assessed by coefficient of variation (CV). Time series of breath by breath VT were inspected for abnormal pattern. SH were assessed by Nijmegen questionnaire (NQ). ETCO2 was monitored by capnography. Differences between healthy controls and SA patients were explored using one-way ANOVA.

Results: Mean NQ score was higher in SA patients than in healthy controls (p>0.00). ETCO2 levels were significantly correlated with NQ score (r = 0.8, p < 0.01) in the SA patients but not in healthy volunteers (r = 0.6, p = 0.01). Time series analysis revealed sporadic episodes of frequent sighs in both groups. No significant differences between groups for any BPP were identified.

Conclusion: The recorded BPP did not differentiate between the SA patients and healthy volunteers in our small study. The higher SH found in the SA group do not appear to be associated with differences in BPP. This study raised doubt that there is a ‘pattern’ that is common within the SA population and therefore BPP must be considered on an individual basis.

P4398

Respiratory occupational therapy (OT) within a community respiratory team: Referral and intervention patterns

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Introduction: OT aims to maximise independence, occupational performance and improve quality of life. Respiratory OT provides a specialist functional and gynecology fields have previously reported that quantification of sonographic echogenicity with histogram were useful for the diagnoses of tissue. Aim: To evaluate whether histogram data collected from EBUS-GS images can contribute to the diagnosis of lung cancer or not.

Methods: Fifty clear EBUS images (25 lung cancer and 25 inflammatory disease) were included in this study. The region of interest (ROI), was set within a 5mm radius from the EBUS probe with 400 pixels (20x20). Histograms were created and compared using imageJ software, with a width of the histogram: (maximum – minimum gray scale)/256 (full gray scale) × 100 (%), height of the histogram: (maximum pixel counts), and the standard deviation of the histogram.

Results: The diagnosis yield by the width of the histogram were sensitivity of 84%, specificity of 88%, and positive predictive value of 87% when the cut-off level was 22 for lung cancer. Standard deviation of histograms also contribute to diagnosis of lung cancer, sensitivity of 80%, specificity of 88%, and positive predictive value of 87% when the cut-off level was 10.7. Height of the histogram was not useful due to low sensitivity.

Conclusion: The width and standard deviation of EBUS image histograms were useful in differentiating lung cancer from inflammatory lesion.

P4400

Aberrant methylation in lung cancer identified by EBUS-TBNA as a marker of advanced staging

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Introduction: Aberrant methylation of DNA results in gene silencing and is frequently observed in tumours from lung cancer patients. Aberrant methylation in lung cancer identified by EBUS-TBNA as a marker of advanced stages of the disease. Objective: To determine the relationship between the methylation status of 5 genes in metastatic lymph node and tumours samples obtained by EBUS-TBNA and the presence of an advanced stage of lung cancer.

Results: 239 OT referrals were recorded in 2011. 33 of these were excluded from the analysis, as OT was not required or the patient had died.

Of the 206 patients who received OT, 47 required physical and psychological intervention, however the intervention requested for 32 of these had been for psychological and 15 for physical only.

Conclusion: We observe from the data that most referrals are for Psy F. However a noticeable proportion of these also required intervention to address Phy F (need identified at OT assessment).

Having received joint physical and mental health training, OT is well placed to identify and address the link between psychological and physical symptoms, which limit daily functioning, in this complex patient group. This supports the need for the specialist respiratory OT role.
Methods: Nodal and tumour samples positive for lung cancer were obtained with EBUS-TBNA. The methylation status of DAPK, p16, RASSF1, APC and CDH1 genes was determined by methylation-sensitive high resolution melting

Results: 23 samples were analysed, 15 samples (6 mediastinal nodules, 1 lobar node and 2 tumour) were early cases of lung cancer (T1/T2) and 8 (4 mediastinal nodes, 3 lobar nodes and 1 tumour) more advanced lung cancer (T3/T4). Percentage of methylated sites for each gene are shown in the figure. The samples from patients with a more advanced stage of lung cancer had significantly more genes methylated (p<0.043) than the samples from patients with early lung cancer, identified by a higher T staging

Published ISS08/01612

P4401
Sampling of ipsilateral mediastinal nodes by EBUS-TBNA in lung cancer staging

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Conclusion: Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) has shown its usefulness in lung cancer (LC) staging. However, determinants of negative predictive value (NPV) of EBUS-TBNA are not well known. Aims: To determine clinical characteristics of LC that are associated with low NPV, that will allow a more accurate selection of patients needing additional staging techniques before surgery in front of a negative result of EBUS-TBNA.

Materials and methods: - NPV of EBUS-TBNA for the identification of mediastinal spread of LC was calculated in patients staged with EBUS-TBNA and treated surgically, performed lymph node dissection during surgery. Results: In 73 patients with T1 (n=35), T2 (n=39) and T3 (n=9) were studied. 48 patients (33.1%) showed mediastinal lymphadenopathy (ML) at computed tomography (CT). EBUS-TBNA got a representative sampling of ipsilateral major lobe parenchyma in 127 patients (87.6%, and 4R, 4L, and 7 in 105 patients (72.4%). The result was false negative regarding mediastinal lymph dissection in 20 patients (13.8%). The identification of mediastinal lymph nodes on CT was more predictive of negative EBUS-TBNA exploration (22.9% versus 9.3%, p=0.02). Unrepresentative sampling is predictive of negative EBUS-TBNA (30 values 8.7%, p<0.001) and unrepresentative sampling in 4R, 4L and 7 (32.5% values 6.7%, p<0.001) were significant predictors of a FN. In multivariate analysis, ML on CT (OR 3.399;CI 1.15-10) and insufficient sampling (OR 10.669;95CI 3.29-34.55) were independent variables of a low NPV.

Conclusions: EBUS-TBNA achieved a successful lymph node sampling of mediastinal regions ipsilateral to the tumor in over 85% of patients. Funded by FIS FIIS0901612.

P4402
Relationship between qualitative analysis of lung tumors using integrated backscatter-intravascular ultrasound (IBIVUS) and pathological diagnosis

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Introduction or background: End-bronchial ultrasound is used by a supersonic wave image to confirm the position relations of a tumor and the participation bronchius through a bronroscope. However, the diagnosis of the organization property of the tumor is difficult. We used integrated backscatter(IB) value which analyzed the reflection wave of the supersonic wave signal in the coronary arteries of human, and was calculated, and enabled a vascular wall organization property diagnosis.

Aims and objectives: The purpose of the study measures integrated backscatter (IB) by end-bronchial ultrasound for the diagnosis of the lungs tumors and analyzes it by comparing a tumor and the distinction of the normal tissue with surgical resection.

Methods: We analyzed lungs tumor and normal lungs organization provided from an autopsy specimen. We observed rejections with the structure of the organization about the lungs tumors.

Result: Surgery excision lungs tumors were 35 non-small-cell lungs cancer (squa- mor carcinoma 9 examples, non-squamous 26 examples). IB value showed lower value in non-small cell lung cancer tissue compared with normal lung tissue.

Conclusion: If the distinction of the normal tissue and tumor tissue is possible and applies it to an endoscopic diagnosis by measuring lungs tumors, normal lung, IB value of the pathology organization diagnosis and invasive level of the tumor may be enabled by bronchoscope endoscopy examination.

P4403
Diagnostic yield, clinical impact and cost aspect of EBUS-TBNA in mediastinal staging in lung cancer patients

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Background: In lung cancer minimally invasive staging of the mediastinum with endobronchial ultrasound transbronchial needle aspiration (EBUS- TBNA) has become an important alternative to the gold standard of mediastinoscopy.

Aims: First: To determine the diagnostic yield of EBUS-TBNA and calculate the reduction in number of mediastinoscopies that can be achieved when this technique is used as initial modality for mediastinal staging in lung cancer. Second: Calculate the reduction in health care costs when EBUS-TBNA is used in this setting.

Methods: In a retrospective cohort study all patients in our hospital in whom EBUS-TBNA was performed for mediastinal staging in lung cancer from September 2008 until January 2011 were identified and the results of EBUS-TBNA were analyzed. If metastatic tumour cells were found there was no indication for additional mediastinoscopy. Diagnostic yield of EBUS-TBNA and the number of mediastinoscopies that were avoided were calculated, as well as the achieved cost reduction.

Results: EBUS-TBNA was performed on 77 patients for mediastinal staging: 47 male and 30 female, average age 62.1 years (extremes 39-81). In 51% of patients (39/77) mediastinal lymph node metastases were found and mediastinoscopy could be avoided. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 91%, 100%, 100%, 86% and 95% respectively. The achieved cost reduction was 82 per patient known.

Conclusion: Mediastinoscopy can be avoided in more that 50% of lung cancer patients when EBUS-TBNA is used as initial staging modality for mediastinal staging, leading to a significant reduction of health care costs.

P4404
Adequacy of endobronchial ultrasound transbronchial needle aspiration samples in the subtyping of non small cell lung cancer

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Introduction: The histological subtyping of non small cell lung cancer (NSCLC) has become increasingly important due to advances in systemic therapy. There are now important differences in the treatment of squamous and non-squamous cancers. Non-squamous cancers (particularly adenocarcinomas) are also suitable for targeted therapy if the epidermal growth factor receptor (EGFR) genetic mutation is present.

Diagnosis is frequently made by fine needle aspiration from lymph node metastases.

Objectives: To analyse endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) data to establish our NSCLC not otherwise specified (NOS) rate and determine the technical success of EGFR testing.

Methods: All EBUS TBNA procedures performed at Leeds Teaching Hospitals between February 2009 and November 2011 were analysed. Data was collected on the indication, final histological diagnosis and whether EGFR mutation testing was possible.

Results: Data from 391 procedures was analysed. The indication was staging of malignancy in 345 patients and suspected non-malignant disease in 48 patients.

Malignant disease was diagnosed in 204 patients (52.2%), small cell 43, squamous cell 64, adenocarcinoma 40, adenosquamous 2, large cell 12, NSCLC NOS 31 and malignant disease of non lung primary 12.

The number of cases of NSCLC NOS was 31 of 149 NSCLCs. The NOS rate was 21.8%.

EGFR testing was requested in 36 patients. The sample was sufficient to allow testing in 32 patients (88.8%).

Conclusion: This data shows that EBUS TBNA samples are of adequate size to allow the determination of NSCLC sub-type and EGFR mutation status provided appropriate laboratory techniques are used.

P4405
How do cytology samples compare with histology specimens when used for EGFR testing in patients with NSCLC?

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Background: With the evolution of individualised treatment strategies in non small cell lung cancer (NSCLC), it is becoming increasingly important to obtain adequate tissue for accurate pathologic subtyping and molecular testing. In most
cases diagnosis and staging is done using small biopsies or cytology specimens obtained by minimally invasive techniques.

Aim: To compare the adequacy of cytology and histology samples used for epidermal growth factor receptor (EGFR) mutation screening.

Methods: Retrospective study of 135 consecutive samples obtained from NSCLC patients between Jan 2010 and Dec 2011.

Results: Of the 135 samples sent for EGFR testing, 13 were positive, 115 negative and 7 were considered inadequate or failed molecular testing. 106 had adenocarcinoma, 11 adenosquamous, 13 NSCLC-NOS (not otherwise specified), 4 squamous and 1 small cell. Positive EGFR was noted in 4 cytology and 9 histology samples (p=0.27).

Cytology samples include 46 endobronchial ultrasound (EBUS) guided fine needle aspiration (FNA), 8 pleural fluid, 7 ultrasound guided or superficial FNA's from lymph nodes or masses, 1 transbronchial (mini-probe), 2 bronchial washings and 2 brush biopsies. Histology includes 29 endobronchial biopsies, 19 CT guided lung biopsies, 8 thorascopic and 1 ultrasound guided pleural biopsies, 1 renal biopsy, and 11 surgical excision samples (bone, brain, lymph node and groin mass).

Conclusion: The overall adequacy rate from both groups was 95% with no difference, suggesting that the cytology samples can be reliably used for molecular testing.

P4406
Is the EBUS TBNA cytology adequate for EGFR analysis?
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Background: Endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) allows safe and reliable sampling of mediastinal and hilar lymph nodes with excellent specificity and good sensitivity. It is a well established technique in the diagnosis and staging of lung cancer including pathologic subtyping and recent studies have shown that the samples may also be adequate for molecular testing.

Aim: To evaluate the adequacy of EBUS TBNA samples used for epidermal growth factor receptor (EGFR) mutation screening.

Methods: Retrospective study of 46 consecutive EBUS-TBNA samples obtained from lymph nodes > 5mm short-axis and central lung parenchymal lesions. Fisher's exact test was used to compare the 2 groups.

Results: Of the 46 EBUS TBNA samples sent for EGFR testing, 38 were obtained from lymph nodes (19 subcarinal, 9 right paraaortic, 4 left paraaortic, 10 right hilar and 4 left hilar) and 8 from central lung parenchymal masses. In the lymph node group, 35 (92%) samples were negative for EGFR mutation, 3 (8%) failed testing and none were positive for EGFR; 30 had adenocarcinoma, 2 squamous and 5 NSCLC-NOS (not otherwise specified). In the central lung mass group (n=8), one positive with exon19 deletion, 6 negative and one failed testing was inadequate; 3 had adenocarcinoma, 3 NSCLC-NOS, 1 squamous and 1 adenosquamous.

The overall EBUS-TBNA adequacy from both lymph nodes and central lung masses was 91% and there was no difference between the groups.

Conclusion: Molecular testing of EBUS TBNA samples obtained from mediastinal masses was 91% and there was no difference between the groups. Positive EGFR was noted in 4 cytology and 9 histology samples (p=0.27).

P4407
Factors related to the diagnostic yield of ultrathin bronchoscope for peripheral pulmonary lesions
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Introduction: The global diagnostic yield of peripheral pulmonary lesions (PPL) not candidates for CT-FNA, is 20-80%. Our aim is to evaluate the factors that affect the diagnostic yield of the fluoroscopy guided ultrathin bronchoscope.

Materials: We performed biopsy and brushing if a lesion was seen and only brushing when it was only detected by fluoroscopy. Bronchial washing (BW) was always sent.

Results: Of 30 patients included (77% men) with a mean age of 66 (SD 9). Median size of the PPL was 27 mm. Endobronchial lesions were visualized in 83% (minor, cosmetic change (6), tumor (5), compression (7) and secretions (1); in 79% of them a final diagnosis was obtained. The diagnostic yield for malignancy was 37%: adeno (3), squamous (3), NSCLC (2), mesenchymal tumor (1) and atypia (2). BW was diagnostic for malignancy in 23%, brushing in 27% and biopsy in 23%. After multivariate analysis the only significant variable was the presence of endoscopic nodule.

Conclusions: Fluoroscopy guided ultrathin bronchoscope obtains specific diagnosis in 43% of the patients, 85% of them with endobronchial abnormality. In 42% of patients with an endobronchial abnormality we were not able to reach a diagnosis. In 37% (11/30) of patients we could not see any endobronchial abnormality. Dedicated needles and more accurate methods to locate and reach the PPL are needed.

Funded by FIS PI09/09017 and SOCAP 2011.
in parenchymal haemorrhage, out of which 1/102 (7.8%) were visually classed as substantial.

None of the patients required insertion of chest drain or transfusion, although 6 patients were kept in the hospital for observation (maximum stay 4 days).

**Conclusion:** We have shown that CT guided biopsy is a safe procedure and can be carried out without major complications in a DGH. In our sample the complication rate (usually described as 2% patients requiring chest drain insertion) was very low. We are at present in the process of re-writing hospital guidelines regarding post procedure observation and patient guidelines.

**P4410**

**EUS-FNA for mediastinal lesions of unknown aetiology: A 4-year experience from a single centre**

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**Aim:** Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) allows access to the posterior mediastinum and tissue acquisition under real-time ultrasound guidance through the oesophageal wall. The aim of this study was to report the experience of mediastinal EUS-FNA in a large UK tertiary centre.

**Methods:** The study included all patients who underwent mediastinal EUS-FNA in our institution from January 2008 to December 2011. Patient and procedure related data were collected from endoscopy reports. Cytology and microbiology culture reports were compared to the final clinical diagnoses made during the follow-up. We calculated sensitivity, specificity, positive and negative predictive value (PPV,NPV) of mediastinal EUS-FNA for most common conditions.

**Results:** 195 patients (n=195, males 65%, mean age 58.6) underwent mediastinal EUS-FNA during the study period. Mean size of the lesions was 15.82mm (range 3.9-43) in short axis and 28.23mm (range 6-60) in long axis. Sub-carinal lymph nodes (n=189) were the commonest (145/195, 73.7%) target lesion.

We have shown that CT guided biopsy is a safe procedure and can be carried out without major complications in a DGH. In our sample the complication rate (usually described as 2% patients requiring chest drain insertion) was very low. We are at present in the process of re-writing hospital guidelines regarding post procedure observation and patient guidelines.

**P4411**

**Performance of fiberoptic bronchoscopy in patients with neoplasia endoscopic findings**

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**Objective:** Knowing the profitability of fiberoptic bronchoscopy (FB) and the samples taken in patients with endoscopic findings of neoplasia.

**Methods:** During 63 months (october 2006-december 2011) we performed 642 FB with signs of neoplasia. We repeated 34 FB, so the final number of FB analized was 676. Mediastinal masses were excluded. We considered a) direct signs of neoplasia (DSN) when there was endobronchial mass or mucose infiltration, and b) indirect signs of neoplasia (ISS), when there was extrinsic compression of the bronchial wall or very hyperemic mucosa areas. According to endoscopic findings, bronchial biopsy, brushing and blind transbronchial needle aspiration (TBNA) of linfadenopathies were carried out. We always took a sample of bronchial secretion and if it was possible, a posFB sputum. We considered as positive samples which allowed to make a therapeutic decision and negative samples those reported as “carcinoma” without specifying the type, presence of “malignant” or “atypical cells”.

The non hospitalized patients were observed 3 hours after the procedure.

**Results:** The TBNA was (+) for neoplasia in 122(66.3%) patients, giving the diagnosis of extension (N2). The average number of punctures per patient was 1.8; in 58 patients (59.7% of TBNA positives) only one puncture was required. In 41 cases (33.6%) was the only positive sample of FB, and gave the extension and pathological diagnosis. The only complications during FB were small hemmorhages. We did not detect significant clinical or radiological complications following the procedure.

**Conclusions:** 1.TBNA of mediastinic adenopathies was useful in the extension diagnosis in 122(66.3%) patients and resulted in diagnosis of lung cancer in 41(33.6%) patients. 2.TBNA was well tolerated and without significant complications.

**P4412**

**Performance of transbronchial needle aspiration (TBNA) of mediastinal lymphadenopathies in the diagnosis of pulmonary neoplasms**

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**Objective:** To know the contribution of TBNA of mediastinal lymphadenopathies in the diagnosis of extension and anatomicopathologic diagnosis of lung neoplasms.

**Methods:** During 63 months (october 2006-december 2011) we made 184 fiberoptic bronchoscopies (FB) with TBNA to patients with mediastinal lymphadenopathies suspected of neoplastic origin. We performed a “blind” TBNA of the lymphadenopathies larger than 1cm, using a 19 or 21ga needle, in the presence of the anatomicopathologist. We took samples from the ganglionic stations 4R, 7, 10R, 11R and 11L. We take samples until we got a positive result or we did 3-4 perforations, depending on tolerance of the patient. We considered as positive samples which allowed to make a therapeutic decision and negative samples those reported as “carcinoma” without specifying the type, presence of “malignant” or “atypical cells”.

The non hospitalized patients were observed 3 hours after the procedure.

**Results:** The TBNA was (+) for neoplasia in 122(66.3%) patients, giving the diagnosis of extension (N2). The average number of punctures per patient was 1.8; in 58 patients (59.7% of TBNA positives) only one puncture was required. In 41 cases (33.6%) was the only positive sample of FB, and gave the extension and pathological diagnosis. The only complications during FB were small hemmorhages. We did not detect significant clinical or radiological complications following the procedure.

**Conclusions:** 1.TBNA of mediastinic adenopathies was useful in the extension diagnosis in 122(66.3%) patients and resulted in diagnosis of lung cancer in 41(33.6%) patients. 2.TBNA was well tolerated and without significant complications.

**P4413**

**Results of echocardiographic ultrasound in mediastinal nodal staging of lung cancer**

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**Aim:** To evaluate the sensitivity and predictive negative value (PNV) of endobronchial ultrasound (EBUS) in patients with non small cell lung cancer (NSCLC).

**Methods:** Descriptive retrospective transversal study of all performed EBUS in a tertiary hospital during a 3 year period, for mediastinal nodal staging of NSCLC with fluorodeoxyglucose positron emission tomography positive nodes. Cases were considered positive (PC) when nodal metastases was demonstrated. If not, were considered as non-positive cases (NPC) and a mediastinoscopy was performed, if the clinical situation of the patient allowed the procedure.

**Results:** A total number of 41 patients were evaluated, 34 of them male and 7 female. Mean age was 65.39 years old. EBUS results were: 22 PC and 19 NPC. Mediastinoscopy was performed to the NPC supporting the negative result in 14
cases, but showed a positive result in other 3 cases. In 2 cases no additional testing was done. We found 3 false negative cases (17.64%), a VPN of 82% and a sensitivity of 88% for EBUS in our patient series. EBUS was able to stage 20 cases as N2 and 2 cases as N3. In four N2 staged cases a neoadjuvant therapy was applied and then a mediastinoscopy was performed previous to the surgery.

Conclusion: In this patient series EBUS allowed us to avoid more than a 50% of prognostic mediastinoscopes in NSCLC, given the high NPV and sensitivity we obtained with this technique. In cases staged as N2 responding to neoadjuvant therapy, a mediastinal reevaluation can be performed through a mediastinoscopy.

P4415 Transbronchial needle biopsy
Vesla Karelis, Martja Karelis. Clinic for Lung Disease, Military Medical Academy, Belgrade, Serbia School of Medicine, University of Belgrade, Serbia.

Introduction: Transbronchial needle biopsy (TNB) is a safe method used to achieve diagnosis for most thoracic lesions, whether the lesion located in the pleura, the lung parenchyma or mediastinum. TNB are performed on an outpatient basis by using only 1% lidocain local anesthesia.

Methods: TNB was performed in 148 patients, 44 (29.7%) women and 104 (71.3%) men, age 28-82, average 74 years; changes in the thoracic wall, pleura, parenchyma et the lung and mediastinum. Needles that were used in the procedure were BardMagnetm 18-19G x 200mm, and sample length was 19 mm. Needles were activated using BardMagnetm automatic trigger, under RT control with the C-arm Ziehm-Vision.

Results: In 148 patients the TNB was done:

<table>
<thead>
<tr>
<th>Localization/Size</th>
<th>20–50 mm</th>
<th>50–100mm</th>
<th>&gt;100mm</th>
<th>Total</th>
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<tbody>
<tr>
<td>Parenchyma changes</td>
<td>39 (35)</td>
<td>54 (52)</td>
<td>11 (10)</td>
<td>104 (97)</td>
<td>90.2%</td>
</tr>
<tr>
<td>Anterior mediastinum</td>
<td>6 (5)</td>
<td>13 (11)</td>
<td>1 (1)</td>
<td>20 (17)</td>
<td>85%</td>
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<tr>
<td>Posterior mediastinum</td>
<td>2 (2)</td>
<td>7 (6)</td>
<td>3 (3)</td>
<td>12 (11)</td>
<td>91.6%</td>
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<tr>
<td>Thoracic wall</td>
<td>1 (1)</td>
<td>9 (9)</td>
<td>2 (2)</td>
<td>12 (11)</td>
<td>100%</td>
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<tr>
<td>Total</td>
<td>48 (43)</td>
<td>89.5%</td>
<td>83 (78)</td>
<td>139</td>
<td>92.8%</td>
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Success of the procedure was greater if the changes were bigger and closer to the thoracic wall. Total diagnostic success is 92.8%.

Carcinoma bronchogene was proven in 134 (90.5%) patients: carcinoma squamo-cellule 62 (46.2%), adenocarcinoma 52 (38.8%), carcinoid macrocelule 5 (3.7%), SCLC 15 (11.1%).

Lymphoma - 5 (3.5%)
TB - 2 (1.3%)
Thymoma malignant - 1 (0.6%)
Carcinoma mesothelium - 4 (2.7%)
Mesothelium - 2 (1.3%)
Complications: pneumothorax - 4 (2.7%), hemoptysis - 8 (5.4%).

Conclusion: TNB is safe and cheap diagnostic procedure for histological and/or cytological confirmation of changes in the lung and mediastinum. Sensitivity of TNB is 92.8% and specificity 100%.

P4416 Positive predictive value of EBUS in lung cancer staging
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Introduction: EBUS (endobronchial ultrasound) is a technique developed for mediastinum diagnosis and staging. A negative puncture in lung cancer staging is 92%, whereas in mediastinum it is 82%.

Methods: Using only 1% lidocain local anesthesia.

Results:

<table>
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<th>Localization/Size</th>
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</table>

EBUS if an adequate sample is achieved is 98%. Sensitivity of TNB is safe and cheap diagnostic procedure for histological and/or cytological confirmation of changes in the lung and mediastinum. Sensitivity of TNB is 92.8% and specificity 100%.

P4417 Is small-bore catheter efficient in different type of pleural pathologies
Serife Liman1, Ayakt Elior2, Asli Akgul1, Salih Topcu1.

Background/Objectives: Problems in the treatment of chronic nonspecific empyema (CNEP) remain relevant.

Material and methods: 207 patients were treated with CNEP in clinics of Lviv Regional Center of Phthisiology and Pulmonology and Lviw Regional Hospital at the past 30 years, aged 15 - 80 years from 1.5 month to 13 years from the date of diagnosed acute suppuration pleura.

Results: Reasons CNEP: purulent inflammation of the lungs with bronchopleural fistula and residual pleural cavity were found in 125 (60.38%) patients; suppuration of hemathorax - in 28 (13.53%), suppuration of pleural effusion - in 22 (10.64%); complications after surgery - in 24 (11.59%), pleural cavity foreign body - in 8 (3.86%). An operations: dekortykation with resection and lung and pleura were performed in 95 cases, including lob -, bilobekotomy - in 23; atypical segmentektomy - in 16; pleuroperulomonotomky - in 7, taking in bronchial fistulas - in 17. If you have problems with smoothing out the lung, intraoperative thoracoplasty operation completed (47 cases). In 4 patients with significantly reduced spirometry and hasmetry was performed ekstrapleural thoracoplasty. In the postoperative period died 6 (2.89%) patients. After thoracoplasty all patients survived.

Conclusion: We believe that the most appropriate and economically justified in patients with radical resection is CNEP lungs and pleura. Nonaccordance volume of hemathorax - in 28 (13.53%), suppuration of pleural effusion - in 22 (10.64%) cases with pneumothorax, 21 cases with hemoperuph-
IL27, cytokine driving Th1 immunity and stimulates cytotoxic response. However, IL27 has not been considered yet as a tool in lung cancer gene immunotherapy. Aims: Construction of a plasmid encoding IL27. Evaluation of its transfection efficacy in non-small (A549) and small (NCI-H82) cell lung cancer model lines. Methods: IL27 cDNA was cloned into pSMx-IG plasmid. Lung cancer cells (A549 and NCI-H82) were transfected either with IL27 construct (pSMx-IL27) or empty plasmid as a control. Transfection efficacy was proved by RT-PCR and anti-IL27 immunostaining. Cell cycle and apoptosis (TUNEL assay) was assessed by flow cytometry. Results: pXMs-IL27-transfected cancer cells expressed IL27, as it was revealed by positive RT-PCR and flow cytometry (A549: 79%; NCI-H82: 56%, median of 5 experiments). Unexpectedly baseline IL27 expression was also found in non-transfected cells, particularly in A549 line (40%). Tumor cells transfected with pXMs-IL27 plasmid showed intense apoptosis, as compared with empty plasmid control. Conclusions: We proposed the model of future lung cancer gene immunotherapy with use IL27 encoding plasmid. However, low IL27 expression in non-transfected lung cancer cells calls in question its antitumor activity as a local immune stimulator. On the other hand, increased apoptosis of transfected cancer cells was observed, suggesting direct impact of IL27 on tumor cells.

P4420 Perioperative considerations for patients with asthma underwent thoracic surgery

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Asthmatic patients are a challenging population for anesthesiologists. Aim: The aim of this study was to determine the perioperative complications in asthmatic patients with symptoms before the surgery. Material and methods: From 2007 to 2011 44 patients with asthma underwent thoracic surgery. We classified the patients into two groups: First group (n =19) - patients with asthma who currently have no symptoms and second group (n=25) - asthmatic patients with symptoms before surgery. Pulmonary function was optimized preoperatively in all patients and airway obstruction was controlled by using steroids and bronchodilators. We conducted deep anesthesia with Sevoflurane, Fentanyl and Pipercuronium. We monitored several parameters: tidal volume, inspiratory, expiratory volume, PEEP, Pplat, ETCO2, PaCO2. Results: Patients in the second group had less incidences of perioperative bronchospasm than those in the second (p<0.025). We detected some statistical differences in the parameters: the gradient between ETCO2, Pplat is bigger in second group (p<0.025) and we detected an increasing PEEP and Pplat in asthmatic patients with symptoms before surgery. Conclusion: Symptomatic asthmatic patients had more the incidence rate of the perioperative complications. With deepening anesthesia level and aggressive pharmacological management the anesthesiologist minimize the risk of complications.

P4421 Application of one-lung high frequency jet ventilation (OHFJV) in lung surgery

Mikhail Kontorovich, Sergey Skornyakov, Igor Medvinsky, Igor Motus, Dmitry Eremeev. Department of Surgery, Ursal Research Institute for Phthisiopneumonology, Ekaterinburg, Russian Federation

Objectives: In any cases lung surgery including thoracoscopic procedures requires ventilation of one lung. The aim of the study was to examine physiologic features of OHFJV in lung surgery. Materials and methods: We compared two groups of patients comparable in terms of surgery, comorbidity, age of patients underwent lung resections. In the group I (n=101) we conducted traditional one-lung controlled mechanical ventilation (OCMV). The regimen was CMV (f = 17-19 cycles in minute, Vm – 260-410 ml, I:E – 1:2). In the group II (n=121) OHFJV was conducted (f – 100 cycles in minute, Vm – 150-170 ml, I:E – 1:2). In both groups FIO2 = 0,21. Results: OHFJV provided more effective intrapulmonary kinetics and respiratory gases distribution. OHFJV being compared with OCMV showed some advantages which are as follows: I. Increasing of the volume of alveolar ventilation (Vd), reducing of the volume of physiological dead space (Vd0), in 2,1 times, reducing proportion (Vd0/Vd) in 5 times, reduction physiological blood shunt by 80%, and increasing PaO2 by 16,7% indices PaCO2 and pH being normal. II. There were significantly lower indices of transpulmonary pressure, contributing to an increased venous return to heart and cardiac output. Conclusion: Thus, OHFJV provides adequate gas exchange, and creates favorable conditions for the surgeon.

P4422 Minimally invasive repair of pectus carinatum: A single institution experience

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Minimally invasive repair of pectus carinatum (MIRPC) has become an alternative technique to open surgery in recent years due to the successful surgical outcomes of the centers performing it. The aim of this study was to investigate the results of MIRPC at our institute. Fifty-eight cases who had had MIRPC between January 2006 and February 2012 were included in the study and were evaluated retrospectively according to the demographic data, form of the deformity, number of prestellar bars, operation duration, perioperative and postoperative complications, length of hospital stay, reoperations, bar removal and patient satisfaction. Fifty-four of the patients were male and the median age was 18.5 (range: 10-27) in the series. The deformity was symmetric in 40 and asymmetric in 18 cases. Follow-up of 5 experiments. Unexpectedly baseline IL27 expression was also found in 40 patients in 10 patients on planned time without any recurrence. Conclusion: Minimally invasive repair of pectus carinatum can be performed for the short operating time, low morbidity and high levels of patient satisfaction.

P4423 Large chest wall resection and reconstruction using titanium meshplate and pedicled muscular flap: Report of 6 cases

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The aim of this clinical study was to evaluate effectiveness of titanium meshplate for chest wall resection and reconstruction after chest wall tumor resection. Between 2009 and 2012, 6 patients with chest wall tumors were treated surgically. There were 3 female and 3 male patients and their ages ranged from 26 to 76 years. The patients were admitted due to chest pain and swelling. Tumors were located on sternum in 4 of the patients and on anterolateral chest wall in 3 of them. After tumor resection, defect size ranged from 10 cm. x 14 cm. to 12 cm. x 20 cm. Chest wall reconstructions were performed using titanium meshplate and pedicled muscular flaps. Titanium meshplates were fixed in ribs and/or sternum by titanium wires or screws.

Postoperative pathology for sternal tumors were condrosarcoma, malign melanoma and liposarcoma, and for chest wall tumors they were osteochondroma, malign fibrous histiocytoma and lymphoma. There were no paradoxal movement, or prosthesis-related complications during the follow-up period. Only in one patient muscular flap necrosis has occurred. Therefore second operation was performed for removal of necrotic muscular flap. The mean postoperative follow-up period was 15 months (range, 2-36 months).

We consider that, titanium meshplate is an easily applicable and suitable material to use in the reconstruction of large chest wall defects.

P4424 Thoracic paravertebral block for awake videothoracoscopic surgical procedures of high risk patients

Svilen Alexon1, Danail Petrov2. 1 Anaesthesiology and Intensive Care Clinic, University Hospital of Pulmonary Diseases “St. Sophia”, Sofia, Bulgaria; 2 Thoracic Surgery Clinic, University Hospital of Pulmonary Diseases “St. Sophia”, Sofia, Bulgaria

Objective: To present our experience and evaluate feasibility of thoracic paravertebral block as adequate anesthesia for some awake video-assisted thoracoscopic surgical procedures in high risk patients.
Methods: Seven (ASA IV) patients had multiple unilateral thoracic paravertebral blocks from Th3 to Th9 levels with 0.5% levobupivacaine as only anesthesia for their VATS procedures. Patients were awake, lightly sedated and spontaneously breathing 100% oxygen via tight mask during the whole procedures. Paravertebral catheters were inserted at Th-5,6 interspace for postoperative analgesia. The performed surgical procedures were: inspection, debridement, evacuation of haematoma, pleural or lung biopsies, pericardial fenestration, partial pleurectomy, talc pleurodesis, packing with wet dressing of povidone-iodine, or combinations of all mentioned above.

Results: Thoracic paravertebral anesthesia provided very good conditions for VATS and postoperative pain relief for presented patients. The mean duration of the procedures was 64 minutes. The procedures were well tolerated, respiratory status was stable, and oxygen saturation was maintained above 95%. Pain and panic attacks were well controlled. Spontaneous breathing and hemodynamics were well maintained during the operations. Recoveries were uncomplicated despite the underlying gross pathology.

Conclusions: Thoracic paravertebral blockage appears to be promising and feasible anesthetic management of some awake VATS procedures, especially when hemodynamic stability, adequate venous return and preservation of spontaneous ventilation are very important anesthetic goals.

P4425

Video-assisted thorascoscopic surgery of mediastinal cysts: Report of 13 cases

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Background: Mediastinal cysts are rare anomalies. The purpose of this study was to present our experience with mediastinal cysts who were thorascoscopic treated in our clinic and to discuss our findings along with those from the literature.

Methods: We retrospectively investigated 13 patients who were diagnosed and thorascoscopic treated for mediastinal cysts in our clinic between January 2008 and December 2011.

Results: Seven patients were female and six patients were male. The average age of the patients was 41.3±0.23 (18-82 years old). The mediastinal cysts comprised five pericardial cysts; four bronchogenic cysts; one hydatid cyst; one benign cystic teratoma; one dymtic cyst; and one neuroneentric cyst. In a case with ruptured hydatid cyst, we passed to thoratomy intra-operatively due to presence of advanced adhesion related to inflammation. Postoperative complication and mortality did not occur in any case. The average postoperative hospitalization period was 3.8 days.2

Conclusion: Video-assisted thorascoscopic surgery in mediastinal cysts is a reliable and effective approach with low morbidity and a shorter hospital stay.

P4426

Impact of pulmonary metastasectomy on lung function parameters

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The lung is a common site of secondary growth in malignant diseases. Surgical resection of pulmonary metastases has been shown to prolong survival in patients with various primary tumor types. Today, even repeated resections of recurrent pulmonary metastases are common practice in thoracic surgery. The impact of metastasectomy on respiratory function has become a relevant factor in the treatment algorithm of these patients.

Since 2009, all metastasectomy patients at the Dept. of Thoracic Surgery, MUV, have been actively followed up every three to six months after surgery. For 45 patients pre- and post-operative lung function data was obtained during the follow-up. In 19 patients metastasectomy were removed by enucleation (laser=10, cautery=9), in 19 patients by wedge resection and 7 patients received lobectomy. Complete resection was obtained in all patients.

We found no difference in loss of FEV1 per resected nodule between laser and cautery enucleation. However, a significant difference in FEV1 and VC was found when comparing enucleation/wedge lobectomy patients (FEV1 3.1±1.5, 7.6±1.5, 13.4±4.9, VC: 15.1±1.7, 4.7±1.7, 16.3±3.3). These findings were confirmed by evaluating the volume of the resected tissue and did not correlate with size of metastases as determined by pre-operative CT evaluations.

The surgical resection of pulmonary metastases is associated with a detectable but mild loss of lung function. Concerning the respiratory impairment, repeated resections of lung metastases should not be withheld from patients.

P4427

EBUS-TBNA as alternative of VATS-procedure for differential diagnosis of mediastinal lymphadenopathy

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Aim: To study of possibilities of EBUS-TBNA in differential diagnosis of tuberculosis and sarcoidosis1.

Materials and methods: From March till December, 2011 30 ultrasonic video bronchoscopies for the purpose of performance of a transbronchial biopsy of lymph nodes of a mediastinum at 30 patients with a mediastinal lymphadenopathy have been executed. Middle age has made 30±8 years, 14 men and 16 women. The syndrome of a mediastinal lymphadenopathy was established on the basis of the data of a spiral computer tomography. The average size of LN - 1.6±0.4 cm, radiological signs of a pathology of lungs were absent. At all patients preliminary clinical inspection hasn’t allowed to differentiate character of a lymphadenopathy. Second step in all were VTS biopsy of lung and histological examination (as gold standard).

Results: We didn’t have any complications. After cytolological examination we find cells of LN in 30 cases. We compared results of cytological and histological examinations. And the results were equal. We found 5 cases of tuberculosis, in 25 patients sarcoidosis. Diagnosis was confirmed by 6 month period of follow-up.

Conclusion: We can see equal results of both examinations. May be in such cases we need not to do of VTS biopsy of lung and histological examination. (Time to change Gold standard?)

P4428

Less pain without pain-killers?

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Objectives: To assess if the mode of closing the thoratomy may have an influence over the post-operative pain.

MATERIAL AND METHODS

Prospective study, with 2 groups of patients, 15 cases each. Group A – for this patients, the stiches used to close the thoratomy were passed between the rib and intercostal nerve (in this way the nerve don’t compressed again the rib when the stich was tightened). Group B – the stiches were passed in classic fashion, inferior to intercostal nerve and when the thoratomy was closed, the passing of the stiches compressed the nerve against the rib. All patients had lateral thoratomy, 3 stiches were used for all patients, no peridural/paravertebral catheter was used and regular analgesia (consisted in Paracetamol, Tramadol and NSAID) was used for all patients. For assessing the pain, we used a scale from 0-10, 0 no pain, 10 pain intensity was the biggest ever felt by the patient. We assess the pain in the first 48 h post-op and after 21 days.

Results: Group A – only 2 patients alleged pain score 10 in first 48 hours post op, 1 patient – score 9, the rest of the group pain was 8 or less. Group B – 13 patients alleged pain score 10 post-op, 1 patient – score 8 and 1- score 7. Pain assessed 3 weeks after: group A pain score range from 0 to 7, and in group B from 0 to 10.

Discussions: Pain is difficult to assess preciselly because the threshold and perception of pain is different from person to person. According with this study, it seems that involvement of the intercostal nerve in the closure of thoratomy increase the post-operative pain, especially in the first 48 hours.
P4430
The feasibility of medical thoracoscopy in the treatment of multi-loculated pleural effusion
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Introduction: Optimal surgical procedure must be selected according to empyema stage of multi-loculated cases. If the empyema is at the stage of multi-loculated effusion, however, it is difficult to select the optimal procedure using conventional staging system. The medical thoracoscopy is an ideal diagnostic tool of pleural disease, we used medical thoracoscopy to evaluate the accurate stage of empyema and to select optimal surgical procedure.

Methods: 108 patients were transferred to treat multi loculated pleural effusion. The type of surgical procedure was selected according to the finding of medical thoracoscopy.

Results: There was no significant difference of morbidity and mortality between two groups (p>0.05). The 20 closed thoracostomy (45.5%), 6 VATS decortication (13.6%), and 18 open decortication (40.9%) were performed in group I. 16 cases of open decortication were undertaken due to the failure of first treatment (12 closed thoracostomy, 4 VATS decortication). In group II, 43 locculation block-up were undertaken due to the failure of first treatment. 12 locculation block-up were performed due to the failure of first treatment (10 closed thoracostomy, 3 VATS decortication). In group II, 43 locculation block-up were undertaken due to the failure of first treatment. In group II, 43 locculation block-up were undertaken due to the failure of first treatment.

Conclusions: The medical thoracoscopy is helpful to decide the optimal procedure in the treatment of multiple loculated empyema. We could decrease the incidence of open thoracostomy to use medical thoracoscopy.

P4431
May the Nuss operation be minimally invasive procedure in adults

The repair of pectus excavatum with Nuss procedure (group N) is well established among pediatric surgeons. It named minimally invasive surgery. Studies on adult patients are rare. We compared Nuss procedures and Ravitch procedures (group R) on adult patients, which of them minimally invasive in respect tors cin incisions. We retrospectively analysed 35 adult patients (16 Nuss procedures, 19 Ravitch procedures) from 2007 to 2011. In two groups all patients aged older than 20, Ravitch procedures performed midsternal vertical incision and substernal metal bar. For Nuss procedures three scinc incisions was performed. Opioid derived was used for post-operative pain. We observed early bar dislocation at four patients, two haemothoraces, three pneumothoraces and one severe post-operative pain. In Nuss procedures should not require chest wall resection and it may do small scinc incisions. But Nuss procedure have lots of complications. In Ravitch procedure, much more effective and less invasive and have little complication. We have lots of question marks.
3 weeks of ET. The 1- and 2-year overall-survival rates were 100%, the 3-year survival 73%. In one patient lung transplantation was performed 6 months after ET.

Conclusion: ET as add-on to medical therapy is effective in patients with CTD-APAH to improve work capacity, quality of life and prognostic parameters and improves the 1-, 2- and 3-year survival rate. Further randomized controlled studies are needed to confirm these results.

**P4434** Respiratory muscle training (REMT) with normocapnic hyperpnoea (NH) improves respiratory muscle strength, exercise performance and ventilatory pattern in COPD patients

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Few data are available about the effect of REMT in COPD patients even if it has been shown that REMT improves endurance performance and decreases VE during exercise in healthy subjects.

Aim: To evaluate the effect of 4 weeks of REMT with NH (Spirotiger®) on respiratory function and exercise capacity in 23 moderate/severe COPD patients.

Materials and methods: 20 M, 3 F (aged 42-80). Respiratory function tests (FEV1, FVC, MIP), QOL (St George’s Questionnaire), 6MWT and endurance exercise test (75-80% of peak-work rate measured during an incremental test and performed to the limit of tolerance, ILIM).

9 of 21 patients were instrumented with a portable inductive plethysmography (Lifeshift System) to evaluate breathing pattern during exercise test. After 4 sur- prised training sessions, the patients trained at home for 4 weeks: 10 min twice a day roughly 55% of MVV (FEVi0x.375). REMT started 3 days a week.

Results: Results are reported in Tables 1 and 2. 6 patients dropped out (poor compliance).

Ventilatory pattern after REMT, during ILIM, is characterized by a significantly lower trend of VE and RR with a higher TP (p < 0.05, ANOVA test).

**P4435** Reduced oxygen uptake efficiency slope in patients with cardiac sarcoidosis

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Background: The non-invasive diagnosis of cardiac sarcoidosis (CS) is difficult. Cardiovascular magnetic resonance (CMR) has become a very valuable diagnostic tool in patients with suspected CS, but usually a combination of different tests is used. Oxygen uptake efficiency slope (OUES) is a parameter of cardiopulmonary exercise testing (CPET), which is used as an indicator for cardiovascular impairment. We investigated the predictive value of OUES for the diagnosis of myocardial involvement in sarcoid patients.

Methods: Retrospectively 37 consecutive patients (44.9 ± 13.8 years) with histologically confirmed sarcoidosis and clinical suspicion of heart involvement underwent noninvasive diagnostic testing including CMR. CS was diagnosed according to the guidelines from the Japanese Society of Sarcoidosis and other Granulomatous Disorders with additional consideration of CMR findings. Furthermore, CPET with calculation of predicted OUES according to equations by Hollenberg et al. was performed to the limit of tolerance, tLIM.

Results: A total of 20 patients (47 ± 14 yrs, mean pulmonary artery pressure = 52 ± 10 mmHg) underwent an incremental exercise test and a steady-state test with arterial blood gases measurement. OUES was significantly lower in CS-group compared to non-CS-group (59.3 ± 22.9 vs. 82.5 ± 21.2, p < 0.01). ROC curve method identified 70%pred. as the OUES cut-off point, which maximized sensitivity and specificity for detection of CS (96% sensitivity, 82% specificity, 89% overall accuracy).

Conclusion: Cardiac involvement of sarcoidosis can be predicted by CPET using OUES. Patient selection for CMR can probably be guided by CPET findings in patients with sarcoidosis.

**P4436** Prognostic implications of delayed heart rate recovery from maximal-incremental exercise in patients with pulmonary arterial hypertension

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Rationale: Early recovery from exercise is characterized by a marked reduction in heart rate (HR) due to sudden reintroduction of vagal tone and progressive withdrawal of sympathetic stimulation. HR recovery (HRR) is delayed in pulmonary arterial hypertension (PAH), a disabling condition associated with autonomic imbalance.

Objective: To investigate the usefulness of HRR to estimate exercise impairment and prognosis in PAH patients.

Methods: We evaluated 72 patients with PAH of varied aetiologies (NYHA class I to IV) and 21 age- and gender-matched controls who underwent a maximal incremental cardiopulmonary exercise test (CPET) with HR being recorded up to the 5th minute of recovery.

Results: HRR was consistently lower in patients compared to controls (p < 0.05). The best cutoff for HRR in one minute (HRR1min) to discriminate patients from controls was 18 beats (AUC 0.76 [0.66-0.86], p < 0.01). "Normal" HRR1min was associated with a range of maximal and sub-maximal variables indicative of better preserved exercise tolerance (p < 0.05). On a multiple regression analysis which considered only CPET-independent variables (6-minute walking distance, NYHA class and PAH treatment), HRR1min was the single predictor of mortality (hazard ratio (HR) 9.5% confidence interval 1.19 (1.03-1.37), p < 0.05).

Conclusions: Preserved HRR1min (>18 beats) is associated with less impaired responses to exercise in patients with PAH. Conversely, an abnormal HRR1min response has negative prognostic implications, a finding likely to be clinically useful when more sophisticated analyses provided by a full CPET are not readily available.

**P4437** Portioning out the contribution of dead space ventilation and low CO2 set point to ventilatory inefficiency during exercise in chronic thromboembolic pulmonary hypertension

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Rationale: The individual relevance of enlarged dead space ventilation as a fraction of tidal volume (VDVT) and low CO2 set-point in promoting exercise ventilatory inefficiency in chronic thromboembolic pulmonary hypertension (CTEPH) remains controversial.

Objective: To determine the contributing role of VDVT and PaCO2 on the exercise ventilatory response to exercise in patients with CTEPH.

Materials and methods: 20 patients (47 ± 14 yrs, mean pulmonary artery pressure = 52 ± 10 mmHg) underwent an incremental exercise test and a steady-state test with arterial blood gases measurement.

Results: Compared to normal standards, patients showed lower resting PaCO2 and peak V′O2 but greater ΔV′E/ΔV′CO2 slope (68 ± 16). Peak V′O2 and ΔV′E/ΔV′CO2 were inversely correlated (r = -0.70, p < 0.05). V′E/V′CO2 ratio during the constant work rate test was also abnormally high (62 ± 15). VDVT increased from 0.31 ± 0.08 at rest to 0.39 ± 0.11 during exercise; on the other hand, end-tidal partial pressure (PET) for CO2 decreased despite a stable PaCO2 (p < 0.05). Consequently, PaCO2/EtCO2 became wider (4.3 ± 3 mmHg to 8.5 ± mmHg), a finding related to greater V′E/V′CO2 (r = 0.81, p < 0.05). On a multiple regression analysis VDVT (partial r = 0.89) and PaCO2 (partial r = -0.37) explained up to 90% of V′E/V′CO2 variability (125.9 VDVT - 2.3 PaCO2 + 77.1, p < 0.001).

Conclusion: Increased VDVT is the main pathophysiologival mechanism leading to an excessive ventilatory response to exercise in patients with CTEPH. Low CO2 set-point responds for a relatively minor portion of this abnormal feature.

**P4438** Association of 6-minute walk distance and maximal work capacity assessed by ergometry in patients with obstructive and restrictive lung diseases

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Background and objective: In patients with chronic lung diseases work load for
endurance training is calculated from maximal load. If this is not known, it might be predicted on the basis of 6-minute walk distance (6MWD). We addressed the reliability of such predictions.

Methods: Within a longitudinal clinical study on the efficacy of rehabilitation, baseline data including 6MWD, maximal work load (Wmax), peripheral muscle force, lung function, fat-free mass (FFM) and dyspnoea (MMRC score) of 255 men with occupational lung diseases (asthma, asbestosis, silicopid COPD) were evaluated.

Results: 6MWD (mean 502m, SD 92m) correlated (r=0.51, p<0.05) with Wmax (mean 112Watt, SD 35Watt), without systematic differences between asthmatic, silicopid COPD. The asthmous group was evaluated separately since the regression line was different. Muscle force, lung function parameters and MMRC score correlated moderately with Wmax (p<0.05 each). Including all statistically significant predictors the correlation was r=0.76 in patients with obstructive lung function impairment and r=0.61 in asthmatics patients. The residual standard deviations of predicted Wmax were 20-28 Watt, depending on the predictors used, and the 95% prediction intervals of Wmax based on the predictor 6MWD 67-65 Watt.

Conclusions: Compared to literature data we observed weaker correlations indicating that the prediction of individual Wmax by 6MWD related measures is not possible. Despite this, the regression lines based on a large sample of subjects might be useful for the comparison of epidemiological studies.

P4439

The relationships between hyperinflation during exercise and symptoms in adults with cystic fibrosis

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Exercise tolerance is reduced in patients with Cystic Fibrosis (CF). Ventilatory limitation, peripheral skeletal muscle weakness and poor nutritional status may contribute to exercise intolerance. The mechanisms of exhalational dyspnoea are less understood, but it seems that dynamic hyperinflation may play a role. So we wanted to investigate the role of exercise dynamic hyperinflation on breathlessness (DYS) and leg fatigue (LEG) in CF patients. 17 stable CF patients (32±8SD yrs, FEV1 2.66±0.71; 68.6±16% pred; IC 3.4±1.0 l, during constant load cycle ergometry at 80% max VO2; max VO2 were studied. Intensity of breathlessness and leg fatigue, by Borg scale, and IC were recorded every 2 minutes. The individual slopes of the change in IC and the rate of increase in DYS and LEG were also computed.

Results: In most patients we did not observe a correlation between changes in IC during exercise vs either DYS (r² =0.03±0.08) or vs LEG (r² =0.3±0.26). In addition, we did not find a close relationship of change in DYS or LEG. Conversely we found a close relationship between the rate of increase in DYS per unit change in IC and the rate of increase in LEG per unit change in IC (r²=0.85 ±0.001).

Conclusions: CF patients show considerable variation in the rate at which symptoms develop during exercise, suggesting that different physiological processes underlie these symptoms. Baseline IC strongly predict the duration of the endurance tolerance, while the degree of resting hyperinflation is poorly predictive of exercise induced changes in DYS and LEG.

P4440

Exercise capacity and limiting factors in older patients with post infectious bronchiolitis obliterans

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Exercise capacity has been poorly studied in patients with post-infectious bronchiolitis obliterans (PBO) and main studies evaluated children with follow-up in older subjects lacking. We evaluated exercise capacity in older patients with PBO and mechanisms of exercise limitation.

This was a cross-sectional study including the oldest patients of our tertiary care center. Cycle incremental cardiopulmonary exercise test with investigation of dynamic hyperinflation and exercise induced bronchoconstriction (EIB) were performed.

Sixteen patients were studied with a mean age of 15.3±3.9 years (range 10-23 years), and post-infectious bronchiolitis obliterans (PBO) resting lung function (% predicted): FVC 88±19.3; FEV1, 67.4±17.5, TLC 115.3±10.7, RV 234±8.71, Dlco 73.6±11.9. Only 7 patients (43.8%) had reduced exercise capacity (VO2peak<0.78±1.0l), during constant load cycle ergometry at 80% peak workload, VO2peak was only correlated with age (r=0.58; p=0.01) and Dlco/CVD pred (p=0.66; p=0.01).

Patients with reduced exercise capacity tended to be younger (13.4±3.3 yr vs 16.8±3.9 years; p=0.09), with greater FEV1 response to BD (18.9±12.8 vs 7.0±11.9%; p=0.08) and lower Dlco (67.8±12.9 vs 81.2±9.2%; p=0.05). No differences were found in relation to ventilatory reserve and dynamic hyperinflation during exercise. Of the 4 patients who presented EIB, 3 (75%) had reduced exercise capacity. Nevertheless, FEV1 alteration post-exercise was not significantly different from those with preserved exercise capacity (-17.8±20.3 vs -5.7±6.7%; p=0.20).

In conclusion, it seems that functional alterations of PBO tend to ameliorate with aging. Those with reduced exercise capacity present lower lung diffusion capacity and greater airway obstruction variability.

P4441

Estimation of the exercise ventilatory compensation point by the analysis of the relationship between minute ventilation and heart rate in patients with pulmonary hypertension

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Background: Incremental cardio-pulmonary exercise test with gas exchange measurement is the gold standard for the identification of the ventilatory compensation point (VCP). It has previously been demonstrated that the change in the slope of increment of minute ventilation over heart rate (AV'E/AHR) can be utilized alternatively to the ventilatory equivalent for CO2 (VE'/V'E) for detection of VCP in healthy subjects. The reliability of this parameter in patients affected by cardiac and pulmonary diseases is still not well elucidated.

Aim: To evaluate the efficacy and reliability of the AV'E/AHR in patients with pulmonary hypertension.

Methods: Twenty subjects (11F – 9M; mean age 44±15.8 SD) with a diagnosis of pulmonary hypertension underwent an incremental maximal exercise test on a cycle-ergometer. VO2, V'E/ V'E CO2 were measured breath-by-breath. Heart rate was also registered. Results are expressed as mean±SD.

Results: All patients reached the VCP showing a mean VO2 max % predicted of 55±15%. As in healthy subjects it was possible to identify two different slopes (61 – 82) of increment in the AV'E/AHR in 14 out of the 20 tested patients (0.78±0.2 vs 1.83±1.0 p=0.002). The remaining 6 patients in whom was not detected a significant difference between the two slopes interestingly showed an altered cardiac function, as shown by the O2 pulse in the final phase of exercise.

Conclusions: AV'E/AHR as a predictor of the VCP, appears to be a useful and reliable method to identify more severe IP patients with an altered cardiac function.

P4442

Critical power for upper limb in patients with COPD

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Introduction: The determinants of the critical power (CP) for whole-body exercise (lower limbs) in patients with COPD have been previously identified. There are no data concerning to its determinants for upper limbs (UL) in this population.

Objective: To characterize the determinants of the CP for UL in patients with COPD.

Methods: Eight patients with COPD (FEV1: 45±1±1.2% of predicted) and seven healthy subjects were assessed. After an arm incremental test on cycle ergometer, three constant workload tests were performed (100%-20%, 90% and 80% of peak workload). From these tests the CP was estimated and an additional test was performed (5-20% above the workload of the estimated CP). Then, CP was deter-

mined by the intercept of the linear regression between workload and reciprocal of time for the four tests and was confirmed in a new test. The inspiratory capacity (IC) was measured before and immediately after each test.

Results: There was no significant difference in the CP workload between patients and controls (30.2±12.7 Watts - 59.8±11.4% of peak workload vs 42.2±16.7 Watts - 66.7±9.3% of peak workload, respectively). The oxygen uptake in CP was lower in the COPD group than controls (0.79±0.28 L/min vs 1.20±0.37 L/min, respectively, p<0.05). The patients presented dynamic hyperinflation and substantial reduction of ventilatory reserve for all tests, including the CP test. Despite the ventilatory limitation, all patients were able to sustain exercise at CP for 20 minutes.

Conclusion: The present study shows that the ventilatory constraint is the most important determinant of the CP for UL exercise in COPD patients.

P4443

Physiological responses at critical load on resistance exercise – Effects of aging process

In this study it was observed that functional alterations of POB tend to ameliorate with aging. Those with reduced exercise capacity present lower lung diffusion capacity and greater airway obstruction variability.
which indicates the transition of moderate to intense exercise. However, it appears
the influence of age on differences in CL remains to be investigated.

Aims: The objectives of the study were to: 1) determine the intensity of CL during
RE, and 2) evaluate the behavior of cardiorespiratory and metabolic responses
during RE at the CL in young and older subjects.

Methods: We evaluated 12 young (23±3 years) and 10 elderly (70±2 years)
apparently healthy males, who underwent: 1) a repetition maximum (1RM) test
on Leg Press and, 2) on different days, three high-intensity resistance exercise
continuous load tests (60%, 75% and 90% 1RM) in order to obtain CL by linear
regression: load X reverse of time (Tim = duration of exercise until fatigue).

Results: Absolute values of both the CL asymptote and curvature constant (kg)
were significantly lower in elderly subjects (p<0.05). In contrast, both groups have
the same value for CL = 52%RM. As expected, actual oxygen consumption (VO2)
and heart rate (HR) values obtained during CL exercise testing were significantly
reduced in older subjects. However, percent-predicted aerobic capacity values were
significantly higher in older subjects (P<0.05). In addition, blood lactate ([La-])
corrected to Tim were greater in younger subjects at all intensities (p<0.05).

Conclusion: These findings suggest that the despite reduced force production
in older subjects, endurance-related parameters are well preserved according to
to age-related predictions. VO2 was also aparently healthy males.

Financial support: FAPESP No. 2009/1842-0.

P4444

Impaired cardiac output responses to incremental exercise measured by
signal-morphology impedance cardiography in advanced COPD
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Background: There is renewed interest in the continuous evaluation of cardiac
output (Q'T) during exercise in patients with chronic obstructive pulmonary dis-
ease (COPD). Signal-morphology impedance cardiography (SMICG) has some
advantages over previous impedance approaches and it might be useful to track
relative changes in exercise Q'T in this patient population.

Objective: To contrast the dynamic changes (Δ) in Q'T as a function of metabolic
demand (O2 uptake, ΔO2V) in patients with advanced COPD and healthy controls.

Methods: 16 males with COPD (11 GOLD stages III-IV) and 9 gender-matched
controls underwent a ramp- incremental test with Q'T being measured by a
commercially-available SMICG system (Physioflow™ PF-05, Manatec, France).

ΔO2V/ΔQ'T relationship was calculated by linear regression.

Results: Patients were significantly younger than controls (61±6 yrs vs. 72±5 yrs,
respective 65%RM). As expected, patients showed lower VO2 (1.02 (1.00-1.04)
compared to controls (p<0.05). There were no significant between-group differ-
ences in the y-intercept or the slope of ΔQ'T (2.0mL/m2/ΔO2V; 2.0mL/minute)(p<0.05).
Interestingly, however, both parameters were lower in patients than controls when
Q'T was expressed as fold-changes (0.90±0.30 vs. 1.22±0.18 and 0.43±0.17 vs.
0.61±0.10, respectively; p<0.05). ΔQ'T at maximal exercise was associated with
peak VO2 in controls (r=0.73; p<0.05) but not in patients (p=0.12).

Conclusions: Semi-quantitative SMICG measurements indicated blunted Q'T ad-
justments to rapidly-incremental exercise in patients with advanced COPD -
even when compared to older healthy controls.

P4445

Exercise ventilatory inefficiency is an independent predictor of mortality
in patients with pulmonary arterial hypertension
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Rationale: An excessive ventilatory (V' E) response to CO2 output (V'CO2) during
incremental exercise is a strong prognosticator in cardiovascular diseases. The role
of ΔV' E/ΔV'CO2 to predict mortality in pulmonary arterial hypertension (PAH),
however, remains to be demonstrated.

Objective: To investigate the value of increased ΔV' E/ΔV'CO2 as a negative
prognostic marker in PAH.

Methods: 80 patients with PAH who underwent a ramp- incremental pulmonar-
diary exercise test (CPET) were followed-up for 5 yrs. ΔV' E/ΔV'CO2 slope was
calculated to the respiratory compensation point (ΔV' E/ΔV'CO2start-RCP) or

Results: 14 patients (17.5%) died of PAH-related causes. Compared to sur-
vivors, deceased patients were younger and had lower peak O2 uptake, O2 pulse,
and maximal lactate concentration but, regardless of the method of calculation, higher
ΔV' E/ΔV'CO2 (p<0.05). None of the other variables (including the six-minute
walking distance) was related to mortality (p>0.05). The best cutoff to death predic-
tion was higher for ΔV' E/ΔV'CO2start-RCP (AUC: 0.73; p<0.05) than ΔV' E/ΔV'CO2start-max
(45-5). An univariate analysis revealed that the former variable was superior to the
later on this regard (p=0.004 vs. 0.02). In fact, a multiple regression anal-
ysis showed that resting heart rate (hazard ratio (HR): 95% CI= 1.04 (1.00-1.08)
(p=0.03) and ΔV' E/ΔV'CO2start-RCP (1.04 (1.01-1.10); p=0.006) were the only
independent predictors of mortality.

Conclusions: A resting variable (heart rate) and an effort-independent marker of
ventilatory inefficiency (ΔV' E/ΔV'CO2start-RCP) are clinically-useful markers of
poor prognosis in patients with PAH.
(Armband\textsuperscript{8}), QoL questionnaire (AQLQ) and walking test (6MWT) with VE analysis (Spiropalm, Cosmed).

**Results:** 19 subjects were obese (OB), 17 overweight (OW), 12 normal weight (NW). FEV1\% was < in subjects with BMI $\geq$ 25 (72.1±17 vs 81.5±17, ns). PAL (METs) in OB was < OW and NW (1.3±0.2 vs 1.5±0.3; 1.5±0.2, *) independently from the severity of obstruction. No difference in QoL was found. OB and OW showed a reduced exercise capacity and SpO2\% in comparison to NW.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>SpO2%</th>
<th>Meters</th>
<th>Dyspnea (Borg)</th>
</tr>
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<tbody>
<tr>
<td>OB</td>
<td>95.7±0.3\textsuperscript{3}</td>
<td>454.7±87.2\textsuperscript{3}</td>
<td>2.5±2.3</td>
</tr>
<tr>
<td>OW</td>
<td>95.6±0.5\textsuperscript{4}</td>
<td>456±96.4\textsuperscript{4}</td>
<td>2.5±2.1</td>
</tr>
<tr>
<td>NW</td>
<td>97.2±0.3</td>
<td>548±52.5</td>
<td>1.2±1.3</td>
</tr>
</tbody>
</table>

\textsuperscript{3}p<0.05 OB vs NW; \textsuperscript{4}p<0.05 OW vs NW.

No difference in dyspnea Borg scale (0-10).

VE analysis during 6MWT. OB showed a higher maximal increase (%) in VE than NW, independently from the level of obstruction and mainly due to the increase in tidal volume (TV).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Increase VE (%)</th>
<th>Increase TV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB</td>
<td>108.3±38.3\textsuperscript{3}</td>
<td>93.6±34\textsuperscript{3}</td>
</tr>
<tr>
<td>OW</td>
<td>93.7±38.3\textsuperscript{3}</td>
<td>56.9±41\textsuperscript{3}</td>
</tr>
<tr>
<td>NW</td>
<td>67.9±6.5</td>
<td>59.8±10.2</td>
</tr>
</tbody>
</table>

\textsuperscript{3}p<0.05 OB vs NW; \textsuperscript{4}p<0.05 OW vs NW.

**Conclusions:** In asthmatics, obesity influences negatively the daily physical activity and exercise capacity through mechanisms which appear independent from the severity of bronchial obstruction.

P4449

**Laboratory exercise tests are not representative of the real physical activity in more severe COPD patients**

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**Background:** Cardiopulmonary exercise test (CPET) is the gold standard to evaluate the exercise tolerance. Incremental shuttle walking test (ISWT) has ventilatory and metabolic responses similar to those of CPET in moderate-severe COPD. Sensewear Armband is a new device to quantify the physical activity of daily life.

**Aim:** To evaluate the correlations among CPET, ISWT and daily physical activity, measured by Armband, in patients with COPD of different severity.

**Subject and methods:** In cross sectional study 45 COPD patients (FEV1\%: 52.5±17, 36 male) evaluated: CPET, ISWT, pulmonary function test (PFT), dyspnea scale (MRC), steps/day and total energy expenditure (TEE) by Armband (as a mean of a 7-day monitoring period). The patients were divided according to FEV1 ($>50\%$ or $\leq 50\%$) and MRC ($\leq 2$ or $> 2$).

**Results:** CPET and ISWT significantly correlated between them, better in patients with FEV1 $>50\%$ and in those with MRC $> 2$. In COPD patients with FEV1 $>50\%$, steps/day (r=0.405, r=0.582) and TEE (r=0.494, r=0.615) significantly correlated with CPET and ISWT, respectively, while this did not occur in COPD patients with FEV1 $<50\%$. Similarly, steps/day (r=0.423, r=0.575) and TEE (r=0.319, r=0.494) significantly correlated with CPET and ISWT in COPD patients with a MRC $<2$, respectively, while this did not occur in COPD patients with MRC $>2$.

**Conclusion:** Exercise tolerance evaluated in laboratory by CPET and ISWT is representative of the real physical activity, as expressed by steps/day and TEE, in patients with moderate COPD but not in patients with severe COPD. In these patients, physical activity evaluation may offer complementary informations to the laboratory exercise assessment.
4512
The effect of passive smoking on body height, body weight, peak expiratory flow rate and motor skills in children
Ivan Pavic, Pero Pavic, Slavica Dodig, Jasna Cepin-Brogovic, Marinka Krmecki

Passive smoking is strongly linked to a range of adverse child health outcome. The objectives of the present study were to assess: 1) proportion of school children passively exposed to cigarette smoke; 2) the impact of passive smoking on body height and body weight; 3) the influence of passive smoking on peak expiratory flow rate (PEFR); and 4) on the motor skills in school children. This prospective study included 133 children, 66 males and 67 females, aged from 11 to 14 years. Subjects were divided in two groups depending on parental smoking habits: Group I - children of smoking parents who smoke 10 or more cigarettes per day (88/133=66.6%) and Group II - children of non-smoking parents (45/133=34%). For the assessment of motor skills 6-minute run test (F-6 test) was used. 88/133 (66.6%) children have been exposed to passive smoking, while 45/133 (34%) children came from families of non-smoking parents. There was no statistically significant difference in either height or in weight. The PEFR (L/min) values for Group I were statistically lower [320 (300-370)] than in control group of children [380 (347-405)] (P<0.0001). The median F-6 test values for Group I were statistically lower [2 (1-3)] than in control group of children [4 (3-5)], respectively (P<0.0001). Children of smoking parents have statistically significant lower grade of motor skills and statistically significant lower PEFR value than children of non-smoking parents. Public health preventive actions should go toward minimizing the exposure of children to passive smoking by counseling the smoking parents that quitting smoking provides enormous health benefits not only to them but also to their children.
4516 Intervention study to evaluate effectiveness of integrated therapy (varenicline plus motivational interviewing) for smoking cessation in diabetic patients
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Background: The prevalence of smoking among people with diabetes is similar to that in the general population. For smokers with diabetes, however, the complications incurred are not equal. All-cause mortality is increased in smokers with diabetes, and the risk of macro and microvascular complications is also increased (1).

Aim and objectives: We designed a study to monitor possible modifications in the smoking habits of 40 diabetic smokers experimenting and Integrated Therapy (Varenicline plus Motivational Interviewing) focusing on smoking reduction and smoking abstinence.

Methods: Study participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. Number of cigarettes smoked, and exhaled carbon monoxide levels were measured at each visit. Smoking reduction and abstinence rates were calculated. Adverse events were also reviewed.

Results: Sustained 50% reduction in the number of cig/day at week-24 was observed in 45% of participants. Sustained smoking abstinence at week-24 was observed in 40% of participants.

Conclusion: The use of Integrated Therapy (Varenicline plus Motivational Interviewing) improves smoking cessation and reduction in diabetic smokers intending to quit.


4517 Earthquake rattled Christchurch residents reach for cigarettes
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The magnitude 7.1 Canterbury earthquake in September 2010 and associated after-shocks have caused untold damage, drastically changed residents’ living, working, social conditions and taken the lives of 184 people. Aims: To assess the impact of the Christchurch earthquakes on changes in smoking status and tobacco consumption of current smokers.

Methods: Semi-structured interviews in public locations with high pedestrian flow, including two city malls and the central bus exchange. The interviews were carried out 15 months after the first major earthquake. A total of 1001 people were interviewed.

Results: At the August 2010 point (prior to any earthquakes) 589 (58.9%) had smoked cigarettes or tobacco at some point in their lives; 406 (40.9%) never smoked and three participants (0.3%) were not sure. Of the 319 people who were not smoking in August 2010, 76 (23.8%) had smoked at least one cigarette since the September earthquake, 29 (38.2%) of whom had smoked more than 100 cigarettes. Of the 273 participants smoking in August 2010, 86 (31.5%) had since decreased consumption, 94 (34.4%) had not changed, deletion and 93 (34.1%) to the earthquakes increased their consumption.

Conclusion: The prevalence of smoking in Christchurch has increased in the 15 months following the first major quake in Sept 2010. 28% of people not smoking prior to the earthquakes smoked one or more cigarettes and people smoking prior to the earthquakes increased their consumption.

4518 Eyjafjalla jökull 2010: Respiratory morbidity and symptoms following exposure to a volcanic eruption
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Introduction: Few cohort studies are available on the association between moisture damage, confirmed by technical inspection, and risk of new asthma. Aims: To study the association between confirmed moisture damage at the age of 5 months on average and risk of asthma by the age of 6 years. Methods: Building inspection was performed by building engineers in the homes of 394 children, and the children were followed up with repeated questionnaires from birth to the age of 6 years. Current asthma was defined as doctor diagnoses of asthma ever and either current asthma medication or wheezing symptoms at the age of 6 years. Odds ratios (OR) were adjusted for potential confounders using discrete time hazard model and GEE.
Results: Severe moisture damage in the kitchen (OR 2.80, 95%CI 1.02-7.64) or in the child’s bedroom (OR 3.65, 95%CI 1.00-13.28) and visible mold in the child’s bedroom (OR 4.02, 95%CI 1.07-15.94) increased the incidence of doctor diagnosed asthma ever in life (p<0.001). Similar associations were observed with current asthma (n=33) and with wheezing apart from cold. Weak associations were observed with moisture damage in the main living areas. No consistent associations were observed with moisture damage in the bathrooms or in other interior spaces of the house. There was some suggestion that the associations were weaker during the latter part of the follow-up.

4519 Outdoor exposure to formaldehyde is associated with increased DNA damage and respiratory symptoms in children
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Background: Exposure to air pollutants emitted by industrial sources may be a health hazard for children living nearby. Objectives: To evaluate whether residential outdoor exposure to formaldehyde was associated with DNA damage and with respiratory symptoms in children who lived in the largest chipboard manufacturing area in Northern Italy (Viadana). Methods: In 2010, randomly selected children (6-12 years) living in the Viadana district were surveyed through a parental questionnaire on respiratory symptoms. A score was devised to evaluate the presence/intensity of asthma-like symptoms. DNA strand breaks and nuclear abnormalities of the oral mucosa cells were analyzed by the comet assay and micronucleus assays respectively. Passive samplers (n=63) were installed in the area to monitor formaldehyde both in winter and summer 2010. Kriging interpolation was used to estimate the concentration of formaldehyde of each child. Appropriate regression models were fitted to the data. Results: 417 out of 656 eligible children (64%) took part in the study. Children living near (<2 km) the chipboard factories had the highest (p<0.001) formaldehyde exposure. A 1-standard deviation increase in formaldehyde (+6.16 μg/m3) was associated with an increase of 10% (95%CI 1.5-20%) in the comet tail intensity and of 10% (95%CI 1.1-19%) in the frequency of nuclear buds. Children exposed to the highest level of formaldehyde (>85th centile) had an increased risk of asthma like symptoms (OR=2.1; 1.1-4.2).
Conclusions: Exposure to pollutants emitted by chipboard industries statistically significantly increased DNA damage and asthma-like symptoms in children.

4520 Confirmed moisture damage and risk of asthma from birth to age 6 years
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Background: The eruption of Eyjafjallajökull, Iceland 2010 posed an opportunity to study health effects of a volcanic eruption in a society with strong infrastructure. The aim of the study was to evaluate the health of the exposed population compared to control population.

Methods: Six months after the eruption, (fall and winter 2010-11), 1148 exposed South Icelanders and 510 unexposed North Icelanders responded to a questionnaire on recent physical symptoms and questions from the European Community Respiratory Health questionnaire. The data was analyzed using logistic regression adjusted for age, gender, education and smoking status.

Results: Demographic characteristics and underlying disease rates were similar in the two groups. The exposed group reported more symptoms during the last 12 months; more phlegm in exposed group, OR 1.5 (95%CI 1.3-1.8) and ruffled stuffed nose, OR 1.4 (95%CI 1.2-1.6). Recent (last month) symptoms were more increased, for example cough, OR 2.6 (95%CI 1.7-3.8) and phlegm, OR 2.1 (95%CI 1.3-3.2), eye irritation, OR 2.9 (95%CI 1.8-4.5) and runny or irritated nose, OR 2.0 (95%CI 1.4-2.9). Respiratory symptoms were more prevalent among those living closest to the volcano. Upper airway symptoms coexisted, so those who reported one symptom were likely to have others also.

Discussion: Six months after the Eyjafjallajökull eruption our results indicate that the presence of volcanic ash is associated with two to three times higher recent upper airway symptom rates among the exposed population compared to the unexposed.

Conclusion: Exposure to volcanic ash may increase respiratory morbidity symptoms six months post eruption, but long-term consequences are still unknown.
Conclusions: The results are consistent with our earlier report over the first 1.5 years of life (Karvonen et al. 2009). The results support earlier conclusions that moisture damage not only increases the risk of respiratory symptoms, but is also associated with increased risk of developing new asthma.

4521
Home dampness and mould, β(1,3)-D-glucan in mattress dust and respiratory symptoms in adults from 10 European countries

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β-glucans are pro-inflammatory fungal cell wall components that have been associated with adverse respiratory health effects in children. We measured β(1,3)-D-glucans in mattress dust samples from 973 randomly selected adults from 22 ECRHS study centres in 10 European countries using an enzyme immunoassay. Information on respiratory symptoms, housing characteristics, dampness and mould was obtained by face-to-face interviews and home visits following a common protocol. Study centre explained 28% of the total variance in glucan concentration, with geometric means ranging from 0.40 to 1.77 μg/g in Reykjavik, Iceland, to 1.77 μg/g in Barcelona, Spain. Damp or mould problems in the previous years were reported by 30% of the participants (range 11-50% across centres) and was significantly associated with a 10% higher glucan level when controlling for centre. Mattresses older than 5 years contained on average 20% more glucan than mattresses less than one year old. The presence of a cat or a dog in the home increased 17-24% the glucan concentration. Nasal symptoms in the previous year (overall 38%) were more prevalent when damp or mould was reported (adjusted Odds Ratio (OR) 1.35; 95%CI 1.00-1.82). However, nasal symptoms were not associated with glucan level (OR 1.00 without indications for heterogeneity across centres). Similarly there was no association of asthma-symptom score with mattress glucan level. In conclusion, β(1,3)-D-glucans are ubiquitous in mattress dust from European homes. Although weakly associated with damp and mould problems there was no evidence that mattress levels of β(1,3)-D-glucans were associated with respiratory health in adults.

4522
Exhaled nitrogen oxide (FeNO) and nasal patency in adults in relation to levels of airborne fungal DNA in dwellings in Lund, Sweden

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Background: Questionnaire studies have reported associations between indoor moulds and dampness, asthma and rhinitis. We investigated if levels of fungal DNA in dwellings were associated with nasal patency, tear film stability, and levels of exhaled NO.

Methods: Totally 49 adults from 42 homes, randomly selected from a larger population survey in the city of Lund, Scania, Sweden. Exhaled NO was measured by NIOX MINO (50 ml/min). Nasal patency was measured by acoustic rhinometry. Tear film break up time (BUT) was monitored as a sign of eye irritation. FeNO was measured by NIOX MINO (50 ml/min). Nasal patency was measured by acoustic rhinometry. Tear film break up time (BUT) was monitored as a sign of eye irritation. FeNO by NIOX MINO (50 ml/min). Nasal patency was measured by acoustic rhinometry. Tear film break up time (BUT) was monitored as a sign of eye irritation. FeNO

Results: Three types of fungal DNA was commonly found in the homes. Exhaled NO was higher at higher concentrations of total fungal DNA (p<0.04). Mean cross-sectional area in the front part of the nasal cavity was decreased at higher levels of Aspergillus/Penicillium DNA (p=0.05), and posterior cross-sectional area was decreased at higher levels of Aspergillus versicolor DNA (p=0.05). No associations were found between BUT and fungal DNA.

Conclusion: Fungal DNA in settled dust in random selected ordinary homes can be a risk factor for nasal inflammation, measured as decreased nasal patency, and lower airway inflammation measured as exhaled NO.

4524
Lung function decline in elderly in relation to phthalate metabolites and bisphenol A levels in serum: A 2-year prospective study

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Background: Some recent studies report associations between phthalate exposure and asthma in pre-school children. We investigated if circulating levels of phthalates and bisphenol A (BPA) predicts lung function decline in an elderly population.

Methods: PIVUS is a cohort, based on a population sample of subjects, aged 70 years in Uppsala, Sweden. Circulating levels of BPA and phthalate metabolites in serum was measured at baseline by LC/MS/MS. Lung function was measured at baseline and after 5 years in 668 subjects. Change of forced expiratory volume in 1 s (FEV1) was calculated. Associations were analysed by multivariate modelling adjusting for height, smoking at 70 and 75 y, pack years of tobacco at 70 y, education level, exercise habits and gender, using log-transformed values for circulating levels, excluding 36 subjects with asthma or COPD at baseline.

Results: BPA median level was 3.75 ng/mL, Monophenyl hexyl phthalate (MEHP) 4.51 ng/mL, monophenyl tetratlate (MEP) 11.6 ng/mL, Monomethyl phtalate (MMP) 1.51 ng/mL, Monoisobutyl phtalate (MiBP) 4.51 ng/mL, monethyl phtalate (MEP) 11.6 ng/mL, Monomethyl phtalate (MMP) 1.51 ng/mL, with no gender differences. The annual decline in FEV1 was -55.6 ml/year. MEHP was associated with an additional decline in FEV1 of -6.0 ml/year (95% CI -8.6 to -3.4) (p<0.001), while MMP was associated with an additional improvement in FEV1 of 6.6 ml/year (95% CI 3.2 to 9.8) (p<0.001). The association for MEHP was significant in both men and women, while the association for MMP was significant in women, only.

Discussion: Associations between circulating levels of some phthalates metabolites and the five year decline of FEV1 were found, with MEHP as a risk factor for lung function decline.

4525
Measuring concern about pollution in questionnaire-based environmental surveys

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Understanding attitudes towards pollution in the population might help to prevent bias in questionnaire-based environmental studies, because subjects living closer to emission sources may be more concerned than those who live farther away, thus tending to over-report adverse health outcomes.

Using data from a survey on parents of 3697 school-age children (response rate 99%) in an industrial area in northern Italy (Viadana), we devised a score on environmental concerns (EC), evaluated its psychometric properties and its association with several determinants.

Six questions surveyed respondents’ concerns about electromagnetic fields (EMFs),...
472. Interstitial lung disease: from bench to bedside

4526 Clinical features common to five cases with secondary pulmonary alveolar proteinosis complicated with Behcet disease

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Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by abnormal accumulation of surfactant materials in the lower respiratory tracts. It is classified into three distinct types according to etiology: autoimmune, secondary, and congenital PAP. Secondary PAP (SPAP) comprises ten percent of acquired PAP. Twenty-eight patients with more than 70% increase in the expression of genes that control important B-MSC functions. The mechanisms affected by the decrease in gene expression include cellular trafficking, cellular growth, and proliferation.

Conclusion: Old B-MSCs have a different expression profile that exhibits a decrease in the expression of genes that control importan B-MSC functions.

4529 LSC 2012 Abstract – Age-related changes in the relative expression of functional genes in mesenchymal stem cells

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Chronic form of extrinsic allergic alveolitis (EAA) may have common features with idiopathic pulmonary fibrosis (IPF). The aim of presented study was to compare serum SP-A concentrations in IPF and chronic EAA patients and detect possible relationships of SP-A levels, bronchoalveolar lavage fluid (BALF) differential cell counts and high resolution computed tomography (HRCT) patterns in both diseases.

Three patients with chronic EAA and 7 patients with IPF were enrolled. All subjects underwent evaluation of SP-A serum concentrations, HRCT of the chest and BALF. HRCT alveolar and interstitial scores (HRCTa, HRCTb) were assessed according to Gay S1.

EAA patients had significantly higher HRCT alveolar score then IPF group (p<0.003). Chronic EAA group exhibited positive correlation between HRCTa and BALF eosinophils (p<0.01) [Fig. 1]. Serum SP-A concentrations did not differ between both groups.

Figure 1. Positive correlation between HRCTa and BALF eosinophils in chronic EAA patients.

Our study shows that SP-A serum concentrations do not differ between chronic EAA and IPF patients and thus should not be used as a biomarker for IPF detection. Prognostic value of serum SP-A concentrations in chronic EAA patients should be the aim of further studies.

Reference:
Effect of nintedanib on silica-induced lung inflammation and fibrosis in mice

Idiopathic pulmonary fibrosis is the most devastating fibrotic diffuse parenchymal lung disease which remains refractory to available pharmacological therapies. Therefore, novel treatment options are urgently required. Protease-activated receptor (PAR)-1 is a heterodimeric G protein-coupled receptor that mediates critical signaling pathways in pathology. Interestingly, bleomycin-induced lung fibrosis was shown to be diminished in PAR-1 deficient mice. We thus hypothesized that pharmacological PAR-1 inhibition may be an interesting therapeutic approach to combat pulmonary fibrosis. Consequently, we explored the effect of P1pal-12 (a peptidomimetic blocking the PAR-1G-protein interaction) during the development of lung fibrosis induced by intranasal instillation of bleomycin. We show that daily treatment with 0.5, 2.5 or 10 mg/kg P1pal-12, reduced severity and extent of fibrotic lesions in a dose-dependent manner (2.5 and 2 fold reduction with 2.5 and 10 mg/kg). These findings correlated with significant decreases in fibronectin, collagen and atheroma expression levels in treated mice. Moreover, fibrin deposition in the lungs was reduced by 26% ± 3% (p<0.05) in 2.5 mg/kg treated mice compared to untreated controls. Finally, P1pal-12 reduced bleomycin-induced IL-6 and MCP-1 levels in lung homogenates by 65% ± 3% (p<0.01) and 36% ± 3% (p<0.05) respectively. Overall, our data show that P1pal-12 limits lung fibrosis suggesting that targeting PAR-1 may be a promising therapeutic strategy for pulmonary fibrosis.

Introduction:

One-year treatment with the receptor tyrosine kinase inhibitor nintedanib (BIBF 1120) specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) was associated with a 68%-reduction in the rate of decline of forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF) versus placebo, which approached statistical significance.

Aim: To further explore its mode of action, nintedanib was tested in a mouse model of silicosis displaying ongoing pulmonary inflammation and fibrosis.

Methods: Silica was administered intranasally to generate a single intranasal administration of silica causing a robust lung inflammation with a significant increase in macrophages, neutrophils and lymphocytes in the BALF, increased IL-1 beta, CXCL1/KC and TIMP1 production, and increased collagen deposition in the lung. To further investigate the pathogenesis of pulmonary inflammation with collagen formation and fibrosis demonstrated by collagen staining.

Results: Nintedanib administered by gavage at 30 and 100 mg/kg/day significantly reduced neutrophil and lymphocyte counts, but had no effect on macrophage counts in the BALF.

Furthermore, IL-1 beta, CXCL1/KC, TIMP1, collagen in lung and lung inflammation with granuloma and fibrosis were drastically reduced.

Conclusion: Nintedanib effectively reduced silica-induced chronic inflammation and fibrosis in mice. The anti-inflammatory and anti-fibrotic features of nintedanib may impact the progressive course of fibrotic lung diseases like IPF or silicosis.

4532 Telomere (TL) shortening is associated with disease severity in scleroderma (SSC) (ILD) patients

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TL length is significantly associated with disease extent in SSC-ILD.

4533 Mechanistic studies in airway cell biology

4534 Acute effect of cigarette smoke on proteasome function

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Background: Chronic obstructive pulmonary disease (COPD) is associated with an abnormal inflammatory response of the lungs to cigarette smoke (CS). The products of CS oxidatively modify proteins thereby inducing severe oxidative cellular damage. The ubiquitin proteasome system serves as the major disposal system for oxidatively modified proteins and is thus essential for proper cellular

Figure 1. Comparison of telomere length in individuals with limited and extensive SSC associated ILD. Box and whisker plot demonstrating mean and 95% confidence intervals with outliers.

Our observation suggests an important role for premature cellular senescence in the pathogenesis of SSC-ILD. HA is an ERS-Fellow.
function. However, its role in CS-induced cell damage is currently unknown. We hypothesized that CS exposure impairs the function of the proteasome resulting in accumulation of oxidatively modified proteins, and exacerbation of cellular stress.

Methods and results: Treatment of human lung epithelial cells with CS resulted in time and dose-dependent decrease of survival and increase of intracellular reactive oxygen species. The increased levels of oxidative stress correlated with accumulation of oxidatively modified proteins. CSE exposure also induced accumulation of polyubiquitinated proteins. Notably, treatment with CSE significantly impaired all three proteasomal activities at high doses. The trypsin-like activity was also reduced in nontoxic CSE doses. Expression of the proteasome was unaffected. To confirm these observations in vivo, mice were exposed for 3 days to CS. Importantly, the trypsin-like activity of the proteasome was significantly reduced in lungs of smoked mice. We also observed increased levels of polyubiquitinated proteins in tissue extracts of smoked lungs compared to controls.

Conclusion: Our data clearly indicate that acute cigarette smoke exposure impairs proteasome function in the lung. Reduced proteasomal protein degradation might thus contribute to the detrimental cellular effects of cigarette smoke exposure in COPD.

4535 Decreased levels of elafin in the lungs of patients with acute lung injury as a result of proteolytic cleavage by the proteasome

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Unregulated protease activity may drive dysregulated pulmonary inflammation implicated in acute lung injury (ALI). Elafin is a potent serine protease inhibitor produced locally in the lung by epithelial and inflammatory cells with anti-inflammatory properties. In this study we assessed the temporal changes in elafin concentration in patients with ALI and evaluated whether a decrease in elafin levels are due to proteolytic degradation. Patients with ALI within 48 hours of onset of ALI (n=37), day 3 (n=19) and day 7 (n=9) as well as healthy volunteers undergoing high-resolution laryngoscopy (BAL) were included. The serum levels of elafin were measured by ELISA. To determine whether elafin was susceptible to proteolytic cleavage. Western blot analysis of recombinant elafin incubated with BAL fluid revealed protease inhibitors was carried out. Elafin was significantly increased at the onset of ALI compared to healthy volunteers (39.5±5mg/l vs 0.5±0.1mg/l; p<0.0004). Elafin levels fell significantly by day 7 compared to baseline (16±4.3mg/l vs 39.5±5mg/l; p<0.01). Incubation of exogenous elafin with BAL ALI fluid revealed that elafin underwent proteolytic cleavage. In contrast, proteolytic cleavage was not observed following incubation of exogenous elafin with healthy volunteer BAL fluid. Pre-incubation of ALI BALF with trypsin and chymotrypsin-like inhibitors abrogated this degradation of elafin. In addition, we demonstrated increased levels and activity of 20S proteasome in the BALF of ALI patients compared to healthy volunteer BAL fluid and confirmed that 20S proteasome was responsible for cleavage of elafin in ALI BALF which inactivated elafin’s anti-elastase activity.

4536 Klotho: An important protein in the formation and development of emphysema

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Objective: Klotho is an anti-aging protein which also possesses anti-inflammatory actions and modulates the cellular responses to oxidative stress. Knockout of klotho in the mouse caused the formation of emphysema. The aim of this study is to investigate the expression of klotho in human emphysema and factors affecting its expression and activity in human bronchial epithelial cells.

Methods: Lung tissue from 5 COPD patients, 8 smokers without COPD and 13 non-smoking, non-COPD. Klotho expression was determined by quantitative real-time PCR. Western blotting and immunohistochemistry. Human bronchial epithelial cells (HBE) were treated with tumor necrosis factor (TNF)-α and hydrogen peroxide (H₂O₂), and the expression of klotho mRNA in cells and protein in cell supernatants was detected by RT-PCR and enzyme-linked immune sorbent assay (ELISA) respectively. Exogenous klotho was also added to HBE and A549 cell cultures and MTT assays were used to detect cell apoptosis.

Results: Klotho was detected in human lung tissue with a clear localization to airway epithelial cells. The level of klotho mRNA and protein in smokers with normal lung function was similar to that in non-smokers but was reduced in COPD patients. The level of klotho expression was similar in COPD patients with emphysema compared with that in non-emphysematous COPD patients. In addition, we found that both TNF-α and H₂O₂ could significantly inhibit the expression and release of klotho in HBE cells. Exogenous klotho inhibited apoptosis in HBE and A549 cells.

Conclusions: Klotho may play an important role in the formation and development of emphysema in COPD. However, further research is needed to explore the underlying mechanism.

4537 Immune activation in α1 antitrypsin deficiency (AATD) emphysema: Beyond the protease/antiprotease hypothesis

Erika Bassani, Simona Lettieri, Francesca Lunardi, Kim Lokar Oliani, Andrea Ballarin, Mario Schiavoni, Graziella Turato, Elisabetta Balestro, Federico Rea, Monica Loy, Manuel Cosio, Marina Saetta, Fiorella Calabrese.

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The protease/antiprotease hypothesis has long set the field in the pathogenesis of AATD related emphysema, while activation of lymphocyte-driven responses has been scarcely investigated in this condition. We performed this study to evaluate the involvement of adaptive immune responses in AATD patients. By immunohistochemistry and molecular analysis we evaluated number, topographical distribution and clonality of lymphoid follicles in native lungs of AATD patients undergoing transplantation for severe emphysema (defects matched compared to patients with similar disease severity, but with normal AAT levels (n=26) and to smoking (n=17) and nonsmoking (n=12) controls. Lymphoid follicles (LF) were significantly increased in the lungs of emphysematous patients, either with AATD (4.1±0.7±1.3 LF/cm²) or without AATD (1.5±0.5±1.3) as compared to smoking (0.0±5) and nonsmoking controls (0.0±1, p<0.05). Somewhat surprisingly the number of LF was even more prominent in patients with AATD than in those with normal AAT levels (p<0.05). Follicles in patients with AATD were predominantly located in the lower lobe, where lung destruction predominates. Molecular analysis confirmed an oligoclonal response in B cells isolated from these follicles. In conclusion, our study shows that organization of lymphocytes in follicles is a prominent feature of subjects with severe emphysema and AATD. These results challenge the current paradigm of α1antitrypsin deficiency-related emphysema from a protease/antiprotease driven process to a more complex scenario entailing activation of adaptive immune responses. Funded by Padua University, CARIPARO, Chiesi farmaceutici.

4538 Impact of cigarette smoke exposure on Pseudomonas clearance in wild-type and serpinB1–/– mice

Triziana Patrizia Cremona, Charaf Benarafa, Theodor Kocher Institute, University of Bern, Switzerland

Opportunistic pathogens colonize the lungs of COPD patients and contribute to exacerbations. Cigarette smoke exposure induces pulmonary inflammation and is associated with increased incidence and morbidity of pulmonary infections but specific mechanisms linking smoke exposure to defective microbial clearance remain to be defined. Knock-out mice for serpinB1 (B1–/–), a potent inhibitor of neutrophil proteases, have a severe defect in Pseudomonas clearance associated with increased inflammation, neutrophil death and proteolysis of antimicrobial molecules. In this study, we investigated the combined effects of cigarette smoke exposure and excess neutrophil proteases on Pseudomonas clearance. B1–/– and wild-type mice were exposed to cigarette smoke or room air (control) for 6 weeks and injected intranasally 24h later. As shown previously, control B1–/– mice had a severe defect in bacterial clearance compared to control wild-type mice 20th post infection. Surprisingly, clearance was dramatically improved in smoke-exposed B1–/– mice, which had very low bacterial counts similar to smoke-exposed and control wild-type mice. At earlier time points (4 & 9h post infection), smoke-exposed wild-type mice also had lower bacterial counts than control wild-type mice. All groups of mice had similar bacterial counts 30min after infection suggesting no effect of prior smoke exposure on initial Pseudomonas survival. No increase in Pseudomonas-specific serum antibodies or neutrophil numbers was seen in smoke-exposed compared to their respective control mice. Our findings indicate that protease inhibitor imbalance and acute cigarette smoke exposure differentially affect the kinetics of Pseudomonas clearance in the lung.

4539 Investigations on the role of region-specific IL-13 receptor α1 expression along the airway tree in mucus production in asthma

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1Department of Experimental Pathology, Research Center, Borstel, Germany; 2Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Helmholtz Zentrum Munich, Germany

Increased mucus production is a critical factor impairing lung function in patients suffering from bronchial asthma. In acute and chronic mouse models of allergic asthma, metaplasia of mucus producing goblet cells (GC) was found in proximal but not in distal airways although secretion of interleukin (IL)-13, the main trigger of mucous production was significantly elevated along the whole airway tree. The current study aimed at elucidating which domains of allergic asthma metaplasia of mucus-producing goblet cells (GC) was found in proximal but not in distal airways although secretion of interleukin (IL)-13, the main trigger of mucous production was significantly elevated along the whole airway tree.
Role of nicotinic receptors in the regulation of cytokines production by human lung macrophages

Charlie Ablashi1, Soňa Šmídková Desínová1, Amapro Buenestado1, Emmanuel Naline1, Roger Papke2, Philippe Devillier1.

Background: In addition to its functions as a neurotransmitter, ACh may also serve as an autocrine/paracrine modulator of pulmonary inflammation. Our aims were to investigate the role of cholinergic receptors in the M1 (proinflammatory)/M2 (immunomodulatory) polarization of lung macrophages (LM).

Methods: LM were isolated from human resected lungs challenged for 24hrs with LPS to obtain M1 LM or with IL-13 to obtain M2 LM. Expression of α4/7 nicotinic ACh receptors (nAChRs), M1-5 muscarinic receptors and cytokines was assessed with RT-qPCR, M1- (TNF-α, CCL3, CXCL8 and IL-6) and M2- cytokines (CCL18, CCL22) were quantified in supernatants.

Results: Expression of α7nAChR and M2 and M3 receptors was found in LM. The selective α7nAChR agonist and desensitizing agent GT1-28 (100 µM) inhibited ~50% the production of M1 cytokines after LPS stimulation and of M2 cytokines after IL-13 stimulation. On the other hand, uninhibited LM in the presence of the α7nAChR antagonist α-bungarotoxin (10µM) showed an increased expression of M1 cytokines at both transcriptional (5- to 15-fold) and protein level (2.5- to 46-fold), whereas M2 cytokines were not affected. Two agonists with mixed nicotinic/muscarinic activity that do not induce stable α7nAChR desensitization (acetylecholine and carbacol) and the muscarinic antagonists tiotropium bromide and 4-DAMP were devoid of effect.

Conclusions: The blockade of α7nAChR in basal conditions favours LM polarization toward the M1 phenotype, whereas ligand-bound, but potentially non-conducting, α7nAChR in proinflammatory conditions inhibit the production of M1 cytokines. α7nAChR may thus constitute a pharmacological target in lung inflammatory diseases.
Our results confirm a possible role of those two miRNAs in lung cancer angiogenesis and suggest the potential new target angiogenic lung cancer therapy.

4545

Overcome the EGFR-TKIs resistance with cucurbitacin BE compound by targeting STAT3, ERK1/2 and AKT

Ming Lin, Lixia Zheng, Chen He, Jun Xu. Guangzhou Institute of Respiratory Diseases, Guangzhou Medical College, Guangzhou, Guangdong, China

Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) therapy, but acquired resistance eventually develops at about 9-12 months. Overcoming the drug resistance is of great clinical and scientific significance. In this study, we showed that STAT3,ERK1/2 and AKT were persistently activated in the resistant cells with T790M mutation(PCR/ER) and 52 tumor samples from EGFR-TKIs resistant NSCLC patients. The growth inhibition of the trizomer compound cucurbitacin BE (Cu BE) was tested in vitro and in vivo against PC9/GR cells. Cu BE can inhibit the growth of PC9 and PC9/GR cells in a dose- and time-dependent manner, resulting in G2/M phase arrest and apoptosis. This was associated with inhibition of activated Stat3,ERK1/2 and AKT, increased level of autophagy(LC3B expression), and down-regulated the expression of caspase 3 and survivin. Moreover, in a nude mouse xenograft model, Cu BE decreased the PC9/GR tumor volume by 46.4% (P < 0.05) compared with the mice treated with erlotinib. These data suggest that treatment with CuBE, which can inhibit the activation of STAT3,ERK1/2 and AKT, appears to be an effective strategy for NSCLC patients with EGFR-TKIs resistance.

4546

Diagnostic yield of ROSE (rapid on-site evaluation) and cell block obtained by endobronchial ultrasound (EBUS) in patients with lung cancer

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Introduction: The cytological diagnosis of lymph node(LN) metastases depends on various factors such as the number of passes made at each station, access to ROSE or type of sample processing. Our objective was to analyze the diagnostic value of ROSE and cell block (CB) obtained for mediastinal staging by EBUS in lung cancer.

Methods: Selective EBUS sampling was performed to patients with lung cancer and mediastinal disease by chest CT or PET-CT. For each fine needle aspiration(FNA), we collected the results of ROSE, final cytology diagnosis and CB. At least 3 FNA per LN were performed if ROSE did not show malignant cells.

Results: We studied 148 patients from June 2010 to August 2011, of which 49 met the inclusion criteria. The diagnostic yield of ROSE was 47.8% and for CB was 70.6%. The % of agreement between ROSE and CB was 94.9%. BC added 3.1% for the total of 130 FNA were performed, being unable to obtain a CB in 23.1% of cases. The level of Prx1, a major 2-Cys peroxiredoxin family member, is frequently increased apoplastic potential through activation of the caspase cascade and suppressed doxorubicin-induced phosphorylation of Akt and its substrate forkhead box O1 (FOXO1). Moreover, treatment with the phosphoinositide 3-kinase (PI3K) inhibitor LY294002 reduced the phosphorylation of FOXO1 and increased the cytotoxicity of doxorubicin in A549 cells. Our findings suggest that Prx1 may modulate the chemosensitivity of lung cancer to doxorubicin through suppression of FOXO1-induced apoptosis.

4548

Overexpression of inhibitor of DNA-binding proteins and angiogenic markers have higher impact on survival of non small cell lung cancer patients

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Background: The inhibitor of DNA binding (Id) proteins have been implicated in oncogenic transformation, progression and in tumor angiogenesis, the last one by regulation of vascular endothelial growth factor (VEGF) expression. Notwithstanding, these mechanisms have not been fully understood. The aim of this study was to evaluate the Id1, 2,3 and VEGF expression and angiogenesis amount in non small cell lung cancer (NSCLC) and their role on patients’ prognosis.

Methods: Immunohistochemistry and morphometry were used to evaluate Ids, VEGF expression and microvessels density (CD34) in neoplastic and stromal cells from 85 patients with surgically excised NSCLC. The impact of these markers was tested on follow-up until death from recurrence lung cancer.

Results: The Kaplan-Meier survival curve analysis showed that expression of Id-1, CD34 and VEGF were associated with poor prognosis (Log Rank Test, p < 0.001). A Cox model analysis controlled for histological type, lymph node stage, Ids, VEGF, CD34 and age demonstrated that only Id1, Id3 and vascular density were significantly associated with survival time. A point at the median for Id1, Id3 and vascular density divided patients into 2 groups, each one with distinctive prognosis. Those with higher expression of Id1, Id3 and vascular density had a higher risk of death when compared to those with lower Id1, Id3 and vascular density.

Conclusion: In resected NSCLC, Id1, Id3, VGF and vascular density were strongly associated with prognosis. Therefore, Id1 and Id3 seem to contribute to tumor progression and should be considered as prognostic markers in NSCLC.

4549

Clinicopathological significance and prognostic importance of circulating plasma DNA expression in advanced non-small cell lung cancer and its efficacy as a diagnostic tool

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Lung cancer is commonest neoplasm. Ther is continuous need for new prognostic markers. Circulating plasma DNA levels is over-expressed in many cancers, including lung.

Aim of work: To study the expression of circulating DNA in NSCLC and assess-ment of its utility as a diagnostic marker and impact on therapeutic efficacy.

Methods: Plasma DNA was determined through the use of polymerase chain reac-tion(PCR) assay. To study the expression of circulating DNA in NSCLC, we assessed plasma DNA levels was correlated with response to therapy, overall survival, and lactate dehydrogenase level.

Results: There was a significant correlation between circulating plasma DNA lev-els and stage, LDH levels and tumor status. Plasma DNA levels were significantly inversely correlated with treatment response.
4552 Effect of fasudil on the bleomycin-induced pulmonary fibrosis and hypertension in mice
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1 Hangzhou Medical College, Hangzhou, China; 2Pharmacology Department, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; 3Pharmacology Department, School of Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; 4Pharmacology Research Institute, Shanghai Jiao Tong University, Shanghai, China

Background: RhoA/ROK kinase (ROCK) pathway is important in regulating vascular tone and vascular remodelling in pulmonary hypertension (PH). It has been shown to be altered in the bleomycin-induced pulmonary fibrosis (PF) and PH in mice. However, the exact mechanism by which it leads to PF and PH remains to be clarified.

Objectives: The present study aimed to assess whether fasudil, a ROK inhibitor, is able to inhibit PF and PH induced by bleomycin in mice.

Methods: Male C57BL/6 mice were randomized into 3 groups: G1 (saline), G2 (bleomycin) and G3 (bleomycin + fasudil). Bleomycin (3.3U/kg) was given intratracheally (day 0) and fasudil (30mg/kg/d) intraperitoneally from day 1 day 14 days. Right ventricular systolic pressure (RVSP) was measured by RV puncture at 7, 14, and 21 days, followed by sacrifice and lung and lung samplings for collagen analysis.

Results: Pulmonary fibrosis was present at 7 days, and became more apparent at 14 days. RVSP increased at 14 days, accompanied by right ventricular hypertrophy. Fasudil improved survival, reversed PF and attenuated PH.

Conclusions: The efficacy of the ROK inhibitor, Fasudil, suggests that RhoA/ROCK is involved in causing PF and PH induced by bleomycin in mice.

4553 Polymorphisms in angiotensin converting enzyme gene are associated with risk of development of and disease severity in scleroderma-related pulmonary arterial hypertension
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Background: While 8-12% of patients with scleroderma (SSc) will develop pulmonary arterial hypertension (PAH), little is known about risk factors for this complication. Angiotensin converting enzyme (ACE) is associated with endothelial dysfunction and may play a role in susceptibility to vascular disease in SSc. We sought to identify polymorphisms in ACE gene that may contribute to risk of PAH in SSc.

Methods: A case-control study was performed in 916 patients of European descent. Of 458 SSc patients, 103 had right heart catheterization-proven PAH; the remainder did not have significant respiratory disease. Three single nucleotide polymorphisms (SNPs) in ACE gene [rs4293, rs3730025, rs4311], previously shown to be associated with cardiovascular disease, were examined. The relative frequency of SNPs and their relationship to presence of PH and severity of PAH were assessed using Cochran-Armitage trend test with PLINK and linear regression association between genotype and hemodynamics.

Results: A strong association was found between SNP rs3730025 and risk of PAH (P=0.009). Carriers of G allele of rs4293 had increased cardiac index (β=0.458, P=0.005) and decreased pulmonary vascular resistance (P<0.137, P=0.018).

Conclusion: In this SSc cohort, a coding SNP in ACE gene was strongly associated with presence of PAH. Further, presence of SNP rs4293 was associated with preserved cardiac function in SSc-PAH. Given the role of these SNPs in the function of ACE and the relationship between ACE and vascular function, further studies are warranted to investigate the role of these SNPs in the pathogenesis of PAH in SSc.
indicating an important role of miR-130a in the development of hypoxia-induced PH.

**Conclusion:** Genetic ablation of the BMPR2 gene in pulmonary ECs is sufficient to predispose to PAH. Our data reveal interplay between BMPR2 signaling and the 5-HT system in ECs within PAH, leading to increased susceptibility to PAH progression.

**4555**

**Hypoxia-induced miR-130a is a novel repressor of BMPR2 gene expression in experimental pulmonary hypertension.**

**Introduction:** Vascular remodelling, a pathogenetic feature of pulmonary hypertension (PH), is associated with decreased expression of the bone morphogenetic protein receptor type II (BMPR2). We recently demonstrated that the inhibition of microRNA 20a (miR-20a) prevents vascular remodelling in hypoxia-induced PH. Here we assessed the role of miRNAs in the repression of BMPR2 gene expression in experimental PH.

**Methods:** The mouse model for hypoxia-induced PH was used. After 21 days of hypoxia, lungs were removed and assessed for mRNA and gene expression. RNA levels of miR-21, -25, -125a, -130a, and -130b and BMPR2 were measured using SYBR-Green real-time PCR. Reporter gene assays comprising the 3′UTR of BMPR2 and TGFBR2 were applied to confirm direct miRNA–target interactions.

**Results:** Using a miRNA prediction program, we identified phylogenetically conserved binding sites of miR-21, -25, -125a, -130a, and -130b in the 3′UTR of BMPR2. Under hypoxic conditions the RNA levels of miR-21, miR-125a, and miR-130a were found to be significantly upregulated (p < 0.05) when compared to normoxic controls. Consistent with previous reports the miRNA expression of BMPR2 was significantly reduced in hypoxic lungs (0.79±0.24 fold, p=0.039) and, most importantly, showed a negative correlation with the expression of miR-130a (R²=0.28, p=0.04). By performing reporter gene assays we confirmed that miR-130a directly targets the 3′UTR of BMPR2. Along this line, we identified the BMPR2-related receptor TGFBR2 as another novel target of miR-130a. BMPR2 was significantly reduced in hypoxic lungs (0.79±0.24 fold, p=0.039) and, most importantly, showed a negative correlation with the expression of miR-130a (R²=0.28, p=0.04). By performing reporter gene assays we confirmed that miR-130a directly targets the 3′UTR of BMPR2. Along this line, we identified the BMPR2-related receptor TGFBR2 as another novel target of miR-130a.

**Conclusion:** We identified miR-130a as a negative regulator of BMPR2 expression indicating an important role of miR-130a in the development of hypoxia-induced PH.

**4556**

**miR-204, miR-149, miR-197, miR-487b and miR-485 were downregulated in PA-derived microvascular smooth muscle cells.**

**Background:** Recent studies are showing the potential role of micro-RNAs (miRNAs) in the regulation of many genes controlling cell growth and proliferation. regulation (p < 0.05) whereas no changes were observed in this gene after treatment with IL-1β or INF-γ. Fully differentiated SMC treated with TNFα, downregulated significantly myocardin, sm22α and calponin. We conclude that slug expression might be associated with a SMC proliferative phenotype induced by inflammatory stimuli. This SMC phenotype switching might contribute to the development and progression of vascular disorders.

**Conclusion:** miR-204, miR-149, miR-197, miR-487b and miR-485 were downregulated in PA-derived microvascular smooth muscle cells.

**4557**

**Slug can contribute to the phenotypic modulation of smooth muscle cells.**

**Background:** Slug is a transcription factor related with transitional changes in cell phenotype. Smooth muscle cells (SMC) may show high plasticity switching from a contractile (fully differentiated) to a proliferative phenotype (dedifferentiated).

**Conclusion:** Recently, we have found that remodelled pulmonary arteries have increased expression of slug, a transcription factor related with transitional changes in cell phenotype. Slug may contribute to the phenotypic switching from a contractile to a proliferative phenotype.

**476. New scientific findings on noninvasive ventilation in the acute setting**

**4558**

**Predicting mortality in patients hospitalised with acute exacerbations of COPD (AECOPD) requiring assisted ventilation.**

**Background:** Prognostic studies in AECOPD requiring assisted ventilation often select patients by place of care and predict failure of non-invasive ventilation (NIV), not mortality. Improved mortality prediction for unselected patients requiring ventilatory assistance is needed.

**Objective:** Identify mortality predictors in patients with AECOPD requiring ventilatory assistance.

**Methods:** Clinical data were collected on consecutive patients hospitalised with AECOPD requiring assisted ventilation (NIV or invasive ventilation) for acidaemic respiratory failure (AECOPD) during their hospital stay. Independent predictors of in-hospital mortality were identified.

**Results:** 199 received ventilatory assistance: mean (SD) age = 73.9 (9.8) years; FEV1, 38.1 (16.1) % predicted and 61.3% were female. 49 (24.6%) patients died in hospital.

**Older age, an ineffectual cough, and severe stable-state dyspnoea were the strongest predictors of mortality.**

**Table 1. Independent predictors of mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.11 (1.04–1.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ineffective cough</td>
<td>5.23 (1.74–15.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI &lt;20</td>
<td>2.08 (1.25–3.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>[HCO3] mmol/L</td>
<td>0.93 (0.88–0.98)</td>
<td>0.008</td>
</tr>
<tr>
<td>Stroke disease</td>
<td>5.54 (1.49–20.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>1.21 (0.06–20.70)</td>
<td>0.012</td>
</tr>
<tr>
<td>Recent weight loss</td>
<td>5.78 (1.26–13.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>Time to recognition of ARF, hours</td>
<td>1.01 (1.00–1.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pao2 (&lt;70 mmHg)</td>
<td>1.10 (1.01–1.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maintenance carboanhydrase</td>
<td>4.03 (1.16–15.2)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*At time of ventilation commencement.*
mortality predictors. The regression model (table 1) showed excellent discrimination for mortality (AUROC = 0.92, 0.88 to 0.96).

Conclusion: Mortality in patients hospitalised with AECOPD requiring assisted ventilation is high but can be accurately predicted using simple to measure indices.

4559 Echocardiographic speckle tracking strain and right ventricular function assessment during non-invasive ventilation in acute respiratory failure patients
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Introduction: During acute respiratory failure (ARF), right ventricular (RV) function can be abnormal due to increased afterload and/or decreased contractility or preload. Speckle tracking strain analysis can diagnose RV dysynchrony. We aimed to test whether RV dyssynchrony exists during ARF and can be reversed during non-invasive ventilation (NIV).

Methods: Prospective study including 13 patients admitted for ARF. Trance thoracic echocardiography (TTE) was performed during spontaneous breathing (SB) activity and during NIV. Usual echo parameters and speckle tracking strain were measured. The software generated 6 segmental RV strain curves. Time to peak strain from each of 6 time-strain curves was determined with dyssynchrony defined as the difference between earliest and latest segments.

Results: 13 patients aged 69 (11) y were included. 11 had chronic respiratory failure. Compared to SB, left ventricular ejection fraction and stroke volume increased during NIV. 59 (6) vs 66 (6) %, 61 (9) vs 65 (11) mL, p < 0.05 respectively, and systolic pulmonary arterial pressure (SPAP) decreased 61 (16) mmHg vs 41 (16) mmHg, p = 0.03. RV dysynchrony improved significantly: 235 (40) vs 182 (149) msec, p = 0.04.

Conclusion: RV dysynchrony measured using speckle tracking strain is observed in our ARF patients. NIV can improve LVEF, RV afterload and RV dysynchrony.

4560 Confirmatory analysis of the impact of case-volume on ICU management of severe COPD exacerbations (1998-2010)
Martin Dee1, Philippe Aegerter2, Ti-Chien Tran3, Antoine Rabbat1
Bertrand Guidet1, Gerard Huchon1, Nicolas Roche1, on the behalf of CUBREA
1Service de Pneumologie et réanimation Médicale, Assistance Publique Hôpitaux de Paris - Hôpital Hôtel Dieu, Paris, France; 2Respiratory Department, Ashford and St Peter’s Hospitals NHS Foundation Trust, Chertsey, Surrey, United Kingdom; 3Respiratory Department, Ashford and St Peter’s Hospitals NHS Foundation Trust, Chertsey, Surrey, United Kingdom

Aims and objectives: The objective of this study was to establish if inappropriate NIV could be correlated with location of set up. Proving this hypothesis would enable us to target locations to provide additional support to reduce and prevent the inappropriate use of NIV.

Methods: Data were collected prospectively from 255 consecutive patients requiring NIV from May 2009 to April 2011 using an adapted version of the BTS NIV data tool.

Results: Of 255 patients, 121 were admitted in CUB-REA ICUs. There was a growing use of NIV and a decrease in the use of IV fluids. This may be due to the lack of expertise in non-respiratory areas. We therefore conclude that NIV should only be initiated in respiratory specialist areas within our hospital.

Conclusion: Patients commenced on NIV outside of respiratory specialist areas are more likely to receive inappropriate NIV with subsequent higher mortality rates. This may be due to the lack of expertise in non-respiratory areas. We therefore conclude that NIV should only be initiated in respiratory specialist areas within our hospital.

4562 Effect of continuous and bilevel noninvasive ventilation for acute asthma exacerbation – A randomized controlled trial
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Guidelines for management of acute asthma exacerbation (AAE) centre on pharmacological interventions and invasive mechanical ventilation. The role of non-invasive positive pressure ventilation (NPPV) or bilevel positive pressure ventilation (BPPV) to standard therapy (ST) would improve lung function and clinical signs faster than ST alone.

Aims: We hypothesized that adding continuous positive airway pressure (CPAP) or bilevel positive pressure ventilation (BPPV) to standard therapy (ST) would improve lung function and clinical signs faster than ST alone.

Methods: Thirty patients with severe AAE [peak expiratory flow rate percentage (PEFR%) predicted < 60%] presenting at an emergency unit were randomized to either ST, CPAP or ST and BPPV.

Results: Groups presented similar baseline characteristics. Mean baseline PEFR% predicted was 35.2 (10.7) % [ST], 30.5 (11.7) % [CPAP] and 33.5 (13.8) % [BPPV]. PEFR significantly improved in the CPAP group from the first 30 minutes of treatment (PEFR = 0.00, PEFR% predicted = 0.00) compared to the BPPV and ST groups. Improvement in respiratory rate (RR) (p = 0.05) and sensation of breathlessness (SB) (p = 0.00) was significantly better in the BPPV group from the first 30 minutes.

Discussion: The significant improvement in PEFR in the CPAP group could be related to its intrinsic effect on the airway smooth muscle and/lung load. The positive effect of BPPV on RR and SB could be related to the inspiratory assistance provided.
Conclusion: The addition of NIPPV to ST in acute severe asthma exacerbation, improved lung function and clinical signs faster than ST, yet CPAP was faster and more effective in reducing bronchospasm than BIPPV.

4563 Outcome of acidotic COPD-patients on hospital admission
Sylvia Hardy, Mike Roberts, Jose Luis Lopez-Campos, Dep. of Respiratory and Crit. Care, Otto Wagner Hospital, Vienna, Austria; Dep. of Respiratory Medicine, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBS), Spain; Dep. of Resp. Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Background: Acidosis is a marker of acute respiratory failure in COPD. Non invasive ventilation (NIV) is the first choice of ventilation for such patients to avoid intubated mechanical ventilation (IMV) and associated complications. The ER'S COPD Audit evaluated the clinical practice of treatment standards in acute exacerbation of COPD (AECOPD) in 422 hospitals of 13 European countries. We present the analysis of treatment standards for acidotic AECOPD patients and associated outcomes.

Methods: Data collection of clinical treatment of all hospital admitted AECOPD for 8 weeks and follow up until 90 days after discharge.

Results: Of 12893 patients 18.8% (2429/16666 male) presented with respiratory acidosis on admission (pH<7.38); with moderate acidosis: pH 7.35±0.25, 4.1% (n=526) with severe acidosis: pH <7.25. Acidotic patients were significantly sicker than non acidotic.

Table 1

<table>
<thead>
<tr>
<th>PEV</th>
<th>% pred smoker</th>
<th>% current smoker</th>
<th>% diabetes</th>
<th>% renal failure</th>
<th>% congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non acidotic patients (n=10464)</td>
<td>43.8</td>
<td>30.4</td>
<td>19.2</td>
<td>5.2</td>
<td>19.3</td>
</tr>
<tr>
<td>Acidotic patients (n=2429)</td>
<td>37.1</td>
<td>30.0</td>
<td>23.0</td>
<td>6.9</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Outcomes were related to severity of acidosis.

<p>| Table 2 |</p>
<table>
<thead>
<tr>
<th>Non acidotic patients</th>
<th>Moderate acidotic patients</th>
<th>Severe acidotic patients</th>
<th>p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (d)</td>
<td>9.8±1</td>
<td>10.7±8</td>
<td>14.0±20</td>
</tr>
<tr>
<td>% hospital mortality</td>
<td>3.8</td>
<td>8.8</td>
<td>17.1</td>
</tr>
<tr>
<td>% 90 d-readmission</td>
<td>35.1</td>
<td>37.8</td>
<td>42.9</td>
</tr>
</tbody>
</table>

4564 Assessment of two methods to withdraw non-invasive ventilation in acute hypercapnic respiratory failure

Background: Acidosis is a marker of acute respiratory failure in COPD. Non invasive ventilation (NIV) is the first choice of ventilation for such patients to avoid intubated mechanical ventilation (IMV) and associated complications. The ER’S COPD Audit evaluated the clinical practice of treatment standards in acute exacerbation of COPD (AECOPD) in 422 hospitals of 13 European countries. We present the analysis of treatment standards for acidotic AECOPD patients and associated outcomes.

Methods: Data collection of clinical treatment of all hospital admitted AECOPD for 8 weeks and follow up until 90 days after discharge.

Results: Of 12893 patients 18.8% (2429/16666 male) presented with respiratory acidosis on admission (pH<7.38); with moderate acidosis: pH 7.35±0.25, 4.1% (n=526) with severe acidosis: pH <7.25. Acidotic patients were significantly sicker than non acidotic.

Table 1

<table>
<thead>
<tr>
<th>PEV</th>
<th>% pred smoker</th>
<th>% current smoker</th>
<th>% diabetes</th>
<th>% renal failure</th>
<th>% congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non acidotic patients (n=10464)</td>
<td>43.8</td>
<td>30.4</td>
<td>19.2</td>
<td>5.2</td>
<td>19.3</td>
</tr>
<tr>
<td>Acidotic patients (n=2429)</td>
<td>37.1</td>
<td>30.0</td>
<td>23.0</td>
<td>6.9</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Outcomes were related to severity of acidosis.

<p>| Table 2 |</p>
<table>
<thead>
<tr>
<th>Non acidotic patients</th>
<th>Moderate acidotic patients</th>
<th>Severe acidotic patients</th>
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<tr>
<td>% 90 d-readmission</td>
<td>35.1</td>
<td>37.8</td>
<td>42.9</td>
</tr>
</tbody>
</table>

4565 Arterial blood gas analysis after 120 minutes of noninvasive positive pressure ventilation can predict outcome in acute cardiogenic pulmonary oedema
Rodolfo Ferrari, Fabrizio Gisiora, Francesca Nustali, Roberto Lazzari, Luigi Bolondi, Mario Cavazza, Dipartimento Emergenza/Urgenza, Chirurgia Generale e dei Trapianti, Unità Operativa di Medicina d’Urgenza e Pronto Soccorso, Policlinico Sant’Orsola – Malpighi, Azienda Ospedaliero Universitaria di Bologna, Università degli Studi di Bologna, Università degli Studi di Bologna, Università degli Studi di Bologna, Università degli Studi di Bologna, Università degli Studi di Bologna

Background: Noninvasive positive pressure ventilation (NIPPV) is first line intervention in Acute Cardiogenic Pulmonary Oedema (ACPO). Arterial Blood Gas Analyses (ABG) is largely available in clinical practice in the Emergency Department (ED).

Aims: To assess the role of ABG to predict outcome in patients with ACPO treated by NIPPV

Materials and methods: Treatment failure defined as hospital mortality or need for invasive mechanical ventilation. Observational clinical study in the ED of the a University teaching Hospital during 5 months, including every patient emergently admitted for ACPO and treated with first-line NIPPV, referring to an institutional protocol.

Results: 214 patients included. Failure rate 14.5%.

Table 1. ABG at presentation

<table>
<thead>
<tr>
<th></th>
<th>Failure</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 mmHg</td>
<td>57.6 (53.7)</td>
<td>61.8 (56.0)</td>
</tr>
<tr>
<td>pH</td>
<td>7.30 (7.31)</td>
<td>7.323 (7.329)</td>
</tr>
<tr>
<td>PaCO2 mmHg</td>
<td>50.6 (49.4)</td>
<td>51.8 (47.8)</td>
</tr>
<tr>
<td>HCO3 mmol/l</td>
<td>25.0 (23.0)</td>
<td>25.6 (25.1)</td>
</tr>
</tbody>
</table>

Media (median).

Table 2. ABG delta (Δ) at 120 minutes

<table>
<thead>
<tr>
<th></th>
<th>Failure</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPaO2</td>
<td>12.6 (22.1)</td>
<td>15.3 (13.7)</td>
</tr>
<tr>
<td>ΔpH</td>
<td>-0.030 (-0.021)</td>
<td>0.074 (0.061)</td>
</tr>
<tr>
<td>ΔPaCO2</td>
<td>1.1 (1.0)</td>
<td>-8.2 (-6.9)</td>
</tr>
<tr>
<td>ΔHCO3</td>
<td>-3.0 (-1.0)</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td>ΔPaO2/ΔFI O2</td>
<td>-5.1 (-3.4)</td>
<td>12 (3.1)</td>
</tr>
</tbody>
</table>

Media (median).

Conclusions: In patients with ACPO treated with NIPPV, ABG at presentation is not able to carefully predict outcome. After 60' of NIPPV both groups (success versus failure) improved without any significant difference. The improvement of ABG after 120' is associated with success; these patients will likely benefit from continuation of NIPPV. The inability to improve gas exchange after 120' of NIPPV in ACPO is predictor of failure; these patients should be closely monitored with a low threshold for endotracheal intubation.

477. Clinical and diagnostic markers and management of paediatric allergic diseases

P4566 Intensive oil baths from six weeks of age reduce xerosis and possibly atopic eczema in infancy
Bente Krane Kvenshagen, Petter Mowinckel, Kai-Håkon Carlsen, Karin L. Carlsen, Pediatric, Oestfold Hospital Trust, Fredrikstad, Norway; Pediatric, Oslo University Hospital, Oslo, Norway

Background: Atopic eczema (AE) is often the first step of the allergic march, with onset early in life, followed by asthma and allergic sensitivities. AE affects up to 20% of children, and is characterized by dry, itchy skin. AE is a complex genetic and environmental disease, with alteration of skin barrier. Restoring of the barrier by emollients and/or oil baths is an important part of AE treatment, but it’s role in preventing AE is not known. Theoretically reducing prevalence of AE could prevent later allergy and asthma development.

The present pilot study aimed to evaluate whether frequent oil baths of infants with dry skin could reduce xerosis and eczema at the age of six months.

Methods: A randomized controlled intervention study of six weeks old infants with dry skin, followed to six months by monthly assessment. They were randomized to either daily oil bathing (0.5 dl) and fat cream in the face (n=24) or observation (normal procedures) (n=31). The outcome was skin quality at six months.

833s
Results: Normal skin was observed at six months in 18 children (75%) with skin treatment, compared to 12 (38%) in the observation group (p<0.001). Frequency of oil baths was 5-7/week (n=19) and 2-4/week (n=5) in the intervention group. Skin care habits in the observation group AE was reported in one child versus five children in the intervention versus the observation group. No adverse reactions reported.

Conclusion: The present pilot study showed that regular oil baths of infants were feasible, reduced xerosis, and also possibly eczema. If verified in further studies, one might speculate if this would reduce development of allergy and asthma.

P4567

Problematic severe asthma in children: A nationwide study in The Netherlands

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1Paediatrics, University Hospital Nijmegen, Nijmegen, Netherlands; 2Paediatrics, University Hospital Groningen, Groningen, Netherlands; 3Paediatrics, University Hospital Rotterdam, Rotterdam, Netherlands; 4Paediatrics, University Hospital Amsterdam, Amsterdam, Netherlands; 5Paediatrics, University Hospital Rotterdam, Rotterdam, Netherlands; 6Paediatrics, Dutch Asthma Centre, Dusseldorf, Switzerland; 7Paediatrics, University Hospital Maastricht, Maastricht, Netherlands; 8Paediatrics, University Hospital Nijmegen, Nijmegen, Netherlands; 9Paediatrics, Academic Medical Centre, Amsterdam, Amsterdam, Netherlands; 10Paediatrics, Groene Hart Hospital, Gouda, Netherlands; 11Paediatrics, Erasmus Medical Centre, Rotterdam, Netherlands; 12Paediatrics, Rinjstate Hospital, Arnhem, Netherlands; 13Paediatrics, Erasmus Medical Centre, Rotterdam, Netherlands; 14Paediatrics, University Hospital Maastricht, Maastricht, Netherlands; 15Paediatrics, Academic Medical Centre, Amsterdam, Amsterdam, Netherlands; 16Paediatrics, Amphia Hospital, Breda, Netherlands; 17Paediatrics, Canisius Ziekenhuis, Nijmegen, Netherlands; 18Paediatrics, Medical Centre, Alkmaar, Netherlands; 19Paediatrics, Academic Hospital Maastricht, Maastricht, Netherlands; 20Dutch PSA Studygroup, Netherlands

Introduction: Epidemiological data on problematic severe asthma in children are sparse.

Methods: A 3 year (2008-2011), nationwide survey on PSA in children 4-18yrs old in the Netherlands through a national surveillance system among all paediatricians. A retrospective study cross sectional study 328 children aged 4-18yrs with PSA, were identified. A prevalence of at least 0.1% of children with asthma. PSA is more frequent in boys than in girls under 12yrs. This sex ratio reverses >12yrs old. Eighty-four children had allergic asthma and in 85% symptoms started before they were 4yrs old. All children included long term inhaled corticosteroids, FENO, trials of steroids, chest radiographs, sweat tests, immunodiagnostics, HRCT, bronchoscopy in various per-
centages of patients. Over 10% had 5-10 exacerbations requiring prednisolone in the last year. In 11%, FENO had exacerbations with no symptoms in between. 40% suffered from very acute asthma attacks and 30% were continu-
ously symptomatic. All despite up-to-date intensive surveillance and treatment. Seventy-five percent received psycho diagnostics and 50% psychotherapy. FEV1 was

Results: Persistent airflow limitation in the past year was present

Seventy-five% received psycho diagnostics and 50% psychotherapy. FEV1 was

Conclusions: In this trial, MEF/MDI 100/10g demonstrated significant bron-
chodilation in children aged 5-11 regardless of the use of a spacer.

P4569

Vitamin D receptor and vitamin D binding protein polymorphisms are associated with asthma control in children

Emmanouil Paraskevakis1, Maria Fioriandou1, Anna Tavridou1, Athanassios Chatzimichael1, Vangelis G. Manolopoulos2

1Department of Pediatrics, University Hospital, Alexandroupolis, Thrace, Greece; 2Laboratory of Pharmacology, Medical School, Alexandroupolis, Thrace, Greece

Introduction: Vitamin D levels have been associated with the onset of asthma and are suggested as a marker of disease severity in asthmatic children. Furthermore, polymorphisms in vitamin D pathway genes have been associated with vitamin D levels.

Aims and methods: 111 children with asthma and 96 healthy controls of Greek origin were analyzed for the VDR Apal, VDBP r7041 and r4588 polymorphisms using PCR-RFLP method. Asthma control level was assessed according to Child-
hood Asthma Control Test (C-AC T) and Global Initiative for Asthma guidelines (GINA).

Results: Genotype distribution for all studied polymorphisms did not differ signific-
antly between asthmatic patients and healthy controls. Frequencies of VDR Apal AA, AC and CC genotypes were 38.4%, 40.7% and 20.9% in the controlled group and 28.7% and 72.6% respectively, in the uncontrolled group according to GINA (p=0.008). This association was verified when we analyzed the VDR Apal genotypes in asthmatic group according to GINA classification (p=0.002). For the VDBP r7041 polymorphism, the frequency of variant G allele was significantly higher in children with controlled asthma compared to C-AC T (66.6% vs 50.0%, p=0.030) and GINA guidelines (62.8% vs 52.8%, p=0.027). For the VDBP r4588 polymorphism the frequency of variant A allele was significantly lower in children with controlled asthma compared to C-AC T (23.5% vs 40.0%, p=0.019) and GINA VI.7% vs 37.5%, p=0.048) guidelines.

Discussion: VDR Apal and VDBP r7041 and r4588 polymorphisms were as-
sociated with asthma control according to C-AC T and GINA classification in asthmatic children.

P4570

Role of vitamin D in asthma severity and control in children

Anissa Berrias1, Eya Tangour2, Hanadi Abid3, Jamel Ammar4, Hafia Maalmi4, Kameel Hamzaoua5, Agnès Hamzaoua5, Pavillon B, Abderrahmen Mami Hospital, Ariana, Tunisia; Pavillon B, Abderrahmen Mami Hospital, Ariana, Tunisia; Pavillon B, Abderrahmen Mami Hospital, Ariana, Tunisia; Pavillon B, Abderrahmen Mami Hospital, Ariana, Tunisia; Pavillon B, Abderrahmen Mami Hospital, Ariana, Tunisia

1Department of Pharmacology, Medical School, Alexandroupolis, Thrace, Greece

Results: In this trial, MF/F-MDI 100/10g demonstrated significant bron-
chodilation in children aged 5-11 regardless of the use of a spacer.

In addition to its role in bone physiology and autoimmune disease, recent data suggest a potential role of vitamin D in asthma since it has immunomodulatory properties. The aim of this study is to determine the relationship between serum vitamin D levels and the severity and control of asthma in children. We measured vitamin D levels in serum collected from 38 asthmatic children in winter and summer, compared to those of 30 healthy children. The mean age is 9.8 years and Sex-ratio was 2:1. Asthma was mild persistent in 60.5% of cases, mod-
erate in 36.8% of children, and severe in 2.7%. The average vitamin D level was significantly lower in asthmatics in summer despite abundant sun exposure (20.74 ng/ml vs 26.77 ng/ml p = 0.001) and levels of vitamin D were signifi-
cantly lower in winter than in summer in both groups (in asthmatics 17.37 ng/ml vs 20.74ng/ml; p=0.036 and 18.97ng/ml vs 26.77ng/ml; p<0.001 in controls). Subjects with well-controlled asthma had higher serum levels of vitamin D than children with partially controlled or non-controlled asthma in summer (24.28ng/ml vs 13.9ng/ml; p<0.001) but not in winter (17.28mg/ml vs 17.67ng/ml). In the same way, children with more severe asthma had lower serum vitamin D levels than children with mild asthma in winter (12.07mg/ml vs 20.80ng/ml; p<0.001) and in summer (13.8mg/ml vs 25.26ng/ml; p<0.001). Our study indicates that vitamin D deficiency is more common among children with asthma and lower vitamin D levels are associated with a greater disease severity and probably with worse disease control. Randomized intervention trials on vitamin D supplementation will be needed to confirm its role in treatment and eventually in prevention of asthma.

834s

WEDNESDAY, SEPTEMBER 5TH 2012
were referred to the asthma clinic of the Mofid Children’s Hospital, were enrolled.

Methods:
80 patients aged 5 to 18 years with physician diagnosed asthma with a
asthma related bronchoconstriction.

Conclusion:
Our results indicated an association between aspergillus antibody level and severity of asthma. It could be recommended that the IgG titer for aspergillus is measured in pediatric patients with asthma, whereas co-morbidity of aspergillosis and asthma increases the risk of asthma exacerbation.

Persistent or recurrent wheezing are common problems in infancy. The aim of this study is to evaluate the diagnostic value of flexible bronchoscopy (FB) and analyze its results in infants with persistent or recurrent wheezing.

Material and method: Ninety-six wheezy infants who had been performed FB between 1999 and 2011 were included in this study. Demographic features, radiological, laboratory and bronchoscopic findings were analyzed.

Results:
Sixty-six patients were male and the median age at FB date was 0.9 (0.6-1.5) years. Median age at symptom onset was 3 (1-6) months. Twenty-eight patients had persistent and 75 had recurrent wheezing. Fifty-five patients had regular asthma therapy before the procedure. Thirty patients had atelectasis on radiological imaging FB revealed a diagnosis in 64 patients.

Conclusion:
Paradoxical bronchospasm is defined as the rapid onset of bronchoconstriction after administrating β2 agonist. Few studies published suggest that it is due to tensive chlorofluorocarbons in the metered dosis inhaler (MDI). Although paradoxical bronchospasm is defined as the rapid onset of bronchoconstriction after administrating β2 agonist, level of asthma severity and control, percentage of FEV1 decrease and bronchodilator response after terbutaline dry powder were collected. Statistical analysis with SPSS.

Results:
32 patients, mean age 8.3 years (56% males). History of allergy in 65.6% (68.4% Dermatophagoides) and obesity in 34.3%. 81.3% patients had controlled asthma at the time of testing, following treatment with montelukast (42.9%) and long acting β2 agonist. Few studies published suggest that it is due to tensive chlorofluorocarbons in the metered dosis inhaler (MDI). Although paradoxical bronchospasm is defined as the rapid onset of bronchoconstriction after administrating β2 agonist, level of asthma severity and control, percentage of FEV1 decrease and bronchodilator response after terbutaline dry powder were collected. Statistical analysis with SPSS.

Results: Nineteen asthmatic patients (10 females and 9 males) had aspergillus IgG antibody. Among them, severe persistent asthma and moderate persistent asthma were detected in 5 and 13 cases, respectively, whereas only one patient suffered from mild persistent asthma. A total of 36.5% of the 96 patients had a history of atopy, whereas 26% had allergic rhinitis. There was an association between the severity of asthma and the presence of aspergillus IgG antibody. Moreover, the positivity for aspergillus IgG antibody was higher in older patients.

Conclusion:
Paradoxical effect of salbutamol in asthmatic children
Maria Teresa Romero Rubio1, Lysbeth Ojeda Gonzalez2, Barbara Fernandez Dominguez2, Laura Aranda Grau1, Amparo Escobedo Montaner1.

Methods: Asthmatic children (2006-2011) in whom FEV1 decreases ≥9% after conventional BT with MDI salbutamol. Age, sex, body mass index, atopy, pharmacological treatment, level of asthma severity and control, percentage of FEV1 decrease and bronchodilator response after terbutaline dry powder were collected. Statistical analysis with SPSS.

Results: 32 patients, mean age 8.3 years (56% males). History of allergy in 65.6% (68.4% Dermatophagoides) and obesity in 34.3%. 81.3% patients had controlled asthma at the time of testing, following treatment with montelukast (42.9%), inhaled corticosteroids (28.5%), both of them (4.8%) or immunotherapy (9.5%). 14.3% patients had moderate to severe asthma, treated with corticosteroids and long acting beta-agonist. 46.9% showed a fall in FEV1 >15%. In this group 40% were obese and 60% allergic, with no differences among asthma severity or pharmacological therapy (p>0.05). 27 patients underwent bronchodilatation with terbutaline dry powder being positive in 81%.

Conclusion: In controlled asthmatic children, especially obese and allergic, MDI salbutamol can produce paradoxical bronchoconstriction that reverts with terbutaline dry powder. Although not a usual situation, it should be considered for the symptomatic management of the disease.
P4576
Evaluation of lung function in children with asthma and gastroesophageal reflux disease association
Iason Adam1, Svetlana Scincic1, Victor Rasco2, Rodica Selevenaru1, 1Pediatric, State Medical and Pharmaceutical University, Chisinau, Republic of Moldova; 2Endoscopy, Mother and Child Center, Chisinau, Republic of Moldova

Aim: The aim of study was to assess the lung function disorders using spirometric measurements in a group of children with asthma and gastroesophageal reflux disease (GERD) association.

Materials and methods: The study included 58 children with moderate asthma aged from 5 to 16 years. The main group entered 38 children with association of asthma with GERD; controls included 20 GERD-free asthmatic children.

Results: Analysis of the mean FVC values showed restrictive character of lung function changes in both groups that partially develop in children with long-term asthma: 64.0±4.2% vs. 72.4±4.2% (p<0.01), also PEF (46.6±2.5% vs. 56.0±3.3% in controls, p<0.05) and MEF25-75 (58.3±3.8% vs. 71.0±3.4%, respectively, p<0.05). Noticeably, significantly more expressed obstructive changes of distal airways and lung function variables were observed in children with associated asthma and GERD: 56.7±2.9% vs. 67.7±3.2% in controls for MEF75 (p<0.05), 59.9±3.9% vs. 75.8±3.6% for MEF50 (p<0.01) and 68.8±5.6% vs. 87.9±6.2% for MEF25 (p<0.05).

Conclusions: Analysis of spirometric variables denotes more severe obstructive changes of lung function in children with association of asthma and GERD, that is showed by lower values of FEV1, PEF, MEF25-75, MEF75 and MEF25, comparing with asthmatic children who are GERD-free.

P4577
Exhaled nitric oxide and serum IgE in children admitted to a pediatric department
Rado Dzamonja1, Carmen Dzamonja2, Gendrovel Dumitra2, 1Pediatrics, University of Medicine, Pharmacy, Craiova, Romania; 2Sports Medicine, Emergency Clinical Hospital, Craiova, Romania; 1Family Medicine, Private Practice, Sadova, Romania

Background: Exhaled nitric oxide (FeNO) is a noninvasive marker to assess airway inflammation in adults and children, but the clinical evidence is still equivocal.

Methods: We aimed to assess the FeNO levels in children admitted to our pediatric department and to correlate the results with other diagnostic tools. We enrolled two groups of children aged 5 to 16 yrs: first (149 cases, M/F 89/60) - admitted for asthma, and the control group (100 cases, M/F 55/45), without known history of asthma.

Results: We measured the FeNO (using Niox Mino, Aerocine, Sweden), total and specific serum Ig E. The statistical analysis was done using the Chi-squared test.

Results: We found a statistical significant difference in specific IgE levels between the two groups: p=0.01; RR=3.76 (0.99-14.25), but similar values for FeNO (p=0.19) and the total serum IgE (p=0.59). Total IgE over 300 kU/l was correlated with high FeNO levels recorded in the asthmatic children: p=0.009; RR=4.28 (1.37-15.44), but the exhaled NO was not correlated with stage, gender nor controller therapy (corticoids and/or leumotin inhibitors or none).

Discussions: In our patients the role of FeNO in monitoring asthma is still uncertain. The correlation with high total serum Ig E (also nonspecific) may be a future approach in increasing the value for the clinical use.

P4578
The relationship between exhaled nitric oxide and compliance/adherence in patients with bronchial asthma using inhaled corticosteroids
Yoko Kaminato1, Naohiko Taba, Yoko Murakami, Chikako Motomura, Hitomi Oda1a, Department of Pediatrics, Fukuoka National Hospital, Fukuoka, Japan

Background: The measurement of FENO is the important index to evaluate the control of the patients with bronchial asthma using inhaled corticosteroids (ICS). When FENO in the patients using ICS is high, we often try to increase the dose of ICS. However, it is necessary to take compliance/adherence of the patients into consideration before that.

Objectives: The aim of this study was to examine whether the measurement of FENO is useful as the index of compliance/adherence to asthma treatment by ICS.

Methods: One hundred forty-seven subjects (4 to 23 years of age; 82 male, 65 female) with bronchial asthma using ICS were recruited from the outpatient division at the Department of Pediatrics at Fukuoka National Hospital between January and December 2011. We measured their FENO and asked them to complete a questionnaire regarding the use of ICS. We asked them how often they inhaled ICS for a month, and classified them into five groups categorized as the grade of compliance. Additionally, we made a questionnaire about adherence. The patients answered that they inhaled ICS by themselves were defined as good adherence group, and otherwise as poor adherence group. We compared FENO in 5 groups categorized as the grade of compliance. Likewise, we also compared FENO in good and poor adherence groups.

Results: FENO in the patients of good compliance groups were significantly lower than that of poor compliance groups (p<0.001). However, there was no significant difference in the good adherence group and the poor adherence group.

Conclusions: It was indicated that the measurement of FENO could be useful as the index of compliance to asthma treatment by ICS.

P4579
Carboxyhemoglobin as a marker for chronic carbon monoxide exposure in school-age children with persistent asthma
Aiena Laluc1, Jasna Laluc2, Majaa Slavkovic-Ivanovic3, Milanka Ljubenovic2, 1Toxicology, Medical Faculty, Niš, Serbia; 2Centre of Medical Biochemistry, Clinical Centre, Niš, Serbia; 3Pediatric Clinic, Clinical Centre, Niš, Serbia

Introduction: When inhaled, carbon monoxide (CO) reacts very rapidly with hemoglobin in the blood and forms carboxyhemoglobin (COHb), decreasing the oxygen delivery to vital organs, leading to free-radical production and cytokines releasing.

Aims: To investigate the adverse effects of CO on the respiratory system using COHb as a marker for chronic CO exposure and forced expiratory volume in one second (FEV1) as a marker for the lung airflow obstruction.

Methods: We examined blood COHb concentrations in school-age children who suffer from moderate and easy form of asthma (n=52), ages 8-16 years, living in urban and suburban areas. COHb was measured in patient’s blood immediately after obtaining by spectrophotometric method and expressed as a percentage of blood hemoglobin. FEV1 parameter was measured using Schiller-spirotet SP-1 spirometer.

Results: Our study show that school-age children, with moderate and easy form of persistent asthma have statistically significant elevation of COHb concentration (3.53% ±0.97) in relation to control group (2.03% ± 0.28, p<0.001) and decrease of FEV1 parameter compared to control group, (p< 0.001). We also studied the influence of environmental factors: air pollution, secondhand smoking, wood-heating, heavy traffic, aspect of living in urban and rural areas. There are positive associations between air pollution concentrations and asthma aggravation in children.

Conclusions: Our results suggest that blood COHb concentration above safe level of 2.5% can be involved in pathogenesis of many respiratory diseases, especially asthma and trigger asthma attacks and allergies. The most important factor in prevention is reducing of air pollution.

P4580
Murine lung airway fibroblasts drive fibrosis through STAT4 signaling after cigarette smoke exposure
Tillie Hackett, Steven Zhou, Joanne Wright, Andrew Churge, Pathology, University of British Columbia, Vancouver, BC, Canada

Cigarette smoke-induced emphysema and small airway remodeling (SAR) are the anatomic bases of chronic obstructive lung disease (COPD), but the pathogenesis of these changes is unclear and current treatments for COPD are minimally effective. We exposed wild type (WT) and STAT4−/− mice to cigarette smoke for 6 months and found that STAT4−/− mice are protected against smoke-induced small airway remodeling but not emphysema. Unexpectedly, we observed that STAT4 is expressed in cultured murine wild type (WT) lung parenchyma-derived and airway-derived fibroblasts, but to a much greater extent in the latter. The same phenomenon was seen in cultured human parenchymal and airway fibroblasts. WT airway fibroblasts proliferated faster than STAT4−/− airway fibroblasts, whereas there was no difference between strains for parenchymal fibroblasts. IL-12 is up-regulated in human and mouse lungs after smoke exposure, and treatment with IL-12 caused phosphorylation of STAT4 in WT airway fibroblasts. Exposure of WT airway, but not parenchymal, fibroblasts to IL-12 caused increased expression of collagen Iα1 and TGFβ, factors involved in SAR, whereas STAT4−/− fibroblasts were unresponsive to IL-12. STAT4 thus controls proliferation and matrix production in airway but not parenchymal fibroblasts, and smoke-induced IL-12 can drive small airway remodeling via STAT4 signaling. These findings suggest that treatment with clinically available anti IL-12/40a drugs might provide a new completely approach to preventing SAR in cigarette smokers.

P4581
LSC 2012 Abstract – TGFβ1 compensates cigarette smoke induced disruption of tight junctions in the bronchial epithelium
Andrea Eickelberg, Nisika Mise, Oliver Eickelberg, Comprehensive Pneumology Center, HMUC, Munich, Germany

Rationale: The airway epithelium protects the body from inhaled insults, such as smoke, or allergens. The integrity of this epithelial barrier is crucial for bronchial homeostasis. COPD and asthma have been associated with defective airway barrier...
function. Tight junctions (TJ) represent the major junctional components, determining the permeability of an epithelial sheet. Cigarette smoke extract (CSE) has been described to impair TJ integrity. The aim of this study was to investigate if CSE also promotes EMT in human bronchial epithelial cells (HBEc), thereby contributing to small airway diseases.

Methods and results: Normal HBEc (16HBE) underwent EMT-like processes in response to TGFβ1 treatment, as characterized by elevated mesenchymal markers (FN1, SNA1, or ZEB1). Epithelial junctional markers (e.g., CDH1, JAM1, or ZO1) were upregulated or unaltered upon TGFβ1 stimulation. 16HBE cells do not change morphological or migrational upon TGFβ1 treatment, as demonstrated by IF or live imaging. CSE downregulated TJ-associated protein expression and destabilized TJ, as observed by IF. Combined long-term treatment (7 days) of 16HBE cells with TGFβ1 and CSE resulted in reduced mRNA and protein levels of TJ proteins. This was accompanied by altered MAP kinase signaling.

Conclusion: TGFβ1 and CSE resulted in EMT-like changes in HBEc. CSE induced TJ disruption, which was compensated by TGFβ1 through modified signaling processes. Thus, TGFβ1 could serve as a protective factor for bronchial epithelial cell homeostasis.

P4582 Antioxidant tetrapeptide UPF1 exerts an immediate effect on cigarette smoke-altered metabolic state of human bronchial epithelial cells

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We evaluated the protective capacity of UPF-1 (4-methoxy-L-tyrosinyl-L-glutamyln-L-cysteinyl-glycine) against cigarette smoke condensate (CSC)-induced alterations in metabolic profile of human bronchial epithelial cells (HBEc). HBEc were exposed to 10 μM CSC for 1, 2, 3, and 6 h. We then measured and compared the expression of upregulated genes by TGFβ1 using RT-qPCR.

Results: CSC upregulated only 16, and of all the upregulated genes, 4 were uniquely upregulated by CSC (cathelin [α1, extracellular matrix protein 1, TIMP 1 and 2]. As expected, TGFβ1 upregulated a variety of ECM proteins (eg collagen I, III, vitronectin), anti-matrix metalloproteinases, and degradative enzymes (eg matrix metalloproteinase MMPs I, II, 12, 13 and 14).

Conclusion: As CSC selectively upregulated a subset of TGFβ1-induced genes, elucidation of the specific mechanisms involved is likely to give novel insight into the pathophysiology of COPD.

P4584 Epithelial growth factor (EGF) and its receptors (ERBBs) in smokers with and without COPD: An index of epithelial repair imbalance?

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Background: The EGF and its receptors are expressed in the lung and orchestrate the epithelial repair process. We hypothesized that EGF pathways are involved in COPD pathogenesis.

Aim: To study EGF and ERBB receptors mRNA expression in lung tissue of smokers with or without COPD and control non-smokers.

Methods: Lung tissue specimens from 45 male subjects were studied: A) 10 patients with mild COPD (GOLD stage I), B) 10 patients with moderate COPD (GOLD stage II), C) 15 non-COPD smokers with normal lung function, and D) 10 non-smokers, serving as the control group. Quantitative Real-Time PCR experiments were carried out for EGF and receptors ERBB1, ERBB2, ERBB3, ERBB4, using beta-actin housekeeping gene as internal control.

Results: All study groups were matched for age. Moderate COPD patients had higher ERBB1 (EGFR), ERBB2 and ERBB3 mRNA levels compared to the other three groups. On the contrary, while moderate-COPD ERBB4 mRNA levels were statistically increased when compared to non-smokers (P=0.041), they did not differ when compared to mild-COPD patients (P=0.19) or to non-COPD smokers (P=0.18). Finally, EGF expression was at least 2-fold increased in moderate- and mild-COPD patients and non-COPD patients, when compared to non-smokers, a finding which was statistically significant only between moderate-COPD patients and non-smokers (P=0.010).

Conclusions: EGF was over-expressed in all three smoking’ study groups. However, its receptors (especially ERBB1-3), were elevated only in moderate-COPD patients. This could reflect the epithelial “repair” or “remodeling” process exerting by the EGF signaling pathway as COPD progresses.

P4586 Effects of α1-antitrypsin on neutrophil extracellular traps formation

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Neutrophils belong to the innate immune response and are essential for elimination of invading pathogens. Apart from phagocytosis and secretion of anti-microbials, neutrophils are also capable of producing neutrophil extracellular traps (NETs) to kill pathogens extracellularly (NETosis). Neutrophil elastase (NE) is a critical initiator of NETosis and also is one of the main components of NETs. The acute
phase protein α1-Antitrypsin (AAT) is a potent inhibitor for NE released from the activated neutrophils. Therefore, we asked a question if AAT inhibits NETosis? We induced NETosis in neutrophils isolated from healthy donors by applying phorbol myristate acetate (PMA, 10 ng/ml) alone or together with purified AAT protein (1 mg/ml). To our surprise, AAT did not inhibit NETs formation but make the structures less adherent to the surface. Remarkably, using anti-AAT antibodies we detected AAT in the NETs either separately or in co-localization with elastase. In the next set of experiments, we isolated neutrophils from emphysema patient with inherited ZZ (Glu342 Lys) AAT deficiency before and after AAT augmentation therapy. In response to PMA, neutrophils isolated before augmentation therapy formed NETs similar to those observed in healthy donors. However, after augmentation therapy, NETs contained large cell aggregates some of which were detached from the specimen. Again, exogenous AAT did not inhibit NETs. We suggest that an increased risk for development of chronic obstructive pulmonary disease (COPD) in subjects with inherited AAT deficiency results from both-increased elastase activity and uncontrolled NETosis.

P4587 Resveratrol attenuates cigarette smoke induced oxidative stress: Possible involvement of SIRT1

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Objectives: Cigarette smoke is known to cause oxidative stress in alveolar epithelial cells. In this study, we investigated the effect of resveratrol, a phytochemical produced by some spermatophytes, on oxidative stress induced by cigarette smoke in airway epithelial cells.

Methods: Rats with or without exposure to cigarette smoke were intraperitoneally injected with resveratrol (5,10,20mg/kg). TNF-α levels in BALF were determined by ELISA. Total glutathione, SOD and H₂O₂ levels in rat lungs were measured by spectrophotometry.

Results: Cigarette smoke exposure significantly increased TNF-α expression in BALF and this upregulation was significantly attenuated by resveratrol (p<0.05). Meanwhile, the treatment of resveratrol increased the expression of glutathione and SOD in lung homogenates, which were attenuated by cigarette smoke exposure (p<0.05). The expression of H₂O₂ was decreased by resveratrol (p<0.05). Exposure of A549 cells to CSE resulted in the elevated ROS expression, which was inhibited by resveratrol. Meanwhile, SIRT1 protein levels were activated by the pre-treatment of resveratrol.

Conclusions: These results suggest that resveratrol attenuated oxidative stress induced by cigarette smoke. The anti-oxidant effect might act through the expression of SIRT1 proteins.

P4588 Chronic obstructive pulmonary disease is characterized with suppressed lipoxin A4 and increased lipoxin receptor expression in lungs

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Persistent inflammation of COPD could be influenced by disorders of arachidonic acid metabolism when synthesis of leukotrienes does not switch to lipoxin metabolism. We described an increase of lipoxin receptor expression in lung homogenates of COPD patients with increased lipid peroxidation.

Aim: To estimate concentration of lipoxin A4 (LXA4), leukotriene B4 (LTB4), as well as expression of LXA4 receptor (FPRL-1) in induced sputum (IS) of COPD patients and healthy controls.

Materials and methods: 17 COPD patients and 7 healthy controls. LXA4 and LTB4 concentration in IS was assessed by ELISA. FPRL-1 expression was detected immunocytochemically.

Results: Concentration of LXA4 in COPD patient’s IS was decreased compared to healthy controls (0.99±0.43 ng/ml vs 2.198±1.89 ng/ml; p=0.009). Ratio LTB4/LXA4 in COPD patients was three times greater compared to healthy persons (8.884±2.789 vs 3.328±0.94; p<0.0071).

In COPD patient’s IS FPRL-1 positive polynuclear cells (PPC) were in greater amount compared to healthy controls (8,802±5,758 cells/mm² vs 2,123±2,232 cells/mm²; p<0.00109). Also, in COPD patients a count of FPRL-1 positive mononuclear cells (PMCs) in IS was increased compared to healthy controls (2.563±1.711 cells/mm² vs 0.655±0.522 cells/mm²; p=0.0311).

Correlation between FPRL-1 PPC and LTB4 concentration in IS (r=0.628; p=0.0013).

Conclusions: Increased LTB4/LXA4 indicate a disbalance of inflammatory media tors in COPD patients that could be one of the causes of inflammation persistence. In this case a decreased receptor expression and its correlation with LTB4 concentration in COPD patients could be one of mechanisms of inflammation adaption that is initiated by LTB4.

P4589 Immunoregulation and Foxp3 expression in the bronchial mucosa of stable COPD patients

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Background: T regulatory cells (T₉) control the immune responses at sites of inflammation. The differentiation and function of T₉ cells is regulated by the transcription factor forkhead box p3 (Foxp3). Conflicting results have been reported in central and peripheral airways of COPD patients regarding numbers of Foxp3+ cells populating the airways (Igauev S, Eur Respir J 2009;33:61).

Objectives: To investigate the expression of T-regulatory molecules in the bronchi of patients with severe/very severe (FEV1 pred:35:69; n=19), mild/moderate (FEV1 pred:66±14; n=13) stable COPD, control smokers (FEV1 pred:104±13; n=12) and non-smokers (FEV1 pred:116±14; n=11).

Methods: Expression of Foxp3 was measured in the bronchial mucosa using immunohistochemistry in cryostat sections.

Results: Immunopositivity for Foxp3 was similar in the bronchial epithelium (cells/mm²) (median(range): 1.1(0.5-2) vs 1.2(0.5-1.7) vs 1.1(0.5-2) vs 1.2(0.2-2.3), Kruskal Wallis (KW), p=0.948, and submucosa (cells/mm²) (86(32-155) vs 92(2-19-187) vs 86(19-306), p=0.990, in control non smokers, control smokers, mild/moderate and severe/very severe COPD, respectively.

Conclusion: We show no significant differences in the numbers of Foxp3+ cells populating the bronchial mucosa in COPD patients and control groups, suggesting that immunomodulation of inflammation is not influenced by Foxp3 in the bronchi of patients with COPD.

P4590 Altered proliferation of alveolar epithelial cells is involved in progressive lung fibrosis-induced emphysema

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Rationale: Chronic obstructive pulmonary disease (COPD) is characterized amongst others by development of emphysema. We showed that a single application of porcine pancreatic elastase (PPE) causes a severe progressing emphysema-like phenotype in C57BL/6 mice. Since the development of emphysema is apparently not completed after PPE application, we aimed to identify possible key mechanisms that drive this process even at late time points.

Methods: Female C57BL/6 mice received a single oropharyngeal application of PPE or PBS, and lung function, histology and gene expression were analyzed on days 2, 28, 56, and 162. Fibroblasts of PPE treated mice were characterized analyzing mitochondrial membrane potential. Furthermore, LA-4 lung epithelial cells were treated with PPE and proliferative and apoptotic characteristics were measured using gene expression or wound healing assays.

Results: PPE treated C57BL/6 mice develop progressive airway enlargement and impairment of pulmonary function during 23 weeks of analysis. Q-PCR revealed elevated expression of apoptosis markers, reduced proliferation and increased expression of matrix components. Lung fibroblasts of PPE treated mice show reduced proliferation and an altered mitochondrial membrane potential. Reduced proliferation was also found in PPE treated LA-4 cells.

Conclusion: Diminished proliferation in PPE treated lung epithelial cell lines as well as in lungs and primary fibroblasts of PPE treated mice could explain the persistent progression of PPE induced emphysema in mice.

P4591 Different pathology of pulmonary arteries in centrilobular and panlobular emphysema

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Two distinct pathological phenotypes have been described in patients with emphysema: Centrilobular Emphysema (CLE) and Panlobular Emphysema (PLE), with distinct clinical and functional characteristics. A different involvement of small airways and parenchyma has been described in CLE and PLE, but the involvement
of pulmonary arterioles has never been analyzed. Therefore, we evaluated remodeling of pulmonary arterioles in surgical samples from 26 patients with CLE, 18 with PLE, 7 smokers without emphysema (SNE) and 8 non smokers (NS). By image analysis we measured total arterial wall, intima, media and adventitial thickness. Furthermore, since mast cells (MCs) are potentially involved in vascular remodeling, we quantified the infiltration of tryptase+ MCs in arterioles. Subjects with CLE have a higher total wall thickness compared to those with PLE (median [range] 61 [21-198] vs 46 [17-143] μm; p<0,001) and NS (51 [20-123]; p<0,05). In particular, thickness of the intima was greater in subjects with CLE than in those with PLE (9 [2-66] vs 6 [2-41]; p<0,05), as was thickness of the media ([97-94] vs 16 [7-63]; p<0,005). Finally subjects with CLE have a higher number of MCs in the adventitial layer than those with PLE (200 [0-1200] cells/mm2 vs 111 [0-1000]; p<0,001). In conclusion, our study demonstrates that pulmonary arterioles show a different pathology in CLE and PLE, suggesting that the mechanism responsible could be different in the two forms of emphysema.

P4594
Proteinase 3 and its potential role in emphysema
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Introduction: Proteinase 3 (PR3) is an elastin-degrading proteinase similar to neutrophil elastase (NE). PR3 is the most abundant serine proteinase in neutrophils, and excessive emphysema in animal models & induces mucus secretion in humans. The main circulating inhibitors are alpha-1-antitrypsin (AAT) and alpha-2-macroglobulin (A2M). Its role in respiratory disease has not been studied in detail.

Aims: 1) To determine how efficiently PR3 activity is inhibited by healthy (PiM), AAT deficient (PiZ) & AAT variant (PiFZ) AAT.

2) To study partitioning of PR3 between its 2 serum inhibitors.

Methods: Serum from subjects with different AAT phenotypes (PiM, PiZ, PiFZ, PiZZ) was taken & AAT concentration measured. Increasing ratios of serum AAT to PR3 were incubated & residual PR3 activity measured. Experiments were reproduced using comparable mixtures of pure AAT & A2M. Association between different PR3 variants in AAT (Kass of PR3 to A2M) & activity were determined using methylene-treatment serum (A2M inactivated).

Results: Increasing the molar ratio of serum AAT to PR3 increasingly inhibited PR3 activity, however even in AAT excess some residual PR3 activity remained which was greater in PiZ serum compared to PiM serum. These results were reproduced using mixtures of pure AAT & A2M suggesting that PR3 bound to A2M remains catalytically active. The Kass values for AAT variants with PR3 & NE are shown in table 1.

Table 1

<table>
<thead>
<tr>
<th>AAT variant</th>
<th>Kass with NE (25°C)</th>
<th>M⁻¹ s⁻¹</th>
<th>Kass with PR3 (25°C)</th>
<th>M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiM</td>
<td>1.4×10⁻³</td>
<td>9.8×10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiZ</td>
<td>9.9×10⁻⁵</td>
<td>1.1×10⁻⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiFZ</td>
<td>7.2×10⁻⁷</td>
<td>1.7×10⁻⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiZZ</td>
<td>7.3×10⁻⁷</td>
<td>1.5×10⁻⁷</td>
<td></td>
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</tr>
</tbody>
</table>

Conclusion: When serine proteinases are released from neutrophils, NE is more likely to be inhibited by AAT than PR3 (due to the lower Kass values) & binding of PR3 to A2M retains its activity.

P4595
Increasing oxidative stress and inflammation in patients with exacerbated chronic obstructive pulmonary disease (COPD) and their association with lung function
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Oxidative stress and chronic inflammation are the milestones in pathogenesis of COPD. It is assumed that their increase is associated with a worse lung function and frequent exacerbations.

Our aim was to assess changes in antioxidant enzymes superoxide-dismutase (SOD) and glutathione-peroxidase (GPx) activities and inflammatory markers in patients with exacerbated COPD, stable COPD and healthy controls and their association with lung function.

We performed a cross-sectional study among 244 participants (mean age 60±9.5 years) divided into 3 groups: 76 were with exacerbated COPD (group 1), 65 were with stable COPD (group 2) and 103 were matched healthy subjects (group 3). We performed a questionnaire to define pack years, spirometry and biochemical tests. Oxidative stress was measured by erythrocyte activities of SOD and GPx. Compared to the control group, patients from group 1 had significantly lower SOD and GPx activities (p<0.0001), with an increasing trend between groups. ESR and CRP activities were significantly higher in patients with exacerbated COPD (p<0.0001). The inflammatory markers correlated positively with pack years (r=0.15, p<0.05 for ESR and r=0.242, p<0.001 for CRP) and negatively with FEV1% (r=-0.187, p<0.05 and r=0.219, p<0.001 resp.). The present study suggests that there is an increased oxidative stress and inflammation in patients with COPD in exacerbation and there is a relationship with the severity of the disease.

P4596
Evaluation of dendritic cell population in chronic obstructive pulmonary disease
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Chronic obstructive pulmonary disease (COPD) is characterized by an increase
479. New understanding of childhood lung disease through physiological measurement

P4598

Phl1 mutation induces altered respiratory response to an airway challenge

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Pelizaeus-Merzbacher disease (PMD) is a disease caused by mutations of the proteolipid protein 1 (PLP1) gene that result in defective CNS myelination. Mice with an extra copy of Phl1, called Phl1/Phl1, develop a syndrome that models the objective of this study. PMD. Patients with all except the mildest forms have respiratory involvement.

Objective: We hypothesized that Phl1/Phl1 mice would lack protective airway responsiveness (AR) to an autonomic drug challenge. To address this, we investigated whether respiratory mechanics in these mice would be different at baseline (BL) or during methacholine (MCh) challenge.

Methods: Wild type (Wt) n=16, carrier (Car) n=8 & affected (Af) n=17 mice, 3 months (3m) and 6 months old (6m), were anesthetized, mechanically ventilated & challenged with 0.16 mg/ml of aerosolized MCh. We calculated resistance (R), dynamic/static compliance (Cdyn/Cstat), airway obstruction (PhTB); lung tissue biomarkers & histological analysis are ongoing. Results: BL differences were found in Wt vs Car (p<0.05) dependent on age (p<0.0001). MCh increased R as a function of dose in Wt & Car, whereas Af mice lacked sensitivity to MCh (p<0.05). No differences in body weight, gender (Wt females vs Car males) & coat were found. Af mice had the highest PhTB. Conclusion: Wt mice compared with Af mice were lacking of AR to MCh at 6m; but not at 3m. These results indicate an age-associated lack of protective autonomic AR in the Phl1Phl1 mouse model and suggest that respiratory autonomic disequilibrium may contribute to the respiratory involvement in PMD patients. The Phl1Phl1 animal model may be used for testing therapeutic interventions.

P4599

Bronchial wall structure is altered in adult mice following neonatal hyperoxia

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Background: Very preterm infants often require supplemental oxygen, and can have an increased risk of poor lung function and asthma in later life. Follow-up studies suggest that factors associated with very preterm birth can cause long-term changes in the small conducting airways. Aim: To determine if bronchial wall structure is persistently affected by neonatal exposure to hyperoxic gas.

Methods: Neonatal mice (C57BL/6J) breathed 65% O₂ from birth until postnatal day 7 (P7), after which they lived in room air until P56 (n=26). Controls breathed room air from birth (n=27). Bronchiolar walls, lung parenchyma and bronchoalveolar fluid (BALF) were analysed at P56. In bronchioles, we measured epithelial thickness, proportions of proliferating epithelial cells, ciliated and Clara cells, the amount of collagen and airway smooth muscle (ASM) and the number of alveolar-bronchiolar attachments. In lung parenchyma, we measured percent tissue space and mean linear intercept (MLI).

Results: In bronchioles, adult mice exposed to neonatal hyperoxia had significantly smaller airway lumen diameters compared to controls; there were no significant differences in bronchial epithelial cell proliferation, Clara cells or ciliated cells. In lung parenchyma, MLI was increased, and tissue fraction reduced (both p<0.05) in hyperoxia-exposed mice, but there was no effect on the number of alveolar-bronchiolar attachments. In BALF there were 60% more immune cells (p<0.05) after hyperoxia. Conclusions: Exposing the developing lung to hyperoxic gas results in persistent airway remodelling and increased numbers of pulmonary immune cells suggesting on-going inflammation in adulthood.

P4600

Long term sensitisation of cough and expiration reflex in adult rabbits by 48 hour postnatal normobaric hyperoxia

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Rationale: Cough is a frequent report in follow up studies of late premature children at school age. On the other hand, the experimental evidence exists in animals that the short term effect of acute hyperoxia is to down regulate cough. The hypothesis that neonatal exposure to hyperoxia may interfere with incidence of cough at school age has not been tested previously. The aim of the study was to determine if postnatal administration of oxygen in pups alters the cough reflex in adult rabbits.

Methods: Rabbis were exposed within the first 8 days of life to 48h normobaric hyperoxia (FiO₂ > 95%; n=12) or ambient air (control; n=9). At age 3 - 4 months the animal was anesthetized, tracheostomized and subjected to a series of discrete mechanical stimulations of the trachea lasting 50, 150, 300 and 600ms. Each stimulus was quadrupled so as to total 24 stimulations per animal. Cough and expiration reflex were identified from breathing flow and volume, respectively as a forced expiratory effort preceded (cough) or not (expiration reflex) by an increased resistance. Results: The incidence of either cough (66/288: 23%) or expiration reflex (124/288: 43%) in hyperoxic rabbits was significantly larger than its respective control (cough: 25/214: 12%; expiration reflex: 60/214: 28%; p < 0.0005). Conclusion: The experimental evidence of long term sensitisation of airway defensive reflexes in rabbits breathing high oxygen soon after birth favours a role for neonatal hyperoxia in the pathogenesis of chronic cough at school age in late premature children.
Routine measurement of the LCI in CF with an ultrasonic device for multiple breath nitrogen washout

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During the last decade multiple breath washout technique (MBW) for calculating the Lung Clearance Index (LCI) has become very popular for assessing ventilation inhomogeneity (VI) as an early manifestation of Cystic Fibrosis (CF) lung disease. However, routine use has been difficult not only due to limited availability of licensed equipment. Inert tracer gases (e.g. SF6, He) certified for medical purposes are not universally available. Switch to nitrogen washout (MBW_N2) using 100% oxygen may overcome this problem.

The aim of this cross sectional study was to assess whether LCI derived from MBW_N2 discriminates as well as MBW_SF6 between patients with CF and healthy controls. 19 controls (7-51 years) and 11 unselected patients with CF (7-25 years) performed 2-3 single MBW_N2 using the EasyOne Pro LAB™ (ndd Switzerland) with 100% oxygen.

Mean (SD) LCI was 6.5 (0.64) in controls and 9.3 (1.93) in CF with a mean difference (95% CI, p-value) of 2.83 (-1.44; 1.51, 0.001) between the groups. Within-test repeatability (CV%) was 5.3% in controls and 7.7% in CF. Assessment of LCI using licensed equipment for MBW_SF6 was feasible and well tolerated in both, children and adults and patients and controls. LCI based on MBW_N2 differed significantly between patients with CF and controls and results were comparable to published data obtained with different equipment and with using SF6 as tracer gas. We conclude that MBW_N2 reflects VI similar to MBW_SF6 and may thus be used for clinical application of MBW in patients with CF.

Bench test of a mass spectrometer based multiple-breath washout system using a realistic lung model

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Background: Lung volume measurement accuracy of multiple-breath washout (MBW) systems should be validated under realistic conditions. Here we used a previously described lung model (ERS meeting 2011) incorporating BTSF conditions to validate a customized mass spectrometer (AMIS 2000; Innovision) MBW system. The aim was to assess the feasibility and accuracy of this new system for lung volume measurement.

Methods: Functional residual capacity (FRC) measurement accuracy was assessed across a range of FRCs (430-4120 mL), tidal volumes (2100-1010 mL) and respiratory rates (36-12 min⁻¹). A wash-in inert gas mixture containing 4% sulfur hexafluoride (SF6) and 4% helium (He) was used for MBW. 63 MBWs were conducted over two test days. Measured gas and flow signals were processed in custom software (TestPoint). FRC was calculated as cumulative expired inert gas fraction (FRC) and mean error (range). Differences between measured and nominal FRC was 46.7 mL (1.7%), upper and lower limits of agreement were 155.3 mL (5.1%) and -62.0 mL (-1.8%), respectively. For 156 FRCs, 124 (79%) were within 5% of the nominal FRC, mean error (range) was 2.1 (0.1-6.0%). Error was associated with respiratory rate (R² = 0.23). FRC was reproducible between tests, coefficient of repeatability was 73 mL (3.4%) and similar using either He or SF6 for FRC calculation.

Conclusion: Using a lung model previously shown to be suitable for MBW system validation under physiological conditions, the custom mass spectrometer MBW system precisely and reproducibly measures FRCs ranging from preschool to adult lung volumes.

Validation of multiple breath washout technology in healthy children and children with CF

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Mass spectrometry based technology is considered the “gold standard” for measuring LC, but is not readily available. In this ongoing study we aim to validate a nitrogen washout system for use in CF children. In a cross-over design, healthy and symptomatic CF children performed MBW by mass spectrometry (AMS 2000; Innovision A/S, Odense, Denmark) using 4% SF6 or by nitrogen washout (Exhalayer D, Eco Medics AG, Switzerland). Results were independently scored by two operators; Bland-Altman plots were used to assess the agreement between the two systems. To date 24 healthy children (median age 11 years (range 3-17)) and 33 children with CF (median age 11 years (range 3-17)) completed MBW measurements using both the mass spectrometry and N2 washout. There was no systematic bias observed in LCI (or as an early manifestation of CF lung disease).

Conclusion: Overall there was good agreement healthy children (95% of all measurements agreed within ±0.44, 0.83); however LCI_SF6 was systematically 0.2% (95% CI 0.06; 0.33) units lower than LCI_N2. The mean difference between the two systems was greater in children with CF (0.4% (CI 0.29 to 0.55) and the limits of agreement were wider (-0.33, 1.17). Agreement between the two methods for moment ratios M1M0 (4.03; 0.63) than M2M0 (-5.72; 8.60), and greater in healthy children compared with children with CF. Inter-observer agreement for nitrogen washout was high (0.08; 0.08) for all outcome. There was no systematic bias between the two systems. LCI measured by nitrogen washout is higher compared to LCI measured by mass spectrometry. Inter-observer variability is low for nitrogen washout if analyzed by trained operators.

Supported by CFF.

Ways to shorten the lung clearance index measurement I – Are three measurements needed?

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Background: Inert gas multiple-breath washout (MBW) derived lung clearance index (LCI) is a sensitive lung function parameter in subjects with mild cystic fibrosis (CF) lung disease, but rarely measured in clinical routine due to lack of available equipment and lengthy protocols. Using an available nitrogen (N2) MBW setup (Exhalayer D, Eco Medics, Switzerland) we assessed shortened N2-MBW protocols for LCI.

Methods: We determined whether the LCI from the 1st (LCI1) and the mean LCI of the 1st and 2nd valid N2-MBW (LCI2), respectively, are comparable to the averaged information obtained from three N2-MBW (LCI3).

Results: LCI1, LCI2, and LCI3 differed significantly between patients with CF and children. LCI1 and LCI2 were strongly associated with LCI3 (R² = 0.98 for both), took less time, and were of similar diagnostic value. Comparing LCI1 and LCI2, LCI2, mean (range) test duration was 2.2 (0.5-5.2), 6.6 (3.6-12.7), and 11.1 (8.0-17.1) min, and upper limits of normal LCI (8.3, 8.5, and 8.4) all correctly classified 71% of children, respectively. Bland-Altman analysis of LCI1, and LCI2 showed good agreement with LCI3; Mean difference was -1.1% and -0.7%, limits of agreement were 6.8 to -9.0% and 5.9 to -7.3%, respectively.

Conclusion: In the current study population, the 1st LCI or the mean of the 1st and 2nd LCI take less time and precises the N2-MBW with physiological measurement variability. Using less N2-MBW measurements seems promising for time-saving LCI measurement in clinical routine.

Abnormalities in lung clearance index in CF infants diagnosed by newborn screening

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Newborn screening (NBS) in CF offers the potential to prevent lung damage before the onset of clinical symptoms. The lung clearance index (LCI), measured by multiple breath washout has shown promise as a marker of early lung disease in patients with CF. Therefore we aimed to determine whether LCI could be used to distinguish between subjects with CF and healthy subjects in the first 2 years of life. Healthy infants (3 months – 2 years) completed MBW testing as part of the infant pulmonary function protocol of the Canadian Healthy Infant Longitudinal Development Study (CHILD Study). Infants (3 months – 2 years) with diagnosed CF attending the Respiratory Medicine Clinic at the Hospital for Sick Children were invited to complete MBW testing. MBW was measured 51 healthy infants and 18 infants with CF diagnosed by NBS. Despite NBS, infants born with CF were smaller (Height-for-age z-score (-1.19 (-0.58; -1.81) and lighter (mean difference weight-for-age z-score (-0.40 (-0.49; 0.19) compared with healthy controls. The LCI was on average 0.4 units higher in CF (mean LCI 7.32 (SD 0.91)) compared to healthy infants (6.92 (SD 0.61)). Adjusting for the relationship between LCI and height in the first 2 years of life, LCI was 0.67 (95%CI 1.34; -0.01) z-scores higher in CF compared to healthy infants, although overlap was considerable (Figure). Therefore, despite newborn screening early abnormalities in LCI are present in CF patients LCI underscoring the need for new treatment approaches to address early lung disease.

Supported by CIHR and the Lynn and Arnold Irwin Foundation.

Assessment of ventilation inhomogeneity in patients with alpha-1-antitrypsin deficiency – A useful tool for monitoring early lung disease

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The risk of developing alpha-1-antitrypsin deficiency (α-1-AT deficiency) related fatal emphysema during adulthood is high in patients with a PiZZ genotype. Currently, the FEV1 is used for detecting and monitoring α-1-AT deficiency related lung disease. However it is likely that the early manifestation starts in peripheral
airways that are not accessible by spirometry. Multiple Breath Washout (MBW) is a sensitive test for detecting ventilation inhomogeneity (VI) within the peripheral airways that can be quantified by calculating several indices such as the Lung Clearance Index (LCI). We performed a preliminary analysis of an ongoing multi centre study assessing the clinical and prognostic value of measuring the LCI in patients with α1-AT deficiency. 19 controls (7.5±1years) and 20 unselected patients with α1-AT deficiency (12-72 years) performed 2-3 simple MBW20 using the EasyOnePro LAB™ (nord Switzerland) with 100% oxygen and subsequent spirometry. Mean (SD) LCI was 6.5 (0.64) in controls and 9.0 (1.98) in patients with a mean difference (95% ci, p-value) of -2.57 (-3.54; -1.60, <0.001) between the groups. Within-test repeatability (CV%) was 5.3% in controls and 6.0% in patients. LCI correlated significantly with age in patients. Assessment of LCI derived from MBW20 was feasible, reproducible and well tolerated in both, patients and controls. LCI differed significantly between patients and controls. In patients LCI appeared with age. We conclude from these preliminary data that the LCI reflects presence of VI in patients with α1-AT deficiency and may thus be useful for monitoring α1-AT deficiency related lung disease.

**P4607 Long clearance index and exercise capacity among children with bronchiectasis**

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**Background:** In paediatric bronchiectasis, there has been limited experience on the relationship between disease severity, as assessed by exercise limitation and lung clearance index (LCI).

**Aim:** To compare LCI and exercise capacity among children with bronchiectasis.

**Method:** Fifteen stable children and adolescents with CF, 14 stable children with non-CF bronchiectasis and 15 healthy children and adolescents, participated in maximal incremental cardiopulmonary exercise testing using a cycle ergometer and they had an LCI assessment.

**Results:** The CF children’s mean age was 13.7 years, mean FEV1 74.4% predicted. The 14 non-CF bronchiectasis children’s mean age was 13.8 years, mean FEV1 78.3% predicted and the healthy children’s mean age was 13.6 years, mean FEV1 94.7%. Among CF patients there was evidence of exercise limitation, with mean Peak Aerobic Capacity (V’Opeak) 62.2% predicted. Among the non-CF bronchiectasis patients there was evidence of exercise limitation, with mean V’Opeak 77.3% predicted. No patient had exercise intolerance significantly among children with CF and non-CF bronchiectasis (p=0.06). LCI was significantly increased among CF patients (mean LCI 13.7), compared to healthy children (p<0.00001). LCI was also found significantly increased among patients with non-CF bronchiectasis (mean LCI 11.8), compared to healthy children (p<0.0001). LCI was not found significantly different among children with CF and non-CF bronchiectasis (p=0.1).

**Conclusions:** Exercise testing and Multiple Breath Washout measurements can discriminate children with bronchiectasis from healthy children. However, the burden of the disease is more prominent in children with CF compared with the non-CF bronchiectasis.

**P4608 Sensitivity of lung clearance index and chest computed tomography in early lung disease among children with non-CF bronchiectasis**

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**Background:** Lung disease starts before clinical symptoms become prominent, among CF children. Computed chest tomography (CT) is the reference method for identifying structural changes. It has been suggested that the Lung Clearance Index (LCI) is a sensitive marker allowing non-invasive monitoring of lung disease. **Aim:** The aim of this prospective study was to investigate the diagnostic accuracy of the LCI in comparison to CT among children with non-CF bronchiectasis, with early lung disease and normal FEV1 (>80% predicted).

**Method:** MBW and low-dose HRCT were performed in 14 patients (6-21 years) with non-CF bronchiectasis and normal FEV1 (>80% predicted) HRCT scans. LCI and FEV1 were recorded. A modified Bhalla score was used to assess HRCT scans. LCI was assessed with Multiple Breath Washout measurements.

**Results:** LCI was abnormal in 12/15 (80%) of children. 11/15 patients (73%) demonstrated both, increased LCI and structural changes on CT. 1/15 (6%) had no normal results in both measurements. There was a significant linear correlation between CT-score and LCI in 12/15 (87%) of patients, whereas no such correlation was observed between CT-score and FEV1. Sensitivity of the LCI to detect structural lung damage was 85%, whereas specificity of LCI was 50%.

**Conclusions:** Diagnostic accuracy of the LCI for detecting CF lung disease in patients with normal FEV1 was good when compared to CT. Results indicate that structural changes are unlikely if a normal LCI is measured. The LCI may be a suitable surrogate marker for monitoring progression of lung disease among children with non-CF bronchiectasis.

**P4609 Lung clearance index in paediatric exercise induced asthma**

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**Introduction:** Exercise induced bronchoconstriction is reported commonly by asthmatic children. We assessed whether lung clearance index (LCI) can detect it.

**Methods:** Following symptom questionnaire, spirometry, and Multiple Breath Washout (MBW, Innocor 0.2% SF6), children performed a standard treadmill exercise challenge. One minute post exercise we measured MBW and spirometry. Measures repeated 10 mins post bronchodilatation. If baseline FEV1 decreased >20% baseline, testing only post salbutamol.

**Results:** 21 asthma patients and 21 healthy controls (13M:8F, mean 12 yrs in both groups). In asthma LCI 7.2(0.7) (mean (SD)) significantly > control 6.8 (0.4), p=0.02. In asthma, post exercise LCI increase by 4.8(10.2)% (Fig 1), with no change in FEV1(0.01(3.3) %). Post exercise LCI >14.5% in healthy volunteers (ns). In those asthma with >20% fall FEV1 (n=3), post salbutamol LCI remained high, 8.0(6.3). Post exercise change in LCI higher in asthma who reported exercise intolerance; No symptoms 2.8(8.5%); controlled symptoms 5.0(9.3%); limited despite salbutamol 17.7(16.7%). No trend for FEV1; 0.3(3.9)% vs -1.0(3.3)% vs -20(20.3)%.

Figure 1. Initial, post exercise and post salbutamol LCI in asthmatic and healthy groups.

**Conclusions:** LCI tends to rise following exercise. However rise in LCI was non-significant, consistent with the discrepancy between symptoms and altered lung function in asthmatic children. Change in LCI is greatest in the symptomatic, with largest LCI change in those reporting poor treatment response (not demonstrated by FEV1).

**P4610 Hand-held tidal breathing nasal nitric oxide measurement as a targeted case-finding tool for primary ciliary dyskinesia**

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**Background:** Nasal Nitric Oxide (nNO) measurement is a sensitive supplemental tool in diagnosis of Primary Ciliary Dyskinesia (PCD). Tidal Breathing (TB)nNO requires minimal cooperation, has potential as more widespread targeted case-finding tool for PCD in all age groups, and discriminative capacity between PCD and non-PCD has been previously established using stationary nNO analyzer (Marthin JK and Nielsen KG. Eur Respir J 2011; 37: 559-565).

**Aim:** Assess validity of handheld TBnNO in a selected population.

**Methods:** TBnNO was measured in PCDs, cystic fibrosis (CF) patients and healthy subjects (HS) using both an electrochemical hand-held device, NIOX MINO® Nasal Breathing System: NIOX® and ANALYZER CLD 88sp®. All systems allow passive nasal sampling at a flow rate of 5 ml/s during tidal breathing. 2 ml/s sampling is an additional option with NIOX MINO® Nasal. Data were analysed by ROC and Bland-Altman plots.

**Results:** TBnNO values were compared in 41 subjects between 0.3 and 57 years: 15 PCDs, 13 CF patients, and 13 HS. MINO discriminated significantly between PCD and HS (P<0.001) and between CF and PCD (P<0.001).

<table>
<thead>
<tr>
<th>MINOS</th>
<th>MINO2</th>
<th>NIOX</th>
<th>ANALYZER CLD 88sp®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off, ppb (PCD vs HS)</td>
<td>442</td>
<td>363</td>
<td>202</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>100</td>
<td>92.3</td>
<td>100</td>
</tr>
<tr>
<td>CV% (all subjects)</td>
<td>10.5</td>
<td>19.4</td>
<td>13.8</td>
</tr>
<tr>
<td>LoA#, ppb (PCD vs HS)</td>
<td>-43.9 to 87.5</td>
<td>-120 to 89.5</td>
<td>-25.5 to 44.8</td>
</tr>
</tbody>
</table>

*LoA# denotes 2 SD above and below his mean.*
**P4611**

Upper and lower airway nitric oxide levels in primary ciliary dyskinesia

Annabelle Liu1, Walker Wood1,2, Amanda Harris1, Janice Cole1,2, Jane Lucas1,2, 3Primary Ciliary Dyskinesia Research Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, United Kingdom; 2 Primary Ciliary Dyskinesia Diagnostic Service, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

Introduction: Patients with primary ciliary dyskinesia (PCD) have low nasal nitric oxide (nNO) and fractional exhaled NO (FeNO). The reasons are unclear but might be related to ciliary function. Analysis of nitric oxide (NO) from different regions of the airway and comparisons with other disease states may guide our understanding.

Aim: To compare differential bronchial (JNO) and alveolar (CalvNO) NO in patients with PCD, cystic fibrosis (CF), asthma and healthy subjects.

Methods: Exhaled NO at different flow rates (50, 100, 200 and 250 msL) and nNO were measured (NIOX flex®, Aerocrine, Sweden) in patients with PCD (n=12), asthma (n=18), CF (n=12) and healthy controls (n=17). JNO and CalvNO were derived using a model of pulmonary NO exchange-dynamics.

Results: FeNO at low and high flow rates were significantly lower in PCD than in healthy subjects, as was JNO, 271 pl/s (228) vs. 965 pl/s (963) (p<0.004) (mean (SD)). However CalvNO was similar between the two, 1.6 ppb (0.5) vs. 2.4 ppb (1.4) (p=0.174). (Table 1 for CF and asthma data).

Conclusion: PCD patients have significantly lower J NO but similar Calv NO to healthy controls. As there are no cilia in the alveolar region this might support the hypothesis that NO biosynthesis is coupled to ciliary function. Data collection continues.

**P4612**

Determinants of functional deficits assessed by spirometry and plethysmography in children with bronchial asthma

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Follow-up in asthmatic children is usually performed by spirometry, and hence without consideration of pulmonary hyperinflation. 'Effective' specific airway resistance (sRaw) measures resistive changes throughout the whole breath cycle concomitantly to changes of resting end-expiratory level [1].

Objectives: Defining the pattern of functional deficits and their changes over time in children with bronchial asthma.

Methods: Serial lung function measurements performed in 216 asthmatic children (age: 4 to 17.9 y) were analyzed retrospectively representing at least 3 annual tests, and providing functional residual capacity (FRCraw), sRaw, volume-time and flow-volume indices (FEV1, FEF25−75, MEF25−75) Data were expressed as SD-score computed by z-transformation using reference equations. Results: Within the 1270 lung function tests spirometry failed to detect abnormal lung function in 24.1% of tests (plethysmography 1.7%). Bronchial obstruction (> 2SDS) was depicted by sRaw in 93.8%, sRaw in 74.6%, FEF25−75 in 73.8%, MEF25−75 in 62.1% and FEV1 in 23.7% of tests. Moreover, pulmonary hyperinflation (FRCraw > 2 SDS) was present in 26.7%, mostly combined with obstruction (23.4%). Independent from age at entry pulmonary hyperinflation remained to a certain degree despite treatment (LABA and ICS).

Conclusions: Apart from spirometry, follow-up of asthmatic children should include plethysmographic measurements, because changes in static lung volumes influence airway dynamics, mimicking normal flow-volume curves. Moreover, patients with pulmonary hyperinflation are less responsive to standard treatment.


**P4613**

Breath by breath specific airway resistance during ventilation in children

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Rationale: Panting is the optimal way to minimize the phase lag between the plethysmographic volume compression signal (Vplet) and airflow due to the thermal artifact when measuring specific airway resistance (sRaw). A drawback in children is that the end expiratory lung volume may be observed to increase during the measurement. It is not known to what extent sRaw is altered by the breathing strategy.

Hypothesis: The hypothesis was tested here that increased end expiratory lung volume during panting does not impact significantly on sRaw.

Objective: To test whether increased end expiratory lung level within the sRaw acquisition results in a systematic trend with time.

Methods: sRaw was measured in 10 children panting in a custom made pressure plethysmograph. Thirty measurements (1-5 per subject) that displayed a steady increase in end expiratory lung level throughout at least 4 breaths were reanalyzed breath by breath.

Results: Panting frequency (mean ± SD) was 3 ± 0.5 Hz. sRaw was found to increase significantly throughout the acquisition (p = 0.006).

Significant breath by increase in sRaw (±50 sec) during panting in 10 children

<table>
<thead>
<tr>
<th>Breath 1</th>
<th>Breath 2</th>
<th>Breath 3</th>
<th>Breath 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0 ± 1.5</td>
<td>7.3 ± 1.8</td>
<td>7.8 ± 1.6</td>
<td>8.1 ± 1.7</td>
</tr>
</tbody>
</table>

Conclusion: The progressive increase in end-expiratory lung volume during panting in children is associated with parallel increase in sRaw. This may be explained by non lineairities in the Vplet - airflow relationship while the end expiratory lung volume increases in relation with imbalance between inspiratory and expiratory efforts. The clinical relevance is not clear and deserves further evaluation.

**P4614**

Lung function and gender at twelve to thirteen years of age in children born very prematurely.

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Lung function abnormalities are common in school aged children born extremely prematurely. Follow up of infants born at 23-28 weeks gestational age from the United Kingdom Oscillation Study (UKOS) showed males had a higher incidence of respiratory morbidity during infancy.

Aim: To test the hypothesis that lung function at 12-13 years of age in children born very prematurely would be worse in males than females.

Methods: Lung function was assessed in 65 children, the first to date assessed in follow-up of UKOS, which randomised babies to high frequency oscillation or conventional ventilation. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, residual volume (RV), transfer factor for carbon monoxide (TLC), functional residual capacity (FRC) and response to cold air challenge (CACH) were assessed. Results were abnormal if two standard deviations (SD) below expected, except RV results which were abnormal if >2.5 SDs.

Results: 29 females and 36 males have been assessed. A greater proportion of males compared to females were oxygen dependent at 28 days (89% versus 69%, p<0.063), had reduced FEV1 (22% versus 3.5%, p=0.036), higher RV (34% versus 6%, p<0.001), and reduced FEV1, FVC and TLC (24% versus 30%, p=0.08). There were no significant differences regarding the proportions with reduced FEV1/FVC (44% versus 31%, p=0.32), or reduced TLC (29% versus 50%, p=0.18 (FEV1 p=0.23) or response to a CACH 24% versus 26%, p=0.94).

Conclusion: Preliminary results suggest that amongst 12-13 year old children born at 23-28 weeks gestation, males have greater airways obstruction than females, but this is not explained by greater airway hyper-reactivity.

**P4615**

Lung function in infants and toddlers after the repair of congenital diaphragmatic hernia (CDH)

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There are only 4 studies on infant pulmonary function testing (IPFT) performed after repair of CDH. We used a wide spectrum of IPFT methods to test babies in whom CDH repair was performed.

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**Abstract P4611** Table 1. Nitric oxide readings by respiratory disease

<table>
<thead>
<tr>
<th>Reading</th>
<th>PCD</th>
<th>Asthma</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>nNO (ppb)*</td>
<td>23 (6-61)</td>
<td>856 (536-988) (p=0.001)</td>
<td>709 (560-1126) (p=0.001)</td>
</tr>
<tr>
<td>FeNO (ppb)**</td>
<td>9.2 (7.9)</td>
<td>21 (22) (p=0.019)</td>
<td>43 (41) (p=0.001)</td>
</tr>
<tr>
<td>JNO (pl/s)**</td>
<td>271 (232)</td>
<td>965 (963) (p=0.004)</td>
<td>2100 (1935) (p=0.018)</td>
</tr>
<tr>
<td>CalvNO (ppb)**</td>
<td>1.6 (0.5)</td>
<td>2.4 (1.4) (p=0.174)</td>
<td>5.4 (3.5) (p=0.001)</td>
</tr>
</tbody>
</table>

*Median (IQR); **Mean (SD); values compared to PCD.
We tested 30 infants and toddlers after CDH repair (BW 3.10±0.54 kg [mean±SD]; body length 49.5±2.2 cm). In 4/30 Goretx patch was used (subgroup Gore). Age at testing was 1.32±0.54 (median 1.07) yrs; body weight 9.76±1.23kg (z-score -0.77); body length 78.8±6.7cm (z-score -0.024). The whole-body plethysmography (to measure FRCp and rEeff), tidal breathing analysis (tPTEF%tE), baby resistance/compliance (specific Crs) and RTC method (V‘maxFRC) were performed. Standard protocol 1.2 and proper reference values 3,4 were used. FRCp equals 126.5±36.9% pred (P<0.002); rEeff reached 109.9±58.9% pred (ns). A parameter of tPTEF%tE decreased (22.8±8.5%) Specific compliance of the respiratory system, rs (Crs/kg) was 14.1±2.3 ml/kPa/6kg (76.1±20.1% pred) A value of V‘maxFRC reached only 112.±4ml/sec (z-score -2.387). Increased value of FRCp was found in Gore subgroup (165.7±51.9 vs. 120.4±31.2, p<0.02).

Our cohort had normal body length but mildly lowered body weight. Neither central airway (aw) obstruction nor restrictive pattern was found. Mild peripher al aw obstruction, mild (secondary) hyperinflation and mildly decreased specific Crs was found.

Supported by the grant NS 10572-3/2009 and grant GAUK 62809.

References:

480. Diagnosis and biology of malignant pleural effusions

P4616

The bedside autofluorescence pleuroscopy for the undiagnosed lung cancer with pleural effusion in a intensive care unit

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Introduction: Autofluorescence bronchoscopy was developed to enhance the detection of lung cancer in the airway. However, its role in evaluation of pleural space has not been published.

Aim: To assess the undiagnosed lung cancer with pleural effusion in a intensive care unit (ICU).

Methods: A flexible bronchoscope(SAFE 3000,Pentax, Tokyo) to entry to assess the pleural space. The evaluation of pleural space was started by Twin Mode and then completed by MIX. Then the specimens send for histological examination and the clinical data retrospectively studied. The whole procedures were done in the ICU bedsides.

Results: 22 patients were recruited. There were 6 patients with cytology negative and normal finding in WLP or AFP but 2 of them were found to have lung cancer. Among the 16 patients with atypia or suspicious cells had abnormal finding in the WLP or AFP, 15 patients finally had lung cancer.

Conclusions: The AFP is useful for detecting the undiagnosed lung cancer with pleural effusion. This is a daily practice performed not only in endoscopic room but in the ICU bedsides.

P4617

Triplet chemotherapy (paclitaxel/gemcitabine/cisplatin) is more active in advanced squamous cell subtype (SCC) non-small cell lung cancer (NSCLC) than doublet treatment (vinorelbine/cisplatin): A randomized phase III trial in 443 NSCLC patients

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Background: A triplet regimen of Paclitaxel/Gemcitabine/Cisplatin was compared to a standard doublet regimen to examine for superiority.

Patients and methods: Histologically verified inoperable NSCLC patients (pts) were randomized to A (paclitaxel 180 mg/m² and cisplatin 100 mg/m² day 1 with gemcitabine 1000 mg/m² day 1 and 8 every 3 weeks) or to regimen B (cisplatin 100 mg/m² day 1 and weekly i.v. vinorelbine every 4 weeks).

Results: 443 pts were randomized (A: 221; B: 222). Median age was 62 years (range 38-75 years) overall, 56% were males, 11% had PS 2, 62% stage IV disease, 46% adenocarcinoma, and 28% SCC, equally distributed between A and B. Both regimens had median 4 treatment courses. Toxicities were largely similar in A and B. Response rates were 43% and 39% in A and B, medians of progression free survival (PFS) were 6.7 and 5.8 mths (p=0.453), and median overall survival (OS) were 11.4 and 10.8 mths (p=0.415), respectively. PFS and OS were significantly higher in A than in B in SCC subtype (median PFS 7.0 mths vs. 4.1 mths, p=0.001; median OS 13.5 mths vs. 9.7 months, p=0.020). response rates were equal (52% vs. 38%, p=0.129).

Conclusions: Triplet paclitaxel/gemcitabine/cisplatin was not superior to doublet vinorelbine/cisplatin in advanced NSCLC. However, the triplet regimen had significantly higher activity compared to the doublet in SCC. This superiority in SCC may likely be due to gemcitabine being more active than vinorelbine in this subtype though the relative contribution of paclitaxel remains to be determined.

P4618

Evaluation of pleural fluid human epidymis 4 (HE4) as a marker of malignant pleural effusions

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Pleural effusions are a commonly encountered problem in clinical practice, and pleural fluid analysis is usually the first step towards identifying the underlying etiology. Numerous studies have been published analyzing the potential utility of measuring biomarkers in pleural fluid as possible indicators of a malignant effusion, however there are no studies that have examined the presence of HE4 in pleural effusions. The aim of this study was to assess pleural fluid and serum concentrations of HE4 in patients with different types of pleural effusions and to evaluate the diagnostic performance of HE4 in detecting malignant pleural effusions.

Patients and methods: A prospective study was carried out of 88 consecutive patients presenting with pleural effusions. The patients were divided into three groups: 22 patients with transudative effusions, 32 patients with non-malignant exudative effusions and 34 patients with malignant pleural effusions. Blood and pleural fluid HE4 levels were measured using a chemiluminescent immunoassay.

Results: Both serum HE4 levels and pleural fluid HE4 levels were significantly higher in patients with malignant effusions than in patients with transudative or non-malignant exudative effusions. A pleural fluid HE4 cut-off value of 1675 pmol/L was found to predict malignant pleural effusions with a diagnostic sensitivity of 85.3% and specificity of 90.7%.

Conclusion: The current study reports a novel finding of increased serum and pleural fluid HE4 levels in patients with malignant effusions compared to non-malignant effusions. This finding has the potential to strengthen the diagnostic performance of tumor markers in detecting malignant pleural effusions.
P4619
Serum thioredoxin-1 as a diagnostic marker for malignant peritoneal mesothelioma
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Background: Diffuse malignant peritoneal mesothelioma (DMPM) is an aggressive malignant tumor of mesothelial origin that shows a limited response to cytoreductive surgery along with intra-peritoneal chemotherapy. Therefore, diagnosing DMPM early is very important. Reactive oxygen species (ROS) play an important role in asbestos toxicity, which is associated with the pathogenesis of DMPM growing. Thioredoxin-1 (TRX) is a small redox-active protein that demonstrates anti-oxidative activity associated with tumor growth. Here, we investigated the serum levels of TRX in patients with DMPM and compared them with those of a population that had been exposed to asbestos but had not have DMPM.

Study: The serum concentrations of TRX were measured in 15 DMPM patients and 34 individuals with benign asbestos-related diseases.

Result: We demonstrated that the patients with DMPM had significantly higher serum levels of TRX than the population that had been exposed to asbestos but had not have DMPM.

Conclusions: Our data suggest that serum TRX concentration is a useful serum marker for DMPM.

P4620
Diagnostic value of vascular endothelial growth factor, glycosaminoglycan, cathepsin S, cathepsin H in the discrimination of transudate exudate and benign malignant patients with pleural effusion
Nalan Goloğlu1, Cengiz Özge1, Gürbüz Polat2, Serin Akbayir2. 1Chest Diseases, Mersin University School of Medicine, Mersin, Turkey; 2Department of Internal Medicine, Hyogo Prefectural Tsuhashi Hospital, Amagasaki, Japan

Pleural effusion is one of the most common problems and it was reported that 4% of the patients applying internal clinics suffer from pleural effusion. Cathepsin S, cathepsin H in the discrimination of transudate exudate and benign malignant patients with pleural effusion

Conclusions: Our data suggest that serum TRX concentration is a useful serum marker for DMPM.

P4621
F-18 FDG PET scan 20 years after talc pleurodesis: Report of 3 cases
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FDG PET scan is used with increasing frequency to investigate pleural abnormalities and determine the possibility of neoplastic invasion. Talc pleurodesis has been reported to cause hypermetabolic pleural thickenings and masses, up to 5 years after the procedure. We report 3 cases of patients who required talc pleurodesis for pneumothoraces in 1989 and 1990 with satisfying results, and who were investigated in 2010–2011 for pleural abnormalities, with positive TEP results, which were deemed secondary to the pleurodesis. Talc pleurodesis functions by creating inflammation, therefore promoting pleural adhesions. The metabolism surrounding this inflammatory reaction could decrease with time, as in other inflammatory processes. However, the fact that talc itself is not metabolized by the body would explain the positive FDG PET scan, possibly as a foreign body reaction.

We discuss radiological differences that can be used to differentiate between hypermetabolic talcoma and neoplastic disease.

Conclusion: Talc pleurodesis can induce an inflammatory reaction, even 20 years after being performed. In patients with pleural abnormalities, it is important to question such procedures and mention them to colleagues interpreting metabolic imaging.

P4622
Relevance of FDG-PET-CT scan for the evaluation of local pleural invasion assessed by thoracoscopy in malignant pleural mesothelioma
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Introduction: FDG-PET-CT scan(PET) is now widely recognized as an important staging modality in many cancers and PET standard uptake value(SUV) is reported as a prognostic indicator in several malignancies. However only a few previous studies have investigated the utility of PET in malignant pleural mesothelioma(MPM). We hypothesized that pleural assessed by PET might be in accordance to pleural characteristics evaluated by thoracoscopy.

Methods: 29 patients with a diagnosis of MPM obtained by thoracoscopy were previously evaluated byPET, and considered valuable for this analysis. Among them, 10.34%, 20.69%, 44.83%, 24.14% were assessed as I,II, III, IV stage respectively. There were 10.34% of patients in stage I, 20.69% in stage II, 44.83% in stage III, and 24.14% in stage IV. The pathological analysis showed 86.21% epithelial, 3.45% sarcomatous and 10.34% biphasic types.

Results: At thoracoscopy there were 16 (55.17%) patients with visceral pleural involvement, 21 (72.41%) with diaphragmatic involvement and 2 (6.90%) with mediastinal involvement. All of them had an invasion of the costal parietal pleura. There was a significant difference (<0.05) of the medium SUV between the patients with a visceral pleural involvement and the patients without this feature. Moreover statistically significant differences of the medium SUV was shown between patients with or without pleural nodules.

Conclusions: These findings suggest that pleural evaluation by PET should in accordance to the characteristics obtained by thoracoscopy. There is a significant difference between the site of pleural involvement and/or the typology of tumoral lesions and the SUV of PET.
and diagnosis by Chi-Squared or Fischer’s exact test in Abrams vs Tru-cut were 93.8% vs 86.7% (p=0.0339) and 89.6% vs 88.3% (p=0.0837) respectively. 

**Conclusion:** Physician led image guided Abrams biopsies had larger size specimens. The diagnostic yield with Abrams is superior to published literimens. The diagnostic yield of Abrams technique is statistically similar to the Physician led image guided Abrams biopsies had larger size specimens. The diagnostic yield with Abrams is superior to published literature. To the best of our knowledge this is the first data series comparing image guided Abrams vs Tru-cut pleural biopsies.

**P4624**

**Value of thoracoscopic pleural brush in the diagnosis of exudative pleural effusion**

Lamia Shaaban, Youssef Ahmed. Chest, Assiut University Hospital, Assiut, Egypt

**Background:** Medical thoracostopy had been established to have greater diagnostic yield in the diagnosis of exudative pleural effusion.

**Aim of this study:** To evaluate the value of thoracoscopic pleural brush in the diagnosis of exudative pleural effusion.

**Setting:** Endoscopy Unit, Chest Department, Assiut University Hospital -Egypt

**Material and methods:** The study was conducted upon 28 patients with exudative pleural effusion from January 2011 to December 2011, in whom both the conventional pleural taping and closed pleural biopsy was not conclusive. All patients submitted for medical thoracostopy, where forceps biopsy and pleural brush specimens were taken for all patients.

**Results:** Thoracoscopic pleural specimens were positive in 26 patients (92.8%). Histo-pathological examination of thoracoscopic specimens revealed malignant lesions in (21 patients), TB in (2 patients) and non specific inflammation in (3 patients). Forceps biopsy was positive in 23 patients, while pleural brush was positive in 17 patients. Thoracoscopic pleural brush was the only diagnostic modality in 3 patients all were adenocarcinoma that allow increased diagnostic yield of medical thoracostopy from 23 patients (82.1%) to 26 patients (92.8%). No complications recorded with pleural brush procedures.

**Conclusion:** Thoracoscopic pleural brush could be done easy and safe and allow obtaining pleural cellular material in areas dangerous to take biopsy specimens. It could augment diagnostic yield of medical thoracostopy.

**P4625**

**Cytology and DNA ploidy techniques in the diagnosis of malignant pleural effusion**

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**Introduction:** Pleural fluid (PF) cytopathy is the first approach to diagnose malignant pleural effusion (MPE). Its sensitivity ranges from 40 to 80% and depends on the quality of slide preparation, histological tumor type and the cytopologist’s skill to differentiate tumor cells from benign reactive mesothelium. Ancillary methods are often required to improve the cytological diagnosis.

**Objectives:** To evaluate the sensitivity and specificity of conventional cytology, and the contribution of fluorescence in situ hybridization (FISH) and DNA ploidy in MPE diagnosis.

**Materials and methods:** PF samples from 85 patients were analyzed by cytology and classified as: malignant (presence of malignant cells; n= 45; 52.9%); suspicious (presence of atypical cells; n=16; 18.8%) or benign (no malignant or atypical cells; n= 24; 28.3%). FISH was performed in the 85 PF samples by the alpha centromeric probes for chromosomes 11 (red) and 17 (green) and classified as normal or aneuploid according to the cut-off previously established. In 43 samples we also performed DNA ploidy by flow cytometry (FC). Patient’s records were consulted for definitive diagnosis.

**Results:**

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>93.2</td>
<td>80.7</td>
<td>89.4</td>
</tr>
<tr>
<td>FISH</td>
<td>94.8</td>
<td>96.1</td>
<td>94.2</td>
</tr>
<tr>
<td>DNA ploidy</td>
<td>59.5</td>
<td>33.1</td>
<td>55.8</td>
</tr>
</tbody>
</table>

**Conclusion:** FISH improved the cytological diagnosis of MPE. In five cases of suspicous and in three cases of negative cytology, the presence of aneuploidy cells reclassified the cases as MPE. In these cases, all patients were confirmed with cancer. CF DNA ploidy showed weak diagnostic performance.

**P4626**

**Ultrasound guided forceps biopsy of the pleura**

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**Background:** Ultrasound guided forceps biopsy of the pleura is a technique that can cover the diagnostic yield gap between the needle biopsy of the pleura and thoracospy or thorotomy. This technique enables the operator to take biopsy from multiple pleural sites.

**Study objectives:** (1) To describe the ultrasound guided forceps biopsy of the pleura as a technique that is not in common use in our practice to obtain pleural biopsy. (2) To evaluate the diagnostic yield of this technique in undiagnosed exudative pleural effusion.

**Setting:** Prospective intervention study.

**Design:** Ultrasound Unit- Chest Department- Assiut University Hospital -Egypt.

**Patients and methods:** All recruited patients (96) had exudative pleural effusion with first pleural tapping undiagnostic. Patients with bleeding tendency or blood coagulation defects were excluded. The procedure was performed under local anesthesia (Xylocaine 2%) and asptic condition. The patients were premedicated by anagisic (Ketorolac thromethamine 20mg). Three to five biopsy fragments were obtained from each case and sent in 10% formaldehyde to the pathology laboratory. The diagnostic yield was compared with that of thoracoscopy.

**Results:** Compared to thoracospy the sensitivity in diagnosis of malignant and tuberculous lesions was 85% and 88% respectively. The technique was absolutely specific in diagnosis of malignant and tuberculous lesions.

**Conclusions:** Ultrasound – guided forceps biopsy of the pleura is a simple, efficient, and safe procedure. It can be carried out easily and safely even in sick and obese patients. On the other hand, the procedure appears similar to the thoracoscopy in obtaining adequate pleural tissue specimens. Yet, it is simpler and less traumatic.

**P4627**

**How much of a role does immunohistochemistry have in reaching a final diagnosis of pleural malignancy in routine clinical practice?**

Kerry Woolnough. Respiratory Medicine, University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom

**Introduction:** Pleural fluid immunohistochemistry is not recommended in the routine pathological work up of a suspected malignant pleural effusion due to its low sensitivity. However, research has demonstrated its usefulness in diagnosing the primary site of a malignancy, particularly in adenocarcinomas.

We wished to ascertain the frequency of its use and the contribution immunohistochemistry made to identifying the source of metastatic pleural deposits.

**Methods:** We retrospectively examined all pleural specimens sent for analysis over a 12 month period in patients with confirmed pleural malignancy. We noted the proportion of specimens stained for tumour markers and evaluated the contribution immunohistochemistry made to localising the primary source of the malignancy. These were grouped into three different categories: (i) undiagnostic, (ii) confirmatory and (iii) diagnostic.

**Results:** A total of 101 pleural specimens were sent for cytological and histological examination. Analysis revealed: 37 adenocarcinomas, 4 squamous cell carcinomas, 1 small cell cancer, 19 malignant mesotheliomas, 1 lymphoma and 1 schwannoma. 10 specimens were reported as malignant cells and 28 samples had no malignant cells present. 42 specimens had additional immunohistochemistry performed. In 2 specimens
immunohistochemistry was undiagnostic. It was a confirmatory test in 38% (n=16) and diagnostic in 47.6% (n=20).

Conclusion: We found that immunohistochemistry was underutilised, particularly when cytological analysis revealed malignant cells or adenocarcinoma. In the specimens where these tumour markers were used it was mostly diagnostic in localising the primary for adenocarcinomas.

**P4628**

The effect of a pleural diseases clinic on pleural effusion admission rates

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Background: Patients with pleural effusion are frequently admitted to hospital on the medical intake. Some of these admissions may be predicted and acute admission avoided.

Aim: A weekly specialist pleural diseases clinic was established in May 2011. We assessed whether provision of dedicated clinic time for patients who may require pleural intervention would reduce hospital admission rates of patients with pleural effusion.

Method: A retrospective review of electronic records for patients attending the clinic between 01/06/11-30/11/11. Hospital records were analysed for pleural effusion admission events (ICD10 codes J90/J91) in this period and between 01/06/10-30/11/10.

Results:

<table>
<thead>
<tr>
<th>Year</th>
<th>Patient number (new- follow-up)</th>
<th>Mean age (years) range)</th>
<th>New patient diagnosis number (%)</th>
<th>Pleural infection</th>
<th>Cardiac failure</th>
<th>Procedural type (%)</th>
<th>Hospital admission rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>89.45</td>
<td>68 - (28 -92)</td>
<td>47.2(8)</td>
<td>16 (18)</td>
<td></td>
<td>64 (6.7)</td>
<td>17</td>
</tr>
<tr>
<td>2010</td>
<td>37</td>
<td>68 - (28 -92)</td>
<td>49 (12.8)</td>
<td></td>
<td></td>
<td>64 (6.7)</td>
<td>17</td>
</tr>
</tbody>
</table>

Conclusion: Development of a pleural clinic is associated with a reduced length of stay for patients admitted with pleural effusion. This could have significant cost-saving implications. However, the number of admissions increased by 21% over the study period. The cause of this rise is not clear.

**P4629**

Incidence of lung entrapment in malignant pleural effusion

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Introduction: Lung entrapment is commonly seen in patients with empyema and complicated parapneumonic effusions. However, the incidence of lung entrapment is not well reported in malignant effusions. We intend to report the incidence in our patient who underwent pleuroscopy in 2011.

Method: A prospective observational study was performed on patients who underwent pleuroscopy in 2011 in Changi General Hospital (CGH). The findings on pleuroscopy were noted for all patients, in particular, the presence of lung entrapment. Biopsies of the parietal pleura were performed during pleuroscopy. Patients with biopsies positive for malignant pleural effusion were included in our analysis.

Results: In 2011, twenty four pleuroscopies performed in CGH. Fifteen (62.5%) were proven to have malignant pleural effusion on biopsy. Of these fifteen patients, 10 (66.7%) had lung carcinoma, 4 (26.7%) had breast carcinoma and the remaining patient (6.7%) had carcinoma of the cervix. Fourteen patients (93.3%) with malignant effusion were noted to have lung entrapment on pleuroscopy of various. Computed tomography scan (CT scan) of the lungs showed patency of the airway. However, bronchoscopy was not performed for these patients.

Conclusion: The incidence of lung entrapment is high in our patients with malignant pleural effusion. This will have an impact on the long term management of such patients. Our finding would suggest that talc pleurodesis may not be the best treatment options. The use of an indwelling pleural catheter may be a better option for our patients with malignant pleural effusion.

**P4630**

Symptoms, emergency admissions and place of death in patients with pleural malignancy

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Pleural malignancy is often associated with a poor prognosis, but qualitative outcomes are rarely published. We describe the journey of these patients, focusing on symptoms, admissions and place of death.

Methods: In August 2011 we reviewed case notes and electronic records of 157 patients with pleural cytology sent during 2009. In 73 patients diagnosed with pleural malignancy we recorded: performance status (PS), nature of diagnosis (tissue or clinical), pleurodesis, emergency admissions, symptomatic effusion at death and place of death.

Results: 71/73 patients (97%) had died by data collection. Important clinical data included:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Mean PS</th>
<th>Tissue Diagnosis</th>
<th>Median Survival (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma</td>
<td>11</td>
<td>1 (n=11)</td>
<td>5 (45%)</td>
<td>39</td>
</tr>
<tr>
<td>Lung Adenocarcinoma</td>
<td>14</td>
<td>1 (n=10)</td>
<td>14 (100%)</td>
<td>13</td>
</tr>
<tr>
<td>Other Lung Malignancy</td>
<td>14</td>
<td>1 (n=10)</td>
<td>11 (83%)</td>
<td>12</td>
</tr>
<tr>
<td>Non-Pulmonary Malignancy</td>
<td>17</td>
<td>1 (n=9)</td>
<td>12 (70%)</td>
<td>15</td>
</tr>
<tr>
<td>Malignancy Not Specified</td>
<td>17</td>
<td>2 (n=12)</td>
<td>0 (0%)</td>
<td>8</td>
</tr>
<tr>
<td>Overall</td>
<td>73</td>
<td>1 (n=52)</td>
<td>42 (58%)</td>
<td>14</td>
</tr>
</tbody>
</table>

The mean (SD) number of admissions and days spent as inpatient were 3 (1.7) and 26 (23), respectively. 21/73 (29%) underwent pleurodesis (13 at VATS), 22/73 (31%) had symptomatic effusion at death, 11/71 (15%) had an intercostal drain inserted in the week preceding death.

Conclusion: Patients with pleural malignancy spend a significant proportion of their remaining time in hospital. The majority in our audit died in acute hospital units, often with symptomatic pleural effusion. Few died at home or in specialist palliative care facilities.

**P4631**

Educational opportunities provided by a specialist pleural diseases clinic

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Background: Recent BTS guidelines strongly recommend the use of thoracic ultrasound (TUS) prior to any pleural procedure. With the instigation of the European Working Time Directive and specialty-based ward care, time for training in pleural interventions is limited despite it being a requisite in the UK training curriculum.

Aim: A weekly specialist pleural diseases clinic was established in May 2011 allowing dedicated clinic time for patients who require pleural intervention. The clinic also provides practical training for specialist respiratory trainees. Junior (FY, CMT) doctors were encouraged to attend and observe the procedure.

Method: A retrospective analysis of patients and trainees attending the clinic during its first 6 months (01/06/11-30/11/11).

Results: 134 patients were seen (mean 5, range 2-10 weekly), all patients had bilateral TUS. An average of 3 procedures was performed weekly. A respiratory registrar attended 80% of the clinic. Junior trainees were present for 65% of procedures. Trainees achieved the requisite numbers 4 RCR Level 1 competency at 5 means clinics.

Conclusion: Development of a pleural disease clinic has contributed to an improvement in the training of junior doctors. Respiratory trainees are able to learn TUS on a 1:1 basis and be observed during acquisition of RCR level 1 competency. Didactic lectures and practical teaching sessions already exist for the junior doctors. This clinic enhances the hands-on training available providing dedicated patient-based opportunities. This is necessary to ensure all trainees gain proficiency in the core pleural procedures needed in general hospital medical practice.

**P4632**

Can serum (CRP) levels estimate the outcome of talc pleurodesis in malignant pleural effusions?

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Objective: To evaluate whether serum C-reactive protein (CRP) could help to predict the success rate and/or side effects of pleurodesis.

Methods: In a prospective study, 25 consecutive patients with recurrent and biopsy-proven malignant effusions were included. Five grams of talc mixed in 150 ml of normal saline were administered via tube thoracostomy. Serial determinations of CRP were made in serum at the beginning of pleurodesis (baseline), and 24 and 72 h after the procedure. Successful therapy was defined as a complete absence or minor reaccumulation of pleural effusion one month after pleurodesis.

Results: Pleurodesis was successful in 22 of 25 patients (88%). The patients
Clinical characteristics, treatment and survival outcomes in malignant mesothelioma

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Objective: We aimed to evaluate the clinical, radiological and survival features of patients with MM.

Methods: The study included 228 patients who were followed up in our center between 1993 and 2010 with the diagnosis of MM.

Results: The mean age was 59.1 years in men and 58.7 years in women (male/female=1.4). Environmental asbestos exposure was present in 86% of the patients for a mean duration of 40±20 years. Closed pleural needle biopsy was the most common diagnostic procedure (56.4%). One hundred-thirteen (66%) patients were treated with platinum-based combination chemotherapy (PBCT) plus supportive care (SC) and 67 (34%) patients received SC alone. The median follow-up time was 10.0 months. The median overall survival was significantly improved with PBCT plus SC compared to SC alone (11.4 vs. 5.1 months; p=0.005). The 6, 12, 18, and 24-month survival rates were significantly improved with PBCT plus SC compared to SC alone (72%, 43%, 19%, and 2% vs. 49%, 31%, 11%, and 1%).

Conclusion: The survival of patients with MM improved in patients treated with PBCT. The survival advantage continued 12- and 24-month after the initial time of combination chemotherapy.
elminating highly reactive ROS and RNS. The aim of the present study was to clarify the effect of H2 gas inhalation on direct lung injury and indirect contralateral lung injury.

Methods: Anesthetized C57BL/6J male mice were intubated, and 5 μL of 0.1 N HCl was administered to the left lung. Mice were randomly grouped to saline treatment instead of HCl (Sham), HCl-treatment (HCl), and 2% H2 gas inhalation with the HCl-treatment (HCl-H2) groups. Extra-vascular wet to dry ratio, myeloperoxidase (MPO) activity in the treated left lung and untreated right lung, and serum IL-6 level were evaluated 4 hrs after the treatment.

Results: This aspiration pneumonia model induced direct lung injury and contralateral lung injury. The extra-vascular wet to dry ratios of the left and right lungs were significantly larger in the HCl group compared to the Sham and the HCl-H2 group (p = 0.01), suggesting that H2 gas was effective not only in the direct injured lung but also in contralateral lung. MPO activity of the left lung was also significantly larger in the HCl group compared to those in the Sham and HCl-H2 groups (p = 0.05). IL-6 was increased in the HCl group, but it did not statistically differ to the level in the HCl-H2 group, suggesting H2 gas did not interfere in the cytokine production.

Conclusion: H2 gas inhalation ameliorated direct lung injury and indirect contralateral lung injury in a murine aspiration pneumonia model.

P4637 Protective effects of keratinocyte growth factor-2 on warm ischemia reperfusion lung injury in rats

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Introduction: Ischemia reperfusion injury manifests as acute lung injury due to the injury of both the endothelium and epithelium. Keratinocyte growth factor-2 (KGF-2) was previously demonstrated to play an important role in the repair of alveolar epithelial damage. Recently, it was also reported to help maintain the barrier function of capillary monolayers.

Objective: Investigate the potential effects of KGF-2 on ischemia reperfusion-induced lung injury and the related mechanisms.

Methods: KGF-2 (2.5-10mg/kg) was administered intratracheally to rats 3 days before surgery. Then the left lung in rats was subjected to ischemia for 60 minutes and reperfusion for 180 minutes. Lung morphology, blood gas analysis, total cell number and protein concentration in the bronchoalveolar lavage fluid were measured. The protective effects of KGF-2 on endothelial cells and related mechanisms were evaluated in vitro.

Results: Pre-treatment with KGF-2 effectively inhibited lung edema, inflammatory cell infiltration, protein exudation and the release of inflammatory cytokines.

P4638 Resistant breathing induces matrix metalloproteinases-9 and -12 expression in the lung

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Respiratory breathing (RB), encountered in obstructive airway diseases, is associated with large negative intrathoracic pressures and has been recently shown to induce acute lung injury and inflammation. Matrix metalloproteinases (MMPs) -9 and -12, implicated in the pathogenesis of both asthma and COPD, are upregulated by inflammation and by mechanical stress per se. We hypothesized that RB induces MMP9 and -12 expression and activity in the lung. Anesthetized, tracheostomised rats were breathing through a 2-way valve. The inspiratory line was connected to a resistance setting peak tracheal pressure at 50% of maximum (RB). Quietly breathing animals served as controls. After 3 and 6hrs of RB, bronchoalveolar lavage (BAL) was performed to measure cell count and cytokine levels by ELISA. Lung injury was evaluated by histology. MMP9 lung levels were measured by zymography and immunohistochemistry (IHC). MMP12 was detected by IHC. Alveolar macrophages from normal rats were incubated with BAL fluid from rats that underwent RB. MMP9 activity was measured in cell supernatants by zymography.

After 3 and 6hrs of RB, lung injury was detected by histology. Increased numbers of alveolar macrophages and neutrophils (p<0.05) and increased levels of IL-1β and IL-6 (p<0.01) were measured in the BAL following 6hrs of RB. MMP9 activity raised by 2-fold after 6hrs of RB (p<0.001). MMP12 was detected in alveolar macrophages and epithelial cells. After 3 and 6hrs of RB, increased levels of Molar macrophages. BAL fluid from animals that underwent 6hrs of RB, induced MMP9 in supernatants by 7.5-fold (p<0.001).

In previously healthy rats, RB resulted in increased MMP9 and -12 expression and activity in the lung.

P4639 Study of cardiac and hemodynamic changes with airway pressure release ventilation and pressure control ventilation in children with acute respiratory distress syndrome

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Cardiology, Faculty of Medicine, Tanta University, Tanta, Gharbia, Egypt

Background: Acute respiratory distress syndrome (ARDS) is associated with high morbidity and mortality. Airway pressure release ventilation (APRV) was suggested to be a suitable mode for ventilating such patients with less liability of lung injury.

Aim: To compare the effect of APRV and pressure control ventilation (PCV) on cardiac and hemodynamic functions in children with ARDS.

Patients and Methods: Twenty children aged 1-14 years fulfilling ARDS criteria were included. The following parameters were recorded after ventilating the patients on PCV and APRV: ventilation parameters [peak inspiratory pressure (PIP) and mean airway pressure (MAP)], oxygenation parameters and oxygen delivery, hemodynamic parameters and urine output.

Results: PIP significantly decreased from 29±7 cmH2O to 24±4 cmH2O with APRV, while MAP was significantly higher during APRV (17±5) than during PCV (13±4) cmH2O. PaO2/FiO2 ratio and oxygen delivery, hemodynamic parameters and urine output increased significantly from 256±25 during PCV to 295±33 during APRV. Oxygen delivery increased significantly from 565±98 during PCV to 1196±127 ml/min during APRV. Cardiac index increased significantly from 3.2±0.2 to 4.1±0.3 ml/min/m² during APRV. Urine output increased significantly from 0.78±0.1 during PCV to 0.97±0.2 ml/kg/h during APRV. The use of sedatives and inotropics were decreased significantly during APRV compared to PCV.

Conclusions: APRV may be a suitable mode for ventilating ARDS patients providing better lung recruitment and oxygenation, avoiding more lung injury and cardiac compromise compared with pressure control ventilation.

P4640 Protease-antiprotease imbalance in airway secretions in subjects with acute respiratory failure

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Studies have shown that in the acute respiratory distress syndrome (ARDS) there is protease-antiprotease imbalance, reflected as an increase in the ratio of Human Neutrophil Elastase (HNE) to several protease inhibitors in BAL and plasma. This imbalance can be related to the pathophysiology of ARDS and may correlate with clinical outcomes. The purpose of the study was to determine if similar protease-antiprotease imbalance could be detected in airway secretions in subjects at risk of developing ARDS.

Free HNE activity (HNEA) and levels of the protease inhibitors alpha-1 antitrypsin (AAT) and secretory leukocyte protease inhibitor (SLPI) were measured in
samples of endotracheal aspirates samples collected serially in subjects intubated because of acute respiratory failure in a medical ICU (n=42 subjects, 10 eventually developed ARDS).

Contrary to reports studying BAL, we observed that free elastase activity is reduced in airway secretions of subjects that develop ARDS compared to subjects that did not. No differences were noted in AAT and SLPI concentrations in airway secretions among these groups. HNEA/AAT and HNEA/SLPI ratios were reduced in 19 subjects. In ARDS subjects, levels of HNEA returned to normal the first day after the onset of ARDS. There were no differences in survival between subjects who had detectable free HNEA compared with those that did not.

Analysis of protease-antiprotease balance in airway secretions of subjects with acute respiratory failure is not useful to discriminate subjects who develop ARDS and does not correlate with survival.

### Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical success</th>
<th>Clinical failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>234/195 (n=429)</td>
<td>24/22 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>Age</td>
<td>79.02±10.39 (n=429)</td>
<td>84.17±9.38 (n=46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>32.49±7.19 (n=439)</td>
<td>33.69±7.81 (n=45)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>107.19±23.24 (n=429)</td>
<td>104.24±25.37 (n=46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>PAM (mmHg)</td>
<td>116.15±25.69 (n=429)</td>
<td>105.90±26.08 (n=46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>pH</td>
<td>7.02±0.12 (n=429)</td>
<td>7.20±0.11 (n=46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>51.08±15.61 (n=428)</td>
<td>48.72±16.96 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>pO2 (mmHg)</td>
<td>25.65±6.45 (n=424)</td>
<td>25.31±6.39 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.93±2.12 (n=429)</td>
<td>3.37±2.89 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.24±2.49 (n=419)</td>
<td>12.86±2.49 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>Device O2 2</td>
<td>90.42±21 (n=46)</td>
<td>94±20 (n=46)</td>
<td>Non significant</td>
</tr>
<tr>
<td>Device NIV</td>
<td>336/426 (79%)</td>
<td>36/45 (80%)</td>
<td>Non significant</td>
</tr>
</tbody>
</table>

Conclusions: We observed that in ACPE patients HLL on admission are no predictive of clinical failure but reduction of lactate independently of baseline levels is associated with clinical success.

### P4641

Is lactate a prognostic factor in acute cardiogenic pulmonary edema (ACPE)?

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ACPE is a common cause of admission to Emergency Dpt(ED). Lactate levels are a key factor in critical patients.

Aims: To investigate in ACPE, patients relationship between high lactate levels (HLL) on admission (T0) and clinical failure and lactate clearance (LC) calculated in first hours(T1)and clinical failure.

Methods: Prospective, observational, multicentric, web-based study on ACPE patients admitted to18 EDs. HLL: >2mmol/L. LC: (LactateT0–LactateT1)/Lactate T0. Clinical failure: in-hospital mortality, ACPE mortality and IOT.

Results: From May2009 to June2011, 475 patients were enrolled. 46patients were in clinical failure. Table1 shows data on admission. There was a significative difference in lactate level on admission. We calculated LC in 392patients. 42patients were clinical failure. There was a significant difference between LC in clinical success (0.31±0.66) and in clinical failure (0.08±0.50).

Conclusion: Lactate levels are a key factor in critical patients.

### P4642

Aminophylline increases ventilation and abdominal muscle contractility in awake canines

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Aminophylline (Amino) is still used in treatment of COPD. However, effects of Amino on ventilation and respiratory muscles are uncertain. Utilizing implants in awake canines, we examined the effects of Amino on costal diaphragm (Jagers et al. Resp Phys, 2009). Here we study the effect of Amino on abdominal muscles of expiration, by measurement of the transversus abdominis (TA).

Sonomometry transducers and EMG electrodes were implanted in the left TA. After recovery, the animals were studied awake, breathing through a mask. Airflow, ETCO₂, heart rate, muscle length, and moving average EMG were recorded during room air, and CO₂ stimulation, before and after Amino. Output included breath-by-breath breathing pattern, muscle shortening, peak EMG, PaCO₂ and heart rate. Results are shown at room air and 3 levels of CO₂.

For N=6 dogs (mean wt 29.8 kg) studied after 25 days, minute ventilation, tidal volume, and respiratory frequency increased significantly with Amino, during room air, and CO₂ stimulation, before and after Amino. Output included breath-by-breath breathing pattern, muscle shortening, peak EMG, PaCO₂ and heart rate. Results are shown at room air and 3 levels of CO₂.

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Conclusions: We observed that in ACPE patients HLL on admission are no predictive of clinical failure but reduction of lactate independently of baseline levels is associated with clinical success.

### P4643

Severity of ventilator induced lung injury does not contribute to ventilator induced diaphragmatic dysfunction

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Mechanical ventilation (MV) is a life-saving intervention for patients with respiratory failure. Even 12h of MV can promote diaphragmatic contracture dysfunction and atrophy (referred to as ventilator-induced diaphragmatic dysfunction, VIDD). The pathophysiology remains unclear but could be linked to inactivity, the physiological impact of positive pressure ventilation (PPV) on the diaphragm and/or ventilator-induced lung injury (VILI).

We tested the hypothesis, if negative pressure ventilation (NPV) compared to PPV will diminish VIDD.

The concomitant influence of VILI on VIDD was also examined.

Rats were ventilated with either PPV or NPV or breathed spontaneously (control) for 12h.

We measured diaphragmatic contracture properties, fiber size and markers of oxidative damage. Lungs were histologically examined and cytokine levels were assayed in bronchoalveolar lavage for evidence of VILI.

Compared to control, both PPV and NPV resulted in significant oxidative damage to the diaphragm along with fiber atrophy and contracture dysfunction. No significant differences existed in these measures between PPV and NPV groups. Both the PPV and NPV groups experienced VILLI, graded by histologic scores or cytokines. Note, that the severity of VILI varied between animals within both the PPV and NPV groups. Nonetheless, the severity of VILI was not significantly correlated with the degree of VIDD.

Both PPV and NPV promote VIDD and VILI. The magnitude of VILI is not correlated with the degree of VIDD. Although these findings do not eliminate the possibility that VILI may play a role in VIDD, our results are consistent with the concept that diaphragmatic inactivation as major contributor to VIDD.

### P4644

Contributions of rib cage (RC) and abdomen (AB) to tidal volume are useful indicators for the assessment of difficult-to-wean patients

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Respiratory muscles impairment is an important determinant of the need for mechanical ventilation (MV) in difficult-to-wean patients. We investigated whether the relative contribution of rib cage (RC) and abdomen (AB) to tidal volume was a useful indicator of successful weaning from MV. The contribution of RC and AB volume changes to tidal volume (Vi) were measured by opto-electronic plethysmography in 7 difficult-to-wean patients, during 20° of MV and 20° of spontaneous breathing (SB) after disconnection from MV.

The contribution of RC and AB volume changes to tidal volume (Vi) were measured by opto-electronic plethysmography in 7 difficult-to-wean patients, during 20° of MV and 20° of spontaneous breathing (SB) after disconnection from MV.
Recordings were repeated at 3 weaning stages: A) tracheostomy and invasive ventilation; B) tracheostomy and non-invasive ventilation (NIV); C) decannulation and NIV. The compartment with the highest % contribution to VT at the start of weaning (stage A) was defined as predominant compartment (PC), the other as secondary compartment (SC). PC was the rib cage in 5 patients and AB in 2. During SB, the contributions of PC and SC became progressively similar from stage A to C, with no significant differences at stage C (see figure).

Our results show that in difficult-to-wean patients the contribution to tidal volume of RC and AB becomes progressively more homogeneous as MV dependency decreases during weaning. Accurate monitoring of RC and AB contributions to VT provides therefore useful indications for weaning assessment.

### P4645

**Abdominal muscle action during sustained hypoxia**

**Authors:** Michael J1, Masato Katagiri1, Teresa Kieser1, Paul Easton1. 1. Department of Critical Care Medicine, University of Calgary, AB, Canada;

**Introduction:** Classical studies suggest that expiratory neuronal activity is inhibited by hypoxia, and action of expiratory muscles during hypoxia is controversial. Isocapnic hypoxia sustained 20-60 minutes elicits a biphasic ventilatory response (roll-off), with initial peak followed by decline to a plateau. We demonstrated during sustained hypoxia, parasternal muscle activity rolls off with ventilation (ERJ 2011;38.S55).

**Aim:** To study ventilation and action of the abdominal expiratory muscle, Transversus Abdominis (TA), during sustained hypoxia in awake canines.

**Methods:** After implantation of somoniconometry transducers and EMG electrodes in TA, and full recovery, we measured airflow, SpO2, ETCO2, many EMG and shortening (SHORT) of TA, during room air breathing (BASE) followed by 25 minutes of isocapnic hypoxia (mean 79.9% SpO2). The canines were awake, breathing through a 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=9 (mean 28.7 kg, 27 days post implant), minute ventilation and tidal volume increased significantly from BASE to PEAK, then decreased to PLATEAU (p<0.01). Concurrently, mean EMG and SHORT of TA increased significantly from BASE to PEAK, then attenuated to PLATEAU (p<0.01).

**Conclusion:** During sustained isocapnic hypoxia, the abdominal expiratory muscle, TA, is markedly activated during initial hypoxia, then attenuated with prolonged hypoxia.

### P4646

**Transthcale lung ventilation with a manual respiratory valve with a variable flow**

**Authors:** Dusan Pavlovic, Wolfgang Fischer. Anesthesiology, Universitätmedizin, Greifswald, Germany

In cannot-intubate, cannot-ventilate situations, a lung ventilation through a thin transthracheal cannula may be attempted. However, it may be impossible to achieve sufficient ventilation if the lungs are spontaneously emptying and dangers of barotrauma may occur. Here we present a valve [1] as a bi-directional manual respiratory pump which low flow during inspiration (by reducing gas supply to the valve) and increased flow during expiration, by increasing gas supply to the valve, permitted more effective venruri effect and efficient expiration, with low gas consumption.

The effectiveness of the valve was tested in vitro. The valve permitted to shorten the expiratory time and achieve higher minute volumes (i.e. volumes of 7L/min of gas or higher), as compared with the ventilation with the similar transthracheal cannula without variable flows (volumes achieved were about 4L/min). Variable flow provided shortening of the inspiratory time and efficient expiratory aid, and permitted LE ratios of 1:1, or even the inverse ratio ventilation. Satisfactory lung ventilation can be assured with transthracheal ventilation with a bidirectional manual respiration valve with variable gas flow.

**Reference:**


### P4647

**Effects of anesthesia, muscle paralysis and controlled ventilation on gas exchanges evaluated by DLCO and pulmonary surfactant protein B**

**Authors:** Fabiano Di Marco1, Daniele Bonacina1,1, Emmanuele Vassena2, Elena Pitino2, Piergiuseppe Agostini3, Stefano Centanni1, Roberto Fumagalli1. 1. Anestesia, Rianimazione, Polmonare e Cardiocircolatorio, Università degli Studi di Milano, Italy; 2. Anestesia Rianimazione, Azienda Ospedaliera San Gerardo, Università Milano-Bicocca, Monza, Italy; 3. Scienze Cardiovascolari, Università di Milano, Italy; 4. Anestesia e Rianimazione Ospedale di Niguarda, Università Milano-Bicocca, Milano, Italy

A recent study demonstrated that patients with no evident pulmonary disease, after at least 24 hours of mechanical ventilation, show a significant worsening of pulmonary gas exchange evaluated through DLCO (diffusing capacity of the lung for carbon monoxide). This worsening may be caused by an early alteration of alveolar-capillary membrane caused by mechanical ventilation itself, as previously demonstrated on animal models. We evaluated, in patients with no pulmonary diseases undergoing elective surgery, the effect of anesthesia, muscle paralysis and invasive controlled ventilation on DLCO, and the plasmatic levels of pulmonary surfactant protein B (SPB), an alveolar-capillary membrane anatomical damage maker. To date we enrolled 11 patients. In comparison to pre-surgery data, we found, just after anesthesia and paralysis, a significant reduction of DLCO (from 15.6±4.8 to 8.2±2.1 mL/mm Hg·1min-1·L-1, p<0.001), due to a reduction of both lung volume (end-expiratory lung volume, EELV, from 2.8±1.3 to 1.5±0.6 L, p<0.001), and the coefficient of diffusion (KCO, from 4.5±8 to 3.7±7 mL/mm Hg·1min-1·L-1, p=0.032). After this point DLCO, EELV, and KCO did not change significantly at 1 and 3 hours of surgery. Our preliminary results show that anesthesia and paralysis themselves can impair gas exchange, through an alteration not only limited to lung derecruitment. The precocity of this phenomenon, however, does not support the hypothesis of a biological effect” on the alveolar-capillary membrane, but a physical effect”, with no modification after 3 hours of invasive controlled ventilation. The SPB analysis is still ongoing.

### P4648

**Prognostic factors of COPD patients admitted in ICU for acute exacerbation requiring invasive ventilation**

**Authors:** Sabrina Lenel1, Julien Moncondrut, Vincent Jounieaux, Claire Andrejak. 1. Respiratory Diseases, Teaching Hospital, Amiens, France

**Background:** For patients with chronic obstructive pulmonary disease (COPD), the first acute exacerbation requiring mechanical ventilation is a breaking point in the disease.

**Methods:** We conducted a retrospective study to estimate the cumulative survival
of COPD patients after their first intubation and the prognostic factors of these patients.

Results: Between January 2000 and December 2010, 110 patients (50.9% stage III and 30.6% stage IV according to GOLD) were admitted in intensive care unit (ICU) for acute exacerbation of their COPD. The main aetiologies of the acute respiratory failure were pneumonia (n=40) and acute cardiac failure (n=30). ICU mortality was 22% and the median survival time was 68 months. In cox multivariate analysis, three independent prognostic factors were found: admission in ICU for proved infectious exacerbation (HR=1.83; 95% CI [1.01-3.34], p=0.047), GOLD Stage III and IV (HR=3.78; CI 95% [1.44-9.92], p=0.007) and acute renal failure (HR=5.79; CI 95% [3.01-11.20], p<0.0001).

Conclusion: Cumulative survival of COPD patients were with acute respiratory failure depends mainly on severity of COPD, exacerbation aetiology and associated acute renal failure.

482. Paediatric respiratory epidemiology. Wheeze: where, how and why?

P4649 Secular trends in childhood obesity, asthma, eczema and hayfever over 45 years
Sarah Smith1, Lorna Aucott2, Nara Tagnyeva1, Leone Craig3, Gealdine McNeill1, Steve Turner1 1Child Health, University of Aberdeen, United Kingdom; 2Public Health, University of Aberdeen, United Kingdom; 3Public Health Nutrition Research Group, University of Aberdeen, United Kingdom

Background: The childhood asthma “epidemic” which took place during the 1980s and 1990s is at least partly explained by changes in lifestyle. Childhood obesity prevalence has also risen, reflecting lifestyle changes. Here we tested the hypothesis that the rise in asthma prevalence in the population paralleled that in obesity.

Methods: A history of asthma, hayfever, eczema and wheeze in the last three years was obtained in 1964, 1989, 1994, 1999, 2004 and 2009. Prevalence of overweight and obesity (IOTF BMI cut-offs equivalent to 25 and 30 at age 18 years) were determined from a separate whole population survey of height and weight at school entry in children in Aberdeen and Aberdeenshire born between 1969 and 2005.

Results: Asthma and related outcomes were determined in 17,951 children in the six surveys and in these years height and weight were available in 29,348 children in the separate study. The prevalence of asthma was between 4 and 28%, for eczema between 5 and 34%, for hayfever between 3 and 27%, for recent wheeze between 10 and 28% and for obesity between 1 and 4%. There were correlations between prevalence at each time point for obesity and asthma (r=0.83, p=0.04), eczema (r=0.94, p=0.005) and hayfever (r=0.94, p=0.005) but not for wheeze. There were no correlations between overweight and outcomes.

P4650 Comparison of two respiratory surveys in an unselected schoolchildren population: 1998 and 2011
Anna Maria Rozzono, Savy Martella, Francesca Ruggeri, Lorenza Chiassi, Anna Rita Mazzotta, Francesco Biagiarelli, Mario Barroto, Maria Pia Villa. NEMSOS, Pediatric Unit, Sant’Andrea Hospital, Faculty of Medicine and Psychology, University “La Sapienza”, Rome, Italy

Objective: To evaluate the prevalence of respiratory symptoms, atopy, and environmental factors in two different populations of Italian schoolchildren studied in 1998 and 2011 in Ronciglione (VT, Italy).

Methods: Data on children was drawn from surveys in the same elementary school 13 years apart. A modified version of the ATS questionnaire for respiratory symptoms was completed by parents that sought on child's history respiratory and smoke exposure. Measurements included spirometry, exhaled nitric oxide, and skin-prick testing. Atopy was defined by at least a positive skin wheal of at least 3 mm.

Results: The 396 children were found similarly distributed by age and sex. (1998 Survey: 9.8±0.7yr, 86 males; 2011 Survey: 9.3±0.9 yr, 111 males). Also similar were the prevalence of reported asthma diagnosis (1998: 13% vs 2011: 10%), exercise-induced asthma, rhinitis, wheeze or cough in the past 12 months and smoke exposure. The 2011 Survey yielded a significant increase of bronchitis in the last 12 months (42.9% vs 14.6%, p<0.000), borderline for pneumonia (4.5% vs 1.0%, p=0.067). Prevalence of atopy in 2011 was similar to that of 1998 (32.3% vs 25.8%). No different functional measurements were observed.

Conclusion: Our data do not support an increase of asthma prevalence among schoolchildren of central Italy in the past 13 years. The concomitant mild decrease of reported asthma and the increase of bronchitis in 2011 could be explained by a shift in medical criteria and parent’s disease perception.

P4651 Elective caesarean section affects the risk of asthma medication in children up to five years of age
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It has been hypothesized that elective caesarean section is related to an increased risk of asthma due to lack of labour and delayed microbial colonization. Few studies have distinguished between elective and emergency caesarean sections and the findings have not been consistent. Some studies have also observed a risk associated with vacuum extraction.

Method: We examined the association between mode of delivery and retrieval of asthma medication in children up to five years of age. The included children were born in Sundvall, Sweden between 1989 and 2005. The inclusion criteria were asthma medication up to 5 years of age. The associations between emergency caesarean section or vacuum extraction and asthma medication in the firstborns could be caused by residual confounding.

Results: Analyses of first-borns demonstrated that elective caesarean section was associated with an increased risk of ICS use in both age groups. The increased risk remained in the sib pair analysis of 2-5 year olds (OR=1.21) and was partly explained by shorter period of gestation (aOR=1.12). The sib pair analysis could not confirm any association between elective caesarean section and ICS use in 6-9 year olds. Emergency caesarean section and vacuum extraction had some association with asthma medication in the analyses of first-borns but all associations disappeared in the sib pair analyses.

Conclusion: Elective caesarean section contributed to a modestly increased risk of asthma medication up to five years of age. The associations between emergency caesarean section or vacuum extraction and asthma medication in the firstborns could be caused by residual confounding.

P4652 Pregnancy complications and respiratory outcomes in very preterm infants
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Very preterm infants have a high mortality and morbidity, due to a combination of
immaturity per se, and of the underlying pathology causing preterm birth. The role of prenatal infection on increasing the risk of bronchopulmonary dysplasia (BPD) is still unconfirmed.

Aim: To test the hypothesis that infection/inflammation disorders (I) (prelabor premature rupture of membranes, spontaneous preterm labor, infection and hemor- rage) and hypertensive disorders (H) (maternal hypertension and intrauterine growth restriction) are differently associated to in-hospital mortality and BPD.

Methods: A population-based prospective cohort of 2085 singleton infants 23 to 31 weeks gestational age (GA) born in 6 Italian regions in 2003-2005 (ACTION study), was analyzed. Infants born of mothers with H (31%) were contrasted with those born after I (63%) with respect to mortality and BPD. Multivariable logistic analyses (generalized estimating equations) were used.

Results: Mortality was 14.3%, with 48.7% of deaths occurring in the first 5 days of life, largely due to respiratory causes. Infants born after H had more respiratory distress syndrome than the group (odds ratio (OR)=1.41, 95% confidence interval (CI): 1.1-1.8), adjusted for GA, sex and antenatal steroids. 12.8% of neonates had BPD. After adjustment for GA, H disorders had a higher risk of mortality (OR=1.4, 95% CI 1.0-2.0) and of BPD (OR=2.5; CI 1.8, 3.6). Further adjustment for maternal age, education, citizenship, and antenatal steroids did not change the results.

Conclusions: Our results support the hypothesis that pathogenetic mechanisms involving the regulation of lung/airways size and vessels are more important than I in the development of BPD.

P4653 Paracetamol in pregnancy and risk of wheezing in offspring: Causation or bias? Franca Rusconi, Lorenzo Richiardi, Enrica Migliore, Daniela Zagna, Claudia Galassi, Tiziana Nannelli. Unit of Epidemiology, A Meyer Children’s University Hospital, Florence, Italy. University of Florence, Italy. Unit of Cancer Epidemiology, University of Turin. CERMS, CPO-Piemonte, Turin, Italy. 3Unit of Cancer Epidemiology, S. Giovanni B University Hospital, CPO-Piemonte, Turin, Italy. 4Department of Public Health, University of Florence, Italy

Background: Many but not all studies have suggested an association between paracetamol (P) use in pregnancy and wheezing in childhood.

Objective: To assess the relationship between P use in pregnancy and wheezing in offspring in an Italian mother and child cohort (NINFIA/CAPE cohort, www.progonetitinafe.it). To evaluate the potential role of confounding by indication of P use.

Methods: Infants born from 1076 mothers who used P were contrasted with those born from mothers with no use of P (701) with respect to wheezing at 6-18 months of life. P use was assessed during pregnancy and 6 months after delivery, while wheezing was assessed 18 months after delivery.

Results: The overall prevalence of wheezing was 25% and it was more common among infants exposed to P in pregnancy (Relative risk (RR)=1.23, 95% confi- dence interval (CI): 0.98-1.54). Adjustment for ever diagnosis of maternal asthma (prevalence: 7.6%) did not change the association. After further adjustment for maternal respiratory diseases in pregnancy (asthma episodes, influenza like illness, bronchitis), maternal smoking and education, child sex and siblings, the RR for wheezing was 1.06 (CI 0.84-1.34). When we analyzed women who suffered from headache, migraine or backache versus all the others, the risk of wheezing in offspring was similar for mothers who used and for those who did not use P in pregnancy for these diseases (RR 1.28; CI 0.85-1.91 versus 1.35; 1.03-1.76).

Conclusions: The association found between P use in pregnancy and wheezing in offspring disappeared after adjustment, raising a problem of confounding. A non-causal relationship is also suggested by the lack of increased risk of wheezing for P use in “non-respiratory” diseases.

P4654 How do patterns of wheeze change over the first 14 years of life? Amina D可视化1 , Marie-Pierre Strippoli2 , Ben Sypress3 , Caroline Beardsmore4 , Erol Gaillard5 , Claudia Kuehni6 . 1Institute of Social and Preventive Medicine, University of Bern, Switzerland. 2Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom. 3Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Aim: Only few studies described changes in clinical patterns of wheeze in children over a wide age range. This study aimed to describe reported symptom patterns of wheeze from infancy to adolescence. When designing questionnaires and planning studies, such differences in patterns of wheezing illness by age should to be taken into account.

Methods: In a population-based cohort study in Leicestershire, UK, we assessed how the following symptoms became more frequent with increasing age: shortness of breath (increasing from 54% at age 1 to 85% at age 14), wheeze apart from colds (32% to 61%), exercise-induced attacks (26% to 71%) and allergen-induced wheezing (5% to 65%).

Conclusions: We found significant age-related changes in wheezing patterns from infancy to adolescence. When designing questionnaires and planning studies, such differences in patterns of wheezing illness by age should be taken into account.

Funding: SNF PDMP5-123162, SNF 3000B0-122341. Asthma UK 070648.

P4655 Automated identification of asthma patients within an electronic medical record database using machine learning Mariellen Enkelkes1, Zubat Afzal1, Hentie Janssen2, Jan Keus1, Martin Schuermeier3, Katja Verhamme3, Mirjam Starrenboom1. 1Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands. 2Pediatric Pulmonology, Erasmus University Medical Center, Rotterdam, Netherlands.

Background: Use of electronic medical record (EMR) databases for epidemiological research on asthma/COPD performs well. The optimal ML method depends on the research question e.g. incidence/prevalence studies require a method with a large Sp, while outcome studies require a large Sp.

Methods: From the IPCI database, a GP database with medical records of >1 million patients, all potential asthma patients, aged 6-18 years between 2000-2011, were identified with a broad automated search on asthma codes, free text and asthma drugs. First, a random sample (n=5039) of all potential cases (n=64327) was manually reviewed by 2 MDs and categorized according to a predefined algorithm. Second, based on this sample set, ML recognizes complex patterns to automatically generate decision trees for case identification. Training and testing was done by 5-fold cross validation.

Results: The sample set consisted of 6% definite, 24% probable, 2% doubtful cases and 68% non-cases. Depending on the sampling strategy, the positive predictive value (PPV) varies from 0.11-0.26, sensitivity (Sn) 0.57-0.94 and specificity (Sp) 0.52-0.89 for definite cases (diagnosis by specialist). For probable cases (diagnosis by GP) PPV varies from 0.49-0.51, Sn 0.84-0.86 and Sp 0.69-0.73.

Conclusion: ML for automatic identification of asthma cases in a huge EMR database performs well. The optimal ML method depends on the research question e.g. incidence/prevalence studies require a method with a large Sp, while outcome studies require a large Sp.
P4657
Asthma and respiratory morbidity thirty years after early childhood bronchiolitis or pneumonia
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Background: Recent studies have suggested that asthma in adulthood has its origin in early childhood.

Aims: To evaluate asthma occurrence and respiratory health related quality of life in adults after bronchiolitis or pneumonia in infancy.

Methods: A group of patients were followed since hospitalized for bronchiolitis or pneumonia at age <24 months in 1981-82. At the age of 28-31 yrs, data on respiratory symptoms were collected by a posted questionnaire and Saint George’s respiratory questionnaire (SGRQ), from 60/78 former bronchiolitis and 24/46 pneumonia patients, and from 166 matched controls. The clinical study consisted of bronchialisation test and home peak expiratory flow monitoring. (48/62% and 22/48%) study subjects and 138 controls attended. Asthma was defined by two ways: current doctor-diagnosed and current self-reported (childhood asthma and current asthma-suggestive symptoms in adulthood; doctor diagnosed asthma included).

Results: Both current doctor-diagnosed asthma (31.9% vs. 11.6%; adjusted p=0.003) and self-reported asthma (36.2% vs. 15.2%; 0.004), as well as repeated on-demand use of bronchodilators (35.4% vs. 14.5%; 0.002) and regular use of inhaled corticosteroids (20.8% vs. 8.7%; 0.023) were more common in the former bronchiolitis group than in controls. Both former bronchiolitis and pneumonia patients had higher total scores in SGRQ than controls: bronchiolitis (median 4.3, IQ 2.75–9.0 8.3; p<0.001), pneumonia (4.9, 1.5–15.5; 0.002), controls (1.0 0.5–3.5)

Conclusion: After hospitalization for bronchiolitis in infancy, an increased risk of asthma, more use of asthma medication and impaired quality of life by SGRQ can be demonstrated in adults at age 28-31 yrs.

P4658
Viral etiology of respiratory infections in children under 2 years old in Blida, Algeria
Rachida Boukari

Introduction: Viral ARI is a leading cause of morbidity and mortality in children especially in developing countries. Viruses are known as the predominant causative agents of ARI. In Algeria, few data concerning these agents are available.

The aim of our study was to investigate the incidence of 10 viruses in children under 2 years old admitted with ARI and to study demographic and clinical differences among different virus.

Methods: Children were prospectively enrolled between December 2010 and April 2011. A standardized questionnaire was used and a nose swab sample was collected. These samples were tested for the detection of RSV, Influenza virus (A/B), rhinovirus, Metapneumovirus, Influenza virus, Adenovirus, Parainfluenza 3- by RT-PCR. Demographic, clinical and laboratory data were obtained. Outcome measurements were age, breastfeeding history, clinical severity score, chest radio- logical findings.

Results: 117 children, median age 3 months, were recruited. A virus was detected in 82.9% of cases. The most frequently detected viruses were RSV (48.4%), rhinovirus (23%), Metapneumovirus (22%), adenovirus (7.5%), influenza (5%), parainfluenza 3 (2%). Co-infections were detected in 25 children (21.4%). Clinical features associated with RSV infection were similar to those of other respiratory viruses. Presenting symptoms between the RSV positive and RSV negative groups were similar.

Conclusion: This study underlines the importance of viral pathogens in ARI hospitalized children < 2 years old. RSV was the most frequently identified virus. HMPV and RV are also important cause of ARI in children in Algeria. Longer surveillance studies are needed to better understand the epidemiology of viral ARI.

P4659
Wheezing and pneumonia during the first year of life: An international epidemiological approach
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Introduction: Acute respiratory infection (ARI) is a leading cause of morbidity and mortality in children especially in developing countries. Viruses are known as the predominant causative agents of ARI. In Algeria, few data concerning these agents are available.

The aim of our study was to investigate the incidence of 10 viruses in children under 2 years old admitted with ARI and to study demographic and clinical differences among different virus.

Methods: Children were prospectively enrolled between December 2010 and April 2011. A standardized questionnaire was used and a nose swab sample was collected. These samples were tested for the detection of RSV, Influenza virus (A/B), rhinovirus, Metapneumovirus, Influenza virus, Adenovirus, Parainfluenza 3- by RT-PCR. Demographic, clinical and laboratory data were obtained. Outcome measurements were age, breastfeeding history, clinical severity score, chest radio- logical findings.

Results: 117 children, median age 3 months, were recruited. A virus was detected in 82.9% of cases. The most frequently detected viruses were RSV (48.4%), rhinovirus (23%), Metapneumovirus (22%), adenovirus (7.5%), influenza (5%), parainfluenza 3 (2%). Co-infections were detected in 25 children (21.4%). Clinical features associated with RSV infection were similar to those of other respiratory viruses. Presenting symptoms between the RSV positive and RSV negative groups were similar.

Conclusion: This study underlines the importance of viral pathogens in ARI hospitalized children < 2 years old. RSV was the most frequently identified virus. HMPV and RV are also important cause of ARI in children in Algeria. Longer surveillance studies are needed to better understand the epidemiology of viral ARI.

Conclusions: In infants who had BN during the 1st year of life, there are some risk factors which are different for WZs and WZ+.

P4660
Risk factors for severe bronchiolitis – A retrospective study
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Introduction: Bronchiolitis is a common disease in children under 2 years old causing ER presentation and sometimes admission. Severity of bronchiolitis (do to acute respiratory failure) accounts for admission criteria. Children with one or more risk factors for severe bronchiolitis (prematURITY, dysmaturity, environmental factors, neurological disease, cardiac disease, airways anomalies, immune deficieny, chronic lung disease, age under 3 months, formula feeding, RSV infection) are among those usually admitted.

Objectives: To reveal the correlation between admissions do to bronchiolitis and the presence of the risk factors.

Methods: A retrospective study was conducted, including 96 children under 2 years old, admitted in our hospital between November 2011 and January 2012. The admission criteria were Wang severity score for bronchiolitis (over 6). We have correlated the hospitalization lasting more than 5 days and/or the Wang score for severity over 10 with the number of risk factors.

Results: All 96 children admitted had at least one risk factor for severe bronchiolitis. Children with Wang score over 10 and hospitalization lasting more than 5 days (34 children) associated at least 2 risk factors, most frequent of them being being crowded living condition (94%), male sex (73.5%), prematurity (50%), age under 3 months (47%) and other comorbidities (29%).

Conclusion: Severity of bronchiolitis correlates with number of risk factors that coexist for the same child.

P4661
Correlation between nasal symptoms and lung function parameters in preadolescent children
Dinomios Spyrras, Anastasios Tziontios, Diamantis Chloros, Evangelia Nena, Anna-Betta Hanidich, Lazaros Sichelidiotis

Introduction: Allergic rhinitis is a frequent medical condition worldwide and it also influences considerably the children’s performance at school.

Aim: Correlation between the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire’s data and respiratory system functional parameters in children between 10 and 12 years old.

Methods: Parents of elementary school pupils in the Municipality of Polichni, Thessaloniki,Greece were asked to fill in the ISAAC questionnaire. All students underwent spirometry, sputum analysis, IgE and eosinophils in the peripheral blood, fraction of exhaled NO (FeNO) and skin prick tests. The control group consisted of those children with no rhinitis symptoms.

Results: 1150 children of 11 elementary schools were included in the study. 971 questionnaires were completed (participation rate: 84.4%). One hundred forty four students had at least one positive answer regarding rhinitis (14.8%). Of those, 20.8% presented with elevated IgE levels, 25.4% had increased blood eosinophils, 20.8% had high FeNO (>200ppb) and 45.1% had at least one positive skin prick test. Body mass index was higher in the rhinitis group (21.1±3.3 vs 20.1±1.8

Conclusions: In children who had BN during the 1st year of life, there are some risk factors which are different for WZs and WZ+.

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kg/m², p=0.019), while the spirometric and rhinomanometric data did not differ between the rhinitis and the control group. IAACQ questionnaire’s score was positively correlated with IgE concentration (p=0.002), eosinophils (p=0.037) and the number of positive skin prick tests (p<0.001).

Conclusion: Our study showed significant positive correlation between the ISAAC questionnaire’s data and allergic parameters. Therefore the ISAAC questionnaire is strongly recommended as a useful tool in primary pediatric care practice.

P4662 Belarus Ukraine Poland Asthma Study (BUPAS) – Prevalence of asthma, respiratory symptoms and allergic diseases in children

Grezegorz Brozek 1, Jan Zedla 1, Olga Fedotova 2, Andrei Shpakova 2, Leonid Hryshchuk 1, Andrei Strizhak 4, Joshua Lawson 5, Donna Rennie 5

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Background: Prevalence of asthma and other allergic diseases in children living in Belarus is unknown. The problem is better described in Ukraine and Poland, but more evidence is needed.

Aims: The objective of the study was to estimate the prevalence of asthma, respiratory symptoms and allergic diseases in children in Belarus, Ukraine and in Poland.

Method: The study was performed as a multicenter cross-sectional study. The study population was children aged 6-14 years randomly selected from Belarus (Grodno), Ukraine (Ternopil) and Poland (Silesia Region). Physician-diagnosed respiratory diseases and symptoms as well as allergic diseases were ascertained using the ISAAC questionnaire completed by the parents.

Results: A total of 13 371 children aged 6-14 years participated in the study. The response rate was 76.7%. Groups were similar in terms of gender and age (p>0.05). Between-country differences were statistically significant (p<0.05) for all comparisons, except chronic and spastic bronchitis as well as hay fever in case of Ukraine/Belarus comparisons.

Conclusions: The findings show a large between-country differences and low prevalence of asthma and allergic diseases in children of Western Belarus and Ukraine.

P4663 Allergic diseases in urban/rural environment: Are there differences in diet, prevalence of asthma and allergic diseases in children of Western Belarus and Ukraine

Leonid Hryshchuk 1, Andrei Strizhak 4, Joshua Lawson 5, Donna Rennie 5

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Background: Prevalence of asthma and other allergic diseases in children living in Belarus is unknown. The problem is better described in Ukraine and Poland, but more evidence is needed.

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Conclusions: The findings show a large between-country differences and low prevalence of asthma and allergic diseases in children of Western Belarus and Ukraine.
high frequency of obstruction upper and lower respiratory tracts, most of these children had recurrent episodes in history. We have found reduction frequency of wheezing in different years of observation from 23.1% to 21.5% (2006 – 23.1%, 2007 – 38.3%, 2010 – 39%, 2011 – 21.5% of children with AIRs). Also we registered high occurrence children with obstructive laryngotracheitis in 2006 – 42.5%, 2007 – 65.7%, 2010 – 50.4%, 2011 – 47% of children with AIRs. All children with wheezing with obstruction received standard treatment. **Conclusion:** Reduction of frequency of wheezing and obstructive laryngotracheitis in children admitted at children’s hospital is connected with introduction of modern principles of therapy obstruction of respiratory tract at a pre-hospital stage.

**489. Clinical diagnosis and treatment of adult asthma**

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While up to 50% of severe asthma patients have no evidence of allergy, IgE has been linked to asthma in epidemiological and immunopathological studies, irrespective of atopic status. Omalizumab (OMA), an anti-IgE monoclonal antibody, is reported to significantly benefit a subset of patients with poorly controlled severe persistent allergic asthma. Therefore biological and clinical effects of OMA were investigated in patients with refractory nonatopic asthma.

**Methods:** 41 patients with severe persistent asthma uncontrolled despite daily high-dose inhaled corticosteroids (with or without maintenance oral corticosteroids) plus a long-acting β2-agonist were randomized to receive OMA or placebo in a 1:1 ratio. Primary end-point was change in expression of high-affinity IgE receptor FceRI on blood basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks. The impact on lung function and clinical parameters was also assessed.

**Results:** When compared to placebo, OMA treatment resulted in a statistically significant reduction in FceRI expression on blood basophils and pDC2 (p < 0.001). The OMA group also showed an overall increase in placebo-adjusted predicted FEV1 compared to baseline (+9.9%; p=0.029). The placebo-adjusted absolute change in FEV1 with OMA was +250 ml (p=0.032). A trend toward improvement in global evaluation of treatment effectiveness scale and asthma exacerbations rate was also observed.

**Conclusion:** Omalizumab treatment may have a therapeutic role in severe nonatopic asthma. These findings support further investigation to assess the clinical efficacy of omalizumab in severe persistent nonatopic asthma. Funded by: Novartis Pharma SAS.

**490. Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control**

Mathieu Molinard1, Vincent Le Gros1, Isabelle Bourdeix1, 1Pharmacology, Victor Segalen University - INSERM U657, Bordeaux, France; 2CR&D, Novartis Pharma SAS, Rueil-Malmaison, France

Evolution of severe asthma after discontinuation of omalizumab (OMA) (Xolair®) for good asthma control is still not very well known. This study provides real-life data in this situation.

**Methods:** Observational, descriptive, cross-sectional, retrospective study in which 24 pulmonologists recorded data on patient and asthma characteristics during OMA treatment prescribed in patients with severe persistent allergic asthma uncontrolled despite best available therapies, and after OMA discontinuation (minimal follow-up required = 6 months), for all their patients in who OMA had been discontinued due to achievement of good asthma control.

**Results:** Data from 61 patients were collected [characteristics at OMA initiation: females 65.6%; mean age 40.7 yrs (min 6, max 82); mean asthma duration 22.3 yrs]. Mean duration of OMA treatment was 22.7 months (CL 95%: 19.4-26.0). Mean duration of good asthma control before discontinuation was 11.8 months (CL 95%: 12.0-18.1). Mean change in FEV1 under OMA was +13%. After OMA discontinuation, median follow-up duration was 9.2 months. Loss of control was observed in 34 patients (55.7%) for whom median time to loss of control was 13 months (CL 95%: 8.2-28.1). The % of patients with an observed loss of control were 69.2%, 59.1% & 45.7% respectively after 1 year, 1-2 years & >2 years of OMA treatment. OMA was reinitiated in 20 out of the 34 patients with loss of control; 14 were responders (70%), 4 not responders (20%) & 2 not yet evaluable (10%).

**Conclusion:** Proportion of observed loss of control depended on prior treatment duration. Most of patients were still responders after OMA reintroduction. Funded by: Novartis Pharma SAS.

**4904. Rhinovirus infection activates coagulation through eosinophilic airway inflammation**

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Introduction: Exacerbations in asthma are most commonly caused by rhinoviruses. Inflammatory conditions, like asthma, are known to activate hemostasis. Vice versa, a prothrombotic state in the lung can also induce or aggravate pulmonary inflammation.

**Hypothesis:** Rhinovirus infection activates coagulation in patients with asthma, but not in normal control subjects.

**Methods:** 14 patients with mild asthma and 14 healthy controls were nasally inoculated with rhinovirus type 16 (10 TCID50) using a validated method. Bronchoalveolar lavage fluid (BALF) was retrieved by bronchoscopy at t=0 and t=6 days. Microparticle-associated tissue factor(TF) activity in BALF was examined by a fibrin generation test (FGT). Three unrelated control cell complexes (TAX and nonatopic) Carcinomatous (ECP) and Cytologic (PCP) Activation of Coagulation in BALF were measured by immunoassay.

**Results:** On day 6 after rhinovirus infection, FGT in BALF became significantly shorter in asthma (t=1: 672s vs. t=6: 516s (medians); p=0.013), whereas there was no change in healthy controls (t=1: 695s vs. t=6: 707s (medians); p=0.75). At t=6 days, FGT correlated (Spearman) with TAX, eosinophils and ECP (r = -0.607, -0.483 and -0.628 resp., all p<0.01) and TAX and eosinophils and ECP (r = 0.482, 0.538, both p<0.05).

**Conclusion:** Rhinovirus infection significantly shortens the clotting time (FGT) when induced by microparticles isolated from BALF of asthma patients, reflecting an enhanced coagulant activity of TF (i.e., a prothrombotic state in BALF). These findings suggest a possible role of this coagulant activation during viral airway infection.

**4905. Exhaled air volatile organic compounds and eosinophilic airway inflammation in asthma**

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**Rationale:** Eosinophilic inflammation in asthma is predictive for responses to inhaled steroids. The application of sputum analysis is somewhat limited by the requirement of lab facilities and not directly available results. Exhaled air metabolomics is associated with eosinophilic inflammation in COPD (Fens et al. ERJ 2011). We hypothesized that breath volatile organic compounds (VOCs) can be adequate surrogate markers of airway inflammation in asthma.

**Aim:** To identify VOCs in exhaled air by gas chromatography and time-of-flight mass spectrometry (GC-TOFMS) that can discriminate eosinophilic asthma from non-eosinophilic asthma.

**Methods:** Breath samples were analysed by GC-TOFMS in 40 patients (>18yr) with moderate/severe asthma (GINA-criteria). All patients were non-smokers and required inhaled corticosteroids (>500mg FP or equivalent). Differential cell counts were measured in induced sputum. Correlation coefficients and corresponding p-values between the peaks and measured sputum eosinophils were calculated by univariate analysis (p-value<0.01).

**Results:** Sputum was successful in 36 patients, of which 21 patients had sputum eosinophils >3%. Linear regression analysis showed associations for 5 VOCs with sputum eosinophils. The correlation coefficients varied between 0.42-0.47. When excluding patients on oral corticosteroids (n=8), 8 VOCs were associated with sputum eosinophils with higher correlation coefficients varying between 0.49-0.62.

**Conclusion:** Exhaled air VOCs are modestly associated with sputum eosinophils.
in patients with moderate/severe asthma on (inhaled) steroids. This suggests that exhale breath analysis requires further optimisation in the assessment and monitoring of airway inflammation in asthma.

4696
IgE-autoantibodies and adipokines in patients with bronchial asthma and obesity
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The adipose tissue represents an important source of inflammatory cytokines with pro-allergic activity. We aimed to estimate the influence of obesity on the characteristics of autoreactivity and cytokine repertoire in patients with bronchial asthma (BA) as compared to allergic rhinitis (AR) and healthy.

Methods: Body mass index (BMI) was evaluated in 80 patients with AR and BA and 25 healthy people. By ELISA we measured serum level of C reactive protein (CRP), IgE-autoAbs to keratin, collagen type III and elastin and production of TNF-a and IL-1 from blood lymphocytes.

Results: Asthmatic patients with BMI >30 kg/m2 had elevated levels of CRP (744±28 ng/ml) and high spontaneous production of TNF-a (45±4 ng/ml) and IL-4 (9.5±2.8 ng/ml) in comparison with normal-weight patients and healthy (7.3±2.7 ng/ml, 3.4±0.6 ng/ml and 1.7±0.3 ng/ml accordingly). The group of obese asthmatics distinguished with highest levels of CRP (1560±28 ng/ml) and IgE-autoAbs to keratin and collagen III, which correlated with BMI (R=0.58) and AR. Serum leptin was overproduced in BA significantly among obese (57±28 μg/L) and showed no difference between healthy subjects independently from BMI (6±1±0.3 ng/ml).

Conclusions: Asthmatics with BMI > 30 kg/m2 show a special phenotype of disease with elevated serum leptin and pro-inflammatory markers, which needs to be managed and treated distinctly. Obesity is attended with higher generation of IgE-autoAbs, which can indicate the disturbance of immune regulation.

4697
Effect of bariatric surgery on asthma: 3 months follow-up
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Background: Asthma in obese subjects is poorly understood and the effect of weight loss on asthma control is not well described.

Aim: To investigate the effects of bariatric surgery on asthma control, quality of life and lung function.

Methods: We performed a prospective study in patients with confirmed diagnosis of asthma (±FEV1 <12% or PD20 <178 nmol/L = BHR) and non asthmatic patients undergoing bariatric surgery (BMI >35kg/m2, age 18-50y). Lung function, medication and quality of life were assessed at baseline and 3 months after bariatric surgery. Obese asthmatics who did not undergo bariatric surgery served as an additional control group.

Results: 35 asthma patients (O+A) and 50 non-asthmatics (O-A) underwent bariatric surgery. 17 asthma patients served as controls (NO+A). There were no differences in ACQ, AQLQ, FEV1, or FeNO between O+A and NO+A at baseline. BMI of NO+A (44±7kg/m2) was significantly lower than O+A (47±9kg/m2). After bariatric surgery, BMI decreased to 38kg/m2 in O+A, and BBH decreased significantly in O+A (80%) to 34%, p<0.003). In addition, use of ICS decreased with 50%. FEV1 improved significantly in O+A (mean 8.6 to 9.4, 6.96, p=0.011). Following surgery, ACQ and AQLQ significantly improved in O+A group (1.1 to 0.5, p=0.022), resp. 5.7 to 6.3 (p=0.004), whereas no change was detectable after 3 months in NO+A. ACQ and AQLQ were significantly better in O+A group compared to NO+A after 3 months (ACQ p=0.027, AQLQ p=0.002). No change in FeNO in any group.

Conclusion: Bariatric surgery improves lung function, asthma control and quality of life in patients with asthma and morbid obesity already after 3 months. So it can be speculated that weight loss is an important component of the management of obese asthmatics.

4698
Substitution of vitamin D in patients with moderate to severe persistent asthma: A randomized, placebo-controlled pilot study
Albrecht Breetenbichler1, Ursina Voit1, David Miedinger2, Jorg D. Leppiu2, Reto Krapf1. 1Pulmonary Division, University Department of Medicine, Kantonsspital Bruderholz, Bruderholz, Switzerland; 2Department of Medicine, University Hospital Basle, Basel, Switzerland

Background: Vitamin D3 stimulates glucocorticoid-induced IL-10 synthesis by regulatory T cells in patients with asthma. IL-10 is a potent antiinflammatory cytokine that can block asthmatic inflammation.

Objective: To study whether short-term calcitriol affects lung function and symptoms in patients with moderate to severe persistent asthma treated with a combination of long-acting beta-2-agonists and inhaled corticosteroids.

Methods: 20 outpatients (8m, 12f) with moderate to severe persistent asthma (mean age 58,4y, 36-83) were enrolled in this randomized, placebo-controlled, double-blind, double-dummy pilot trial with random crossover design. All were treated with a stable dose equivalent to ≥400 ng/day of budesonide and ≥12 μg/day of formoterol for at least 4 weeks. Patients were randomized to receive either calcitriol 1.0 μg once daily or placebo. Each treatment phase lasted for 4 weeks, interrupted by a 3-week washout period. Treatment effect was calculated by subtracting baseline values from end of treatment values and using a linear mixed effects model to correct for period and sequence effect.

Results: Baseline FEV1 was 69% pred. (±11; 9), 25-hydroxyvitamin D level 46.6 nmol/L (±28.1; 8.5). FEV1 increased by 1.4% (±7.5) during calcitriol compared to 0.2% (±5.5) during placebo treatment (p=0.64, n.s.); FEV1, bronchial hyperreactivity, peak flow, asthma symptom scores and use of short-acting beta-2-agonists were also not significantly different between calcitriol and placebo periods.

Conclusion: Calcitriol did not improve lung function and asthma symptoms in this short term pilot study (ClinicalTrials.gov number, NCT 00712205).

4699
BTS Difficult Asthma Registry: Effect of omalizumab dosing table expansion on size of population of severe persistent asthmatic patients potentially eligible for omalizumab therapy
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The dosing of omalizumab is determined by baseline serum total IgE and body weight. In 2010, the EU licence for omalizumab increased the maximum baseline total IgE in the dosing table from ≤700 IU/mL (‘Standard’ dose) to >700-1500 IU/mL (‘Expanded’ dose). Using data from the BTS Difficult Asthma Registry we evaluated the effect of this expansion on the size of the patient population with severe persistent allergic asthma potentially eligible for omalizumab therapy. 582 adult and adolescent patients were identified from all seven Specialist Centres that submit data to the Registry. Mean age was 21.4 (±18.6) years and mean IgE was 301 (±1546) IU/mL. With the expansion of the dosing table, the percentage increase in the pool of patients with severe persistent allergic asthma potentially eligible for omalizumab was less than 23%, when applying the omalizumab licence criteria (Population A). With the addition of the NICE criteria (Population B) an even smaller percentage increase in the patient pool was seen (Figure).

Figure 1. BTS = British Thoracic Society; SPT = skin-prick test; RAST = radioallergosorbent test; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist.

In conclusion, despite the expansion in license and application of NICE criteria, the change in the number of patients eligible for omalizumab treatment is relatively modest.
490. Exercise testing in disease

4700 Inspiratory resistive loading exacerbates calf vasconstriction in patients with coexisting COPD-CHF compared to COPD and healthy controls
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Rationale: Sympathetic overstimulation is a marker of chronic heart failure (CHF) and might also be present in advanced chronic obstructive pulmonary disease (COPD). Inspiratory resistive loading (IRL) can trigger a sympathetically-mediated metaboreflex which increases peripheral vascular resistance, leading to impaired blood flow. Coexistence of COPD and CHF is likely to potentiate these abnormalities.

Objective: To investigate the effects of IRL on calf blood flow (CBF) and resistance (CVR) in patients with COPD presenting or not with CHF as a co-morbidity and healthy controls.

Methods: Twelve patients with COPD on isolation (FEV1=42±14% pred), 10 patients with coexisting COPD-CHF (FEV1=46±10% pred, left ventricular ejection fraction<45%) and 10 age-matched controls breathed through an inspiratory resistance at 60% of maximal inspiratory pressure (MP) to task failure. CHF was measured by venous occlusion plethysmography.

Results: COPD-CHF had significantly lower MIP than COPD and controls (p<0.05). The former group, however, stopped earlier the IRL trials (185±35 s vs. 284±82 s vs. 365±88 s, respectively; p<0.01). COPD-CHF had lower CBF and higher CVR in this former group. In addition, IRL led to greater decrements in CBF and increases CVR in COPD-CHF compared to either COPD or controls (p<0.05). During IRL on controls was inversely related to MIP across the groups (r=-0.66, p<0.01).

Conclusions: CHF as a co-morbidity of COPD exacerbates peripheral vasconstriction induced by inspiratory muscle overloading. This might contribute to further impair muscle blood flow during exercise in this patient sub-population.

4701 Effects of exercise on ubiquitination and proteasome activity in skeletal muscle in COPD patients
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Objective: COPD patients have reduced exercise capacity and skeletal muscle function. The aim of this study was to investigate exercise effects on proteasome activity in skeletal muscle of COPD patients. We wanted to evaluate ventilatory limited and unlimited exercise by comparing whole body training against small isolated muscle training. The effects of oxidative stress and systemic inflammation were also evaluated.

Methods: In total, 21 patients with moderate to severe COPD were studied. Spirometry, peak oxygen uptake (VO2-peak), ubiquitin activity, proteasome activity, protein carbonylation and systemic inflammation were measured before and after a 10 week intervention fraction.<

Results: At baseline both groups did not differ in pulmonary function, fat free mass, or exercise capacity. Maximal workload and walking distance improved in both groups but to a greater extent in the hypoxic group (27.5 versus 10.5%, p<0.06; 23.7% versus 6.9%, p=0.01, respectively). Fiber cross sectional area and citrate synthase activity increased significantly in the normoxic group only (both p<0.05). Levels of phosphorylated AKT, p70S6K and GSK3 tended to increase with training in the normoxic group in favour of an upregulation of anabolism while decreased significantly in the hypoxic group (p=0.01). mRNA levels of anabolic genes (IGF1, MGF) and catabolic genes (MurF-1, Atrogin, Fas-F1 and -3, Myostatin) did not change with training in both groups.

We conclude that in COPD patients with chronic hypoxemia, pulmonary rehabilitation improved exercise capacity while the markers of muscle remodelling remained unchanged. It deserves to be studied whether changes in genes expression occurred earlier during rehabilitation in these patients.

4703 Distinguishing pulmonary hypertension in interstitial lung disease by ventilation and perfusion defects as measured by cardiopulmonary exercise testing
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Introduction: Pulmonary hypertension (PH) is common in interstitial lung disease (ILD) and is associated with worse prognosis. Comparing ventilation (VD) and perfusion defects (PD) on cardiopulmonary exercise testing (CPET) can detect PH, but has not been assessed in ILD.

Aims and objectives: We proposed using CPET to detect PH in patients with ILD by assessment of VD and PD by mixed expired CO2 (PeCO2) and end-tidal CO2 (PetCO2).

Methods: 75 patients with ILD referred for CPET were included who had pulmonary function tests, right heart catheterization, CPET all done within 4 months of each other. Data were assessed at rest, end of unloaded warm up (WU), ventilatory threshold (VT), and peak exercise (Pe) for PeCO2, PetCO2, PeCO2/PetCO2 and the activity pattern of PeCO2 versus PetCO2.

Results: ILD patients with PH demonstrated significantly lower PetCO2 and PeCO2 at all levels of exercise and low PeCO2/PetCO2 only at WU.

VD and PD in CPET in ILD patients

<table>
<thead>
<tr>
<th>Activity</th>
<th>PetCO2 (mmHg)</th>
<th>PeCO2 (mmHg)</th>
<th>PeCO2/PetCO2</th>
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</thead>
<tbody>
<tr>
<td>Rest PH</td>
<td>30.3</td>
<td>16.1</td>
<td>0.54</td>
</tr>
<tr>
<td>WU PH</td>
<td>35.7*</td>
<td>18.0*</td>
<td>0.51</td>
</tr>
<tr>
<td>VT PH</td>
<td>36.5*</td>
<td>20.7*</td>
<td>0.37*</td>
</tr>
<tr>
<td>No PH</td>
<td>37.9</td>
<td>22.7*</td>
<td>0.61</td>
</tr>
<tr>
<td>PE PH</td>
<td>28.5</td>
<td>18.5</td>
<td>0.66</td>
</tr>
<tr>
<td>No PH</td>
<td>37.9*</td>
<td>23.6*</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Activity pattern has marked changes with exercise in ILD patients with PH.
4704
Effects of sildenafil intake on the dynamics of skeletal muscle oxygenation at the onset of and recovery from exercise in CHF
Priscila Sperandio1, Mayron Oliveira1, Miguel Rodrigues1, Erika Trépont1, Dirceu Almeida2, L. Eduardo Nery1, J. Alberto Neder1, Department of Medicine, Division of Respiratory Diseases, Federal University of Sao Paulo, SP, Brazil; 2Department of Medicine, Division of Cardiology, Federal University of Sao Paulo, SP, Brazil
Rationale: Nitric oxide (NO) exerts an important role in temporally and spatially match microvascular O2 delivery (QO2sm) to utilization in the skeletal muscle.
Objective: To investigate the effects of increased nitric oxide (NO) bioavailability induced by sildenafil intake on muscle QO2sm to oxygen uptake (V'O2) matching at the transition to and from exercise in patients with chronic heart failure (CHF).
Methods: 10 males (ejection fraction= 27±6%) underwent a supra-gas exchange threshold exercise test to the limit of tolerance 1 hour after sildenafil (50 mg) or placebo intake. The dynamics of V'O2, fractional O2 extraction in the vastus lateralis (Δ[deoxygen-Hb+Mb]) by near infrared spectroscopy, and cardiac output (CO) were evaluated by non-linear regression procedures.
Results: Sildenafil increased exercise endurance compared to placebo by ~20%, an effect that was related to faster on- and off-exercise V'O2 kinetics (p<0.05). Active treatment, however, failed to accelerate CO dynamics (p>0.05). On-exercise [deoxygen-Hb+Mb] kinetics were slowed by sildenafil with a subsequent response “overshoot” being significantly lessened or even abolished. In contrast, [deoxygen-Hb+Mb] recovery was faster with sildenafil (~15%). Improvements in muscle oxygenation with sildenafil were closely related to faster on-exercise V'O2 kinetics and greater increases in exercise capacity (p<0.05).
Conclusions: Sildenafil intake enhanced on- and off-exercise QO2sm to V'O2 matching and V'O2 kinetics with positive consequences on exercise tolerance in CHF. The lack of effect on CO suggests that improvement in blood flow to and within skeletal muscles underlies these effects.

4705
Effects of proportional assist ventilation on skeletal muscle reoxygenation after high-intensity exercise in chronic heart failure
Andrey Borehi-Silva1, Claudia Carrascossa, Cristiano Oliveira, Adriano Barroco, Danilo Berton, Debra Vilaça, Edgar Lira-Filho, Dirceu R. de Almeida, Luiz Eduardo Nery, José Alberto Neder. Physiotherapy Department, Federal University of Sao Carlos, SP, Brazil; 2Pulmonary Function Department, Federal University of Sao Paulo, SP, Brazil
Background: Respiratory muscle unloading can enhance the haemodynamic responses to exercise thereby allowing a closer matching between skeletal muscle O2 delivery and utilization in patients with chronic heart failure (CHF).
Objective: To assess whether proportional assist ventilation (PAV), compared to sham ventilation, would improve the dynamic coupling between microvascular O2 delivery and O2 uptake (V'O2) during recovery from heavy-intensity exercise in patients with CHF.
Methods: Twelve patients with CHF (NYHA class II and III and left ventricle ejection fraction= 2h±6%) underwent two high-intensity, constant-workrate (80% peak) cycle ergometer tests receiving PAV or sham ventilation. Off-exercise kinetic of the “primary” component of V'O2, an index of fractional O2 extraction by near infrared spectroscopy (~[deoxygen-Hb+Mb]) in the vastus lateralis) and cardiac output (QT) by impedance cardiography were assessed.
Results: PAV speeded the recovery kinetics of all variables compared to sham ventilation.
Table 1: Kinetic parameters for sham and PAV ventilation

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>PAV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V'O2 (s)</td>
<td>76.3±17.5</td>
<td>55.9±27.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ[deoxygen-Hb+Mb] (s)</td>
<td>42.3±6.9</td>
<td>31.2±5.9</td>
<td>0.008</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>85.8±15.4</td>
<td>46.7±6.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are mean±SE. V'O2 = Pulmonary oxygen uptake, t = constant time, MRT = mean response time, QT = cardiac output, Δ[deoxygen-Hb+Mb] = variation of deoxygenhemoglobin + myoglobin concentration by NIRS.

Conclusions: These data indicate that PAV has beneficial effects on recovery of muscle metabolism and central haemodynamics after high-intensity exercise in CHF patients.
Financial Support: FAPESP

4706
Dynamic hyperinflation and effects of pursed lips breathing on chest wall kinematics during exercise in patients with asthma
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To assess the effects of exercise on lung volumes and the influence of Pursed Lips Breathing (PLB) on operational lung volumes in asthma patients. In 14 patients, 33.9±10 years old, FEV1: 65.7±18.6, lung volumes were assessed by opto-electronic plethysmography. Two incremental submaximal cycling tests (ISET) sets based on 3 min. rest, 1 min. unloaded pedaling and 30w increase in workload every min. during free breathing and PLB were done. We identified two patterns of changes in operational volumes at 100%max. workload in free breathing Patients that increase End Expiratory Lung Volume (EELV) ΔEELV=0.27±0.5L and developed Dynamic Hyperinflation (DH),hyperinflators (HG,n=6) and patients that decrease EELV euvoluences (EVE,n=4) ΔEELV=-1.07±0.8 L,Rib cage pulmonary (RCP) was the main responsible to increase in EELV in HG Variation of End Inspiratory Lung Volume (ΔEILV) in HG was significantly different from EG, 1.5±0.8 vs 0.31±0.4 PLB induced changes in EELV in both groups during in chest wall and RCP compartment. In abdominal compartment ΔEILV significantly increased with PLB in all moments except at 50%max. workload.PLB induced changes on EELV in RCP compartment at 100%max. workload in EG and at 50%max. workload, 1st and 2nd recovery time in HG.
Exercise induces different changes in operation lung volume in patients with asthma. PLB modulate breathing pattern and improve operational lung volumes.

4707
Reliability of the 6-minute walk test in patients referred for pulmonary rehabilitation
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Introduction: The 6-minute walk test (6mwt) has been widely used as an easy assessment of physical performance and as an outcome parameter in pulmonary rehabilitation (PR). However, uncertainty remains about the need to perform multiple tests because of the possible occurrence of a learning effect contributing to the reliability of the test.
Aims and objectives: The aim of this study was to evaluate the reliability of three consecutive 6mwt in a large group of patients referred for PR.
Methods: From June 2006 to December 2011, 1112 patients referred to a PR center performed a 6mwt on 3 consecutive days (t1-t3) as part of the routine pre–PR assessment. Tests were performed during a clinically stable period according to the guidelines of the American Thoracic Society. Retrospectively, absolute differences between the tests were evaluated and correlation coefficients between the three tests were calculated.
Results: The mean distance of the 6mwt (mean in SD) was 352±122 m on t1, 378±124 on t2 and 393±125 m on t3. All differences between the tests were statistically significant (p<0.001). 51% of patients walked their maximal distance on t3 but only 8% on t1. When considering a minimal clinical important difference (MCID) of 54 m, 35% of the patients showed differences beyond the MCID in favour of t3 when compared to t1, 11% when compared to t2 and 22% when t2 was compared with t1. Significant correlations exist between t1-t2 (r=0.933, p<0.001), t1-t3 (r=0.912, p<0.001), t2-t3 (r=0.851, p<0.001).
Conclusion: These data show that a single 6mwt is not reliable in these patients with severe pulmonary disease. At least two 6mwt are required to obtain a reliable test.
4708 Bronchoscopy and endobronchial biopsies in children: Useful or not? Fardous Heida 1, Marielle Pijnenburg1, Leonie Vanlaeken2, Wim Timens1, Bart Rottier1. 1Pediatric Pulmonology, University Medical Center, Groningen, Netherlands; 2Pediatric Pulmonology, Erasmus Medical Center, Rotterdam, Zuid-Holland, Netherlands

Introduction: Bronchoscopy and endobronchial biopsies are diagnostic tools in the evaluation of difficult asthma and other paediatric airway diseases. The yield of these procedures in clinical practice is uncertain. Therefore our aim was to evaluate if bronchoscopy and endobronchial biopsies change management.

Methods: Retrospectively we collected data on diagnosis and treatment before and after bronchoscopy in all children undergoing bronchoscopy with endobronchial biopsies between 0 and 18 yrs. Difficult asthma was defined as uncontrolled asthma despite high dose ICS dose and LABA. In endobronchial biopsies reticular basement membrane (RBM) thickness was measured.

Results: Of the 74 children (37 male, mean age 7.8 yrs), 26 had asthma and 13 had difficult asthma. The diagnosis of children undergoing bronchoscopy changed in 31.3% of the cases: 10 children got a second diagnosis, which could explain the persistent symptoms, 8 children were misdiagnosed. In these 18 children airwaymucocilia (n=10) and atrophic abnormalities (n=7) were the most common. In 95.5% of the cases biopsies changed the diagnosis; in 3 of them ciliary dyskinesia was suspected. In 25% medication was changed after bronchoscopy. Children without asthma had a RBM of 5.6 μm [SD ±1.4]; in children with asthma RBM thickness was 5.1 μm [SD ±1.05] and in those with difficult asthma 6.0 μm [SD ±1.34] (p<0.49).

Conclusion: Bronchoscopy showed an important role to reveal underlying causes of persistent symptoms such as airwaymucocilia and atrophic abnormalities. In 25% of patients bronchoscopies led to a change in treatment. We found no significant difference in RBM thickness between nonasthmatic, asthmatic children and children with difficult asthma.

4709 IL-33 and airway remodelling in paediatric severe therapy resistant asthma

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Background: Associations have been reported between epithelial interleukin (IL)-33 expression and severe asthma in adults, but its role in the pathophysicsology of paediatric severe therapy resistant asthma (STRA) remains unknown.

Objectives: We quantified IL-33 expression in endobronchial biopsies from children with STRA and explored its relationship with parameters of airway remodelling.

Methods: Children (n=55) (median age 11 yrs) (range 5-16) years) with STRA underwent detailed investigations including bronchoscopy and endobronchial biopsy. IL-33+ cells were quantified in the epithelium, smooth muscle and submucosa in biopsies from children with STRA and compared to that in age matched non-asthmatic controls. Reticular basement membrane (RBM) thickness was quantified as a marker of airway remodelling, and related to IL-33+ cells.

Results: Submucosal, but not epithelial or smooth muscle IL-33+ cells were significantly higher in children with STRA compared to controls (p=0.01, 0.21, 0.68 respectively).

In addition, there was a positive correlation between IL-33+ cells and RBM thickness in children with STRA (Spearman r=0.35, p=0.018), but not in controls (p=0.33).

Conclusions: In contrast to adult studies, we have shown increased submucosal IL-33 expression in children with STRA, and for the first time have shown an association between this mediator and airway remodelling. These data suggest therapies that block IL-33 may be suitable for paediatric STRA, and specifically may impact on structural airway changes.

4710 Exhaled nitric oxide in children with severe asthma

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Introduction: Exhaled nitric oxide (FENO) is a biomarker of eosinophilic airway inflammation, but the relationship between FENO and asthma severity is uncertain.

We compared FENO normalized against reference values (%FENO) in children with problematic severe (PA) and controlled (CA) asthma and investigated whether increased %FENO is associated with morbidity, irrespective of predefined severity classification.

Methods: Children with PA had recurrent symptoms despite treatment with at least 800 μg Budesonide, those with CA had few symptoms with 100-400 μg. The protocol included Asthma Control test, sputum (percentage of neutrophils, %PMN), methacholine provocation (dose response slope), FENO (ppb), computerized tomography (CT) of the lungs (PA only) and blood sampling for eosinophils (10^3 X L^-1) and IgE (kU/L). The difference between measured and expected FENO (Ln(FENO) = 0.0112 x height (cm) + 0.641) were given in percentages (%FENO).

Results: Children with PA (n=57, age 13y) had a trend towards higher levels of FENO and %FENO compared to children with CA (n=39, age 19y: 22 (10-40) vs. 17 (9-26), p=0.13 and 210% (101-216), p=0.07, respectively. When analysing all children (n=96), those with %FENO>200 had reduced asthma control (18.5 (17-20) vs. 20.4 (19-22), p=0.04) and FEVi/FVC (77 (74-81) vs. 81 (86-91), p=0.04) and increased bronchial hyperresponsiveness (54 (5-76) vs. 2 (0-4.36), p=0.001), bronchial wall thickening on CT (51 (29-119) vs. 17 (14-19), p=0.04), eosinophils (0.5 (0-4.6) vs. 0.3 (0-2.3), p=0.01) and IgE (539 (253-1525) vs. 140 (43-425), p<0.001) compared to those with %FENO<200.

Conclusion: Children with high %FENO have increased morbidity which is partly independent of predefined severity classification.

4711 Fibroelastosis and bronchial remodelling in children with severe asthma

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Rationale: Preschool wheeze follows two broad clinical patterns; i) multi-trigger wheeze (wheeze both with and between colds) and ii) episodic viral wheeze (wheeze exclusively with colds). Whether these patterns reflect stable, distinct phenotypes with different underlying inflammation remains unclear.

Hypothesis: We hypothesised that preschool children with multi-trigger wheeze have chronic pulmonary leukotriene activation, and therefore higher baseline urinary eosinocoids, than episodic viral wheezers.

Methods: Children aged 10 months to 5 years with wheeze and no respiratory comorbidity were recruited from three UK hospitals. Wheezing pattern was obtained from parental history. Urine was collected between viral-triggered attacks and frozen at -70°C. Samples were analysed using high performance liquid chromatography tandem mass spectrometry for a range of eosinocoids (Table 1).

Results: See Table 1. There was no significant demographic difference between multi-triggered (n=46) and episodic (n=115) wheezers. There was no significant difference in baseline eosinocoid excretion between the 2 groups (P=NS by unequal t-test, Table 1).
Table 1. Baseline urinary eosinocytes (pg/ml of creatinine)

<table>
<thead>
<tr>
<th>Episode</th>
<th>Multigeneration</th>
</tr>
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<tbody>
<tr>
<td>Leukotriene B4</td>
<td>1216.47</td>
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<tr>
<td>13,14-dihydro-15-keto-PGD2</td>
<td>455.03</td>
</tr>
<tr>
<td>13,14-dihydro-15-keto-PGF2α</td>
<td>198.32</td>
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<tr>
<td>13,14-dihydro-15-keto-tetranor-PGE2</td>
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</tbody>
</table>

Changes in skin prick test (SPT) from the age of 1 to 6 years (yrs) and...allergy-related genes may be influenced by farm exposure in general and (b) change over the first years of life. We studied the rural birth cohort PASTURE (Protection against allergy: study in...and Medical Biometry, Ulm University, Ulm, Germany; 4 National Institute for Social and Preventive Medicine, University of Bern, Switzerland; 5 Department of Infection, Immunology & Inflammation, University of Leicester, United Kingdom.

Conclusions: We found no evidence that the multi-trigger phenotype is associated with increased baseline eosinocytosis activity. Dedicated to the memory of Prof Andrzej Szczeklik who would have been a co-author.

4713 Changes in skin prick test (SPT) from the age of 1 to 6 years (yrs) and relationship to specific IgE and atopic dermatitis: The French arm of PASTURE European study

Alain Chaneac1, Marie-Laure Dalphin1, Vincent Kaukel2, Stephanie Drillon3, Anne Leydier1, Caroline Roduit4, Erika von Mutius4, Dominique Angèle Vuillon5, Jean Charles Dalphin6, 1Pediatrics, University Hospital, Besançon, France; 2: Respiratory Disease, University Hospital, Besançon, France; 3Pediatrics, University of Zurich, Children’s Hospital, and Christine Kühne-Center for Allergy Research and Education, Zurich, Switzerland; 4Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Hannover, Germany; 5EA Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; 6EA 3181, University of Franche-Comté, Besançon, France.

The “PASTURE” study (Protection against Allergy: STudy of Rural Environment) examines the influence of exposure to a dairy-farm environment on the occurrence of allergy in a cohort of European children from the 3rd trimester of pregnancy to 10 yrs. The aim of this study was to analyze the course of SPTs to aero- and food allergens from the age of 1 to 6 yrs in the French children of PASTURE, whether they live or not on a farm and to evaluate their relationship to specific IgE and atopic dermatitis (AD).

Two hundred and four children, which 95 of the farmer group, were included. SPTs, AD assessment and specific IgE assays were performed at 1, 4.5 and 6 yrs.

One hundred and forty children participated in all three visits. The prevalence of positive SPTs increased with age (9.5% at 1 yr, 14.2% at 4.5 yrs, 22.6% at 6 yrs). It was lower in the farmer group, regardless of age and category of allergens considered (statistically significant only for seasonal allergens at 4.5 yrs). Positive SPTs were transient at 1 yr whereas they were persistent between 4.5 and 6 yrs. The prevalence of AD was not significantly different in the two groups and decreased with age. Positive SPTs at 1 yr were predictive of the occurrence of AD during the follow-up. The correlation between SPTs and specific IgE was poor for an IgE cut-off at 0.35U/ml, but increased with age and with higher cut-off.

In conclusion, our study showed that skin reactivity (1) increased with age, (2) was lower in the farmer group, (3) at 1 yr was transient but predictive of the occurrence of AD. Correlation between SPTs and specific IgE was poor, especially at one yr.

4714 DNA methylation in asthma and allergy related genes is influenced by farm exposure and time trends in early childhood

Sven Michel1, Florence Banout2, Jon Gennet1, Juha Pekkanen4, Charles Dalphin1, Josef Riedler5, Nicolas Mazaleyrat1, Erika von Mutius4, Juliane Weber1, Charlotte Braun-Fahrlander1,2, Roger Lauener1,2,3, Michael Kabesch1, Jörg Tost2, the PASTURE Study Group.

Aim: DNA methylation in asthma and allergy related genes is influenced by farm exposure in general and (b) change over the first years of life. We studied the rural birth cohort PASTURE (Protection against allergy: study in...and Medical Biometry, Ulm University, Ulm, Germany; 4 National Institute for Social and Preventive Medicine, University of Bern, Switzerland; 5 Department of Infection, Immunology & Inflammation, University of Leicester, United Kingdom.

Method: We assessed BF in the first years of life in children from Leicestershire, UK. At school age (9-14 yrs), we performed SPT for 4 allergens (cat, dog, dust, grass) in 1515 children. A child was defined as atopic if any wheal size was ≥3mm.

Results: 465 (31%) children were not breastfed, 435 (29%) had BF <3 months (mo), 256 (17%) BF 4-6 mo and 348 (23%) BF >6 mo. 437 mothers (29%) had hayfever. We found no evidence for differences in risk of atopy by BF; the odds-ratios (95% confidence intervals) for BF<3 mo, BF=4-6 mo and BF>6 mo were 0.97 (0.69,1.37), 1.07 (0.72,1.59) and 1.19 (0.83,1.71), respectively, compared with no BF (p-trend=0.297). We did not find differential association by maternal hayfever (p-interaction=0.489) nor evidence for reverse causation.

Conclusion: Using objective measures and controlling for reverse causation, our study did not find evidence for an effect of breastfeeding on atopy in children of mothers either with or without hayfever. We can continue recommending breastfeeding for atopic and non-atopic mothers.

Funding: Asthma UK 070048; SNF 3200B-122341; SNF P40PM-121362.
4717 Airway hyperresponsiveness to mannitol as a predictor of treatment response to ciclesine in patients with suspected asthma: A double-blind, randomised, placebo-controlled trial

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Background: Inhaled corticosteroids (ICS) are the basic treatment in patients with asthma. The aim of the study was to find predictors which detect subjects who clinically benefit from ICS using a combined endpoint (improvement in either FEV1 (>12% and >200ml), Juniper asthma control questionnaire [ACQ] >0.5 or asthma quality of life questionnaire [AQLQ] >0.5).

Methods: 70 treatment-naive subjects (mean age 40.3 years (range 18-70); 21 male) with suspected asthma were randomised to inhale ciclesine (320mg/day, n= 34) or placebo (n= 36) in a double-blind manner for 1 month. Spirometry, airway hyperresponsiveness (AHR) to mannitol and to methacholine, exhaled nitric oxide, ACQ and AQLQ were assessed before and after treatment.

Results: An improvement in the combined endpoint was seen in 16 subjects (47%) in the ciclesine group (1 FEV1, 9 ACQ, 14 AQLQ) and in 15 subjects (42%) in the placebo group (2 FEV1, 5 ACQ, 13 AQLQ). AHR to mannitol was found to be significantly higher (8/16 responders and only 3/18 non-responders in the ciclesine group (sensitivity 88% specificity 50%, PPV 72%, NPV 65%, p=0.038). Using a logistic regression analysis, AHR to mannitol was the only significant predictor of a response to ciclesine with an odds ratio of 5.0 (95%CI 1.33-24.28, p=0.046).

Conclusions: In subjects with suspected asthma, AHR to mannitol is a predictor of subsequent response to ICS treatment.

4718 Electromyography of the parasternal intercostal muscles in bronchial hyperresponsiveness testing

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1 Department of Respiratory Medicine, King’s College London, United Kingdom; 2 Chest Unit, King’s College Hospital NHS Foundation Trust, London, United Kingdom; 3 Department of Child Health, King’s College London, United Kingdom; 4 Department of Respiratory Medicine, King’s Health Partners, London, United Kingdom

Background: Bronchial hyperresponsiveness testing (BHT) can be used to support or refute a diagnosis of asthma, but requires technically-acceptable spirometry to be performed. Para sternal intercostal muscle electromyography (EMGpara) provides a non-invasive, effort-independent method to assess load on the respiratory system. The relationship between EMGpara and spirometry in adults undergoing BHT is unknown.

Methods: 16 subjects (mean (SD) age 29.5 (7.4) years) underwent methacholine provocation. EMGpara was recorded bilaterally from the 2nd intercostal space, at baseline and between consecutive methacholine doses. EMGpara was converted to root-mean-square (RMS) and mean peak RMS EMGpara per breath calculated.

Results: Significant relationships were observed between methacholine concentration, EMGpara and FEV1 (all p<0.001). Subjects with a positive test response (‘responders’), defined as change in FEV1 ≥20%, n=8) showed a significant median fall of 20% in FEV1 as PC20. By this technical approach, however, changes in end-expiratory lung volume cannot be determined. MCT using EMG para technology has been reported in the Jaeger whole-body plethysmograph features the possibility to evaluate changes of airway dynamics concomitantly with changes of lung volumes.

Conclusions: We aimed to assess changes of FRCpleth, IC, ERV and hence RV and TLC during MCT, and comparing changes of effective specific airway conductances (sGlu, sGlu, sGlu) in relation to changes effected to FEV1 and MEF200. We retrospectively analysied data from our hospital database including 540 tests (pneumatics and controls; 50 males; 81 females; age 11 to 82 y), in which MCT have been performed. Methacholine was administered during 3 consecutive cumulative challenge levels (P1:0.2 mg; P2:1.0 mg; P3:2.2 mg) computerized by the APS system.

Results: During MCT not only airway mechanics, but also static lung volumes (FRCpleth, IC) changed consistently.

Conclusions: In the assessment of AHR by MCT sGlu and sGlu qualified as most sensitive target parameter, taking into account changes of airway dynamics concomitantly with changes of lung volumes. Comparison between volume-time and flow-volume parameters with plethysmographically assessed sGlu, sGlu during MCT is presented in abstract 850930.


4721 Bronchial hyperresponsiveness using mannitol in morbid obesity before and after bariatric surgery

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Introduction: The association between bronchial hyperresponsiveness (BHR) and morbid obesity (MO) is common.

Objective: To investigate the prevalence of BHR using mannitol (MAN) in patients with MO before and one year after bariatric surgery (BS).

Methods: We determined BHR in 70 patients with MO (46±11 yr; BMI, 46±6 kg/m²; 53 females; smokers, [33±26 pack-yr] 59%). BHR was defined as a PD15<63.5mg. Severe OSA (apneas+hypopneas Index [AHI] ≥30 events/h) was present in 31 patients.

Results: Before BS, patients had FEV1, 93±15%; FEV1/FVC, 0.83±0.05; bronchodilator test, <9±4%. Fifty two had BHR+(PD15<78 mg) with an FEV1 fall of -20±2%. BMI and central obesity (abdominal circumference and waist-hip ratio) were higher in patients with BHR+(n=17) than in those BHR-(n=53) (p<0.05 each).

Likewise, the AHI was higher (51±10 vs 29±4.5 events/h) in patients with BHR+(p<0.05) than in those BHR-(p>0.05).

The ratio-dose-response (RDR) to MAN was positively associated with BMI (r=0.30, p<0.05).

Results: Before AH, all but one BHR+ patient, reverted their BHR(PD15>635 mg) with an FEV1 fall of -8±2%, and IL-8 levels increased in all patients (p<0.05).

Conclusions: In MO the prevalence of BHR with MAN is elevated, which is associated with increased BMI, central obesity and AHI. Our findings suggest that...
obstructive sleep apnea and central obesity can in MO share a similar pathogenic mechanism related to development of BHR.

Supported by FIS P080331 CIBERES, Almirall and Esteve.

4723  Sensitivity and specificity of airway hyperreactivity (AHR) based on methacholine challenge (MCH) tests – Comparison of sG_{Eeff} with FEV_1 and MEF_{200} as target parameter

Richard Kraemer 1, Gabi Giger 1, Thomas Sigist 1, Martin Frey 1. 1Department of Clinical Research, University of Berne, Inselspital, Berne, Switzerland; 2Clinical Research Unit, Klinik Barmelweid, Switzerland

Rationale: Airway hyperreactivity (AHR) is a characteristic feature of asthma, and methacholine challenge tests (MCT) are well established, mostly defining a fall of 20% in FEV_1 as PC_{20}. In contrast to this spirometric technique, whole-body plethysmography features the possibility to evaluate changes of airway dynamics concomitantly with changes of lung volumes (see also abstract 850929).

Objectives: Assessment of sensitivity and specificity of MCT, comparing changes of effective specific airway conductances (sG_{Etot}, sG_{Eeff}, sG_{A}) with changes effected to FEV_1 and MEF_{200}.

Methods: Data from 140 test persons (asthmatics and controls; 59 males; 81 females; age: 11 to 82 y), in whom MCH was administered during 3 consecutive cumulative challenge levels (P_{1.0 mg}; P_{2.0 mg}; P_{3.2 mg}) computerized by the APS system, were retrospectively evaluated.

Results: Highest response rates were found for sG_{Etot}PD_{10} (82.1%) and sG_{A}PD_{20} (77.1%); lowest for FEV_{1}PD_{20} (34.3%) and intermediate for MEF_{200}PD_{45} (45%). sG_{Eeff} reached its PD_{50} at 0.56±0.48 mg, FEV_{1} its PD_{20} only at 0.94±0.57 mg MCH. Sensitivity of MCH-tests (s) and specificity (f) were obtained as follows: sG_{Eeff} (s: 95.7%; f: 80.0%), sG_{A} (s: 91.3%; f: 88.0%), FEV_{1} (s: 38.3%; f: 84.0%) and MEF_{200} (s: 48.7%; f: 72.0%).

Conclusions: In comparison to FEV_{1}, assessment of AHR by sG_{Eeff} and sG_{A} reaches their PD at much lower MCH doses, in a much higher percentage of tests. The advantage of MCT by plethysmography, measuring changes of airway dynamics in relation to changes of the volume history, features the advantage to perform MCT with better safety for the patients.

4722  Relationships of mannitol challenge to methacholine challenge and inflammatory markers in asthmatics receiving inhaled corticosteroids

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Background: Mannitol is a novel osmotic indirect bronchial challenge agent related to development of BHR.

Methods: Screening data were analysed of 143 mild to moderate asthmatics, all taking inhaled corticosteroids (ICS), who had mannitol and/or methacholine challenges, fractional exhaled nitric oxide (FeNO) and salivary eosinophilic cationic protein (ECP) measured together. Mannitol AHR was grouped by PD10: mild (315-635mg), moderate (75-315mg), severe (0-75mg).

Results: PD10 groups were significantly different overall for FeNO (p=0.023): 43% higher in the severe vs. mild group. There was a significant overall difference for methacholine PC20 (p=0.006): a 2.1 doubling dilution difference between severe vs. mild mannitol groups.

No significant differences were found across groups for: salivary ECP, FEV_{1}, or ICS dose. Mannitol PD10, methacholine PC20 and FeNO as continuous variables all correlated with each other.

Conclusions: Mannitol challenge reflects both underlying inflammation using FeNO and direct AHR using methacholine. Thus mannitol may be a useful screening tool for the assessment of asthmatic patients receiving ICS.

4724  The influence of emphysema heterogeneity on the magnitude of benefit following endoscopic thermal vapor ablation (InterVapor™) in patients with heterogeneous emphysema

Felix J.F. Herth 1, Armin Ernst 2, Peter Hopkins 1, Jim J. Egan 3, Franz Stanzel 4, Anshag Valipour 5, Manfred Wagner 5, Christian Witt 3, Kim Baker 2, Mark H. Gotfried 10, Steven Kesten 11, Gregory Snell 12. 1Pneumology and Critical Care Medicine, Thoraklinik Heidelberg, Germany; 2Pulmonary, Critical Care and Sleep Medicine, St. Elizabeth’s Medical Center, Boston, United States; 3 Lung Transplant Unit, Prince Charles Hospital, Chermside, Australia; 4Advanced Lung Disease Program, Mater Misericordiae University Hospital, Dublin, Ireland; 5Clinical Department, Upstate Medical Corp, Tustin, United States; 6PACT, Pulmonary Associates, Phoenix, United States; 7Allergy Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, Australia; 8Pneumology and Critical Care Medicine, University of Iowa, Iowa City, United States; 9PACT, Pulmonary Associates, Phoenix, United States; 10Oncology, University of Iowa, Iowa City, United States; 11PACT, Pulmonary Associates, Phoenix, United States; 12Allergy Immunology & Respiratory Medicine, St. Elizabeth’s Medical Center, Boston, United States

Introduction: Endoscopic thermal vapor ablation (InterVapor™) has been demonstrated to induce lung volume reduction through the local delivery of heated water vapor to targeted lung segments. We examined patient subgroups based on emphysema heterogeneity for differential responses.

Methods: Subgroup analysis from a single-arm trial of InterVapor (single upper lobe treatment at 10 calig of tissue) in patients with upper lobe predominant emphysema. Inclusion criteria: FEV_{1} 15%-45% predicted, RV>105%, TLC>100%, 6 minute walk distance (6MWD)>140 m, DLOC>20%. Primary efficacy endpoints: FEV_{1} ≥12% or SGRQ ≤4 units at 6 months. Secondary efficacy: lung volumes (body plethysmography, HRCT), mMRC dyspnea, and 6MWD. Endpoints were analyzed for associations (Pearson correlation) and categorized based on tertiles of heterogeneity index (HI) (lower to upper lobe tissue to air ratio from HRCT).

Results: 44 patients received InterVapor. Demographics: 50% men, age 63 years, FEV_{1} 0.86 L (31% predicted), SGRQ 59 units, 6MWD 500 m. Results at 6 and 12 months (mean change from baseline):

<table>
<thead>
<tr>
<th>HI&lt;1.45 (n=15)</th>
<th>HI=1.45–1.90 (n=15)</th>
<th>HI&gt;1.90 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–no change</td>
<td>0–no change</td>
<td>0–no change</td>
</tr>
<tr>
<td>12 m</td>
<td>12 m</td>
<td>12 m</td>
</tr>
<tr>
<td>Lobar reduction (%)</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>-203</td>
<td>-88</td>
</tr>
<tr>
<td>FEV_{1} (%)</td>
<td>119</td>
<td>87</td>
</tr>
<tr>
<td>mMRC</td>
<td>0.46</td>
<td>0.67</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>169</td>
<td>20</td>
</tr>
<tr>
<td>SGRQ (units)</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

Conclusion: Efficacy from InterVapor for the treatment of heterogeneous emphysema appears to increase with increasing HI (i.e. upper lobe predominance). HI should be considered when projecting the magnitude of benefit after InterVapor.

4725  Associations among one-year efficacy outcomes following endoscopic thermal vapor ablation (InterVapor™) for heterogeneous emphysema

Peter Hopkins 1, Felix J.F. Herth 2, Gregory Snell 3, Kim Baker 2, Christian Witt 3, Mark H. Gotfried 4, Anshag Valipour 5, Manfred Wagner 5, Franz Stanzel 3, Jim J. Egan 1, Steven Kesten 1, Armin Ernst 1. 1Lung Transplant Unit, Prince Charles Hospital, Chermside, Australia; 2Pneumology and Critical Care Medicine, Thoraklinik Heidelberg, Germany; 3Allergy Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, Australia; 4Advanced Lung Disease Program, Mater Misericordiae University Hospital, Dublin, Ireland; 5Clinical Department, Upstate Medical Corp, Tustin, United States; 6PACT, Pulmonary Associates, Phoenix, United States; 7Pneumology, Charité University Medicine, Berlin, Germany; 8Pneumology, Charité University Medicine, Berlin, Germany; 9Pneumology, Charité University Medicine, Berlin, Germany; 10Lung Transplant Unit, Prince Charles Hospital, Chermside, Australia; 11Pneumology, Klinikum Nürnberg, Germany; 12Allergy Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, Australia

Background: The understanding of interactions or associations over the long-term may assist in understanding and predicting changes over time in chronic diseases such as emphysema. 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 not considered redundant.

Objectives: Determine the correlations of improvements in patient-reported outcomes, exercise capacity and BODE score with lung function and lobar volume
44 patients received InterVapor. Demographics: 50% men, age 63 years, spirometry, body plethysmography, lobar volume reduction (LoVR) by HRCT, Germany; 3Pulmonary, Critical Care and Sleep Medicine, St. Elizabeth’s Medical Center, Boston, United States; 5Pulmonary Diseases, University Medical Center, Groningen, Netherlands

Results: At 6 months (mean change from baseline):

<table>
<thead>
<tr>
<th>FEV1 (%)</th>
<th>6/12 mo</th>
<th>LoVR (%)</th>
<th>6/12 mo</th>
<th>6MDW (mL)</th>
<th>SGRQ (units)</th>
<th>RV (L)</th>
<th>6/12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 (n=22)</td>
<td>14.3 / 8.8</td>
<td>-54.0 / -51.6</td>
<td>31.7 / 26.7</td>
<td>-13.7 / -11.6</td>
<td>-0.413 / -0.330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥350 (n=12)</td>
<td>18.8 / 11.4</td>
<td>-42.2 / -39.2</td>
<td>58.6 / 49.7</td>
<td>-15.7 / -9.6</td>
<td>-0.400 / -0.281</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Baseline 6MDW was associated with differences that were more pronounced with the subsequent 6MDW and SGRQ at 12 months. Other outcomes showed no consistent pattern of association. A bias such as regression to the mean cannot be ruled out in this analysis.

Introduction: The NETT noted that baseline exercise tolerance may influence long-term outcomes following endoscopic thermal vapor ablation (InterVapor) in patients with heterogeneous emphysema.

Methods: Post hoc subgroup analysis from the Vapor trial, a multicenter single-arm trial of InterVapor (single upper lobe treatment at 10 cal/g) in patients with upper lobe emphysema. Inclusion: FEV1 15%–45% predicted, RV >150%, TLC >100%, 6MDW >140 mL, DLCO >20%, prior pulmonary rehabilitation. Outcomes included spirometry, body plethysmography, lobar volume reduction (LoVR) by HRCT, SGRQ, mMRC dyspnea, 6MDW and LoVR (CT). Pearson correlation coefficients were calculated for associations of changes from baseline to 12 months.

Results: 44 patients received Vapor. Mean age: 63 years, men 50%, FEV1 88.6% (31%) predicted, RV 60.1% (26%) predicted, DLCO 35% predicted, SGRQ 59 units, 6MDW 300 m, mMRC 2.9.

Conclusion: Among lung function tests, FEV1 appeared to correlate the strongest with health outcomes, followed by RV and FRC at one year. The strong correlation of outcomes with LoVR are consistent with the proposed mechanism of action.

4726 The influence of baseline exercise tolerance on long-term efficacy outcomes following endoscopic thermal vapor ablation (InterVapor) in patients with heterogeneous emphysema

Introduction: The influence of baseline exercise tolerance on long-term efficacy outcomes was examined in a study of endoscopic thermal vapor ablation (InterVapor) in patients with heterogeneous emphysema.

Methods: Post hoc subgroup analysis from the Vapor trial, a multicenter single-arm trial of InterVapor (single upper lobe treatment at 10 cal/g) in patients with upper lobe emphysema. Inclusion: FEV1 15%–45% predicted, RV >150%, TLC >100%, 6MDW >140 mL, DLCO >20%, prior pulmonary rehabilitation. Outcomes included spirometry, body plethysmography, lobar volume reduction (LoVR) by HRCT, SGRQ, mMRC dyspnea, and 6MDW. Endpoints were dichotomized based on two thresholds for baseline 6MDW.

Results: 44 patients received InterVapor. Demographics: 50% men, age 63 years, FEV1, 0.86 L (31% predicted), SGRQ 59 units, 6MDW 300 m. Results at 6 and 12 months (mean change from baseline):

<table>
<thead>
<tr>
<th>FEV1 (%)</th>
<th>6/12 mo</th>
<th>LoVR (%)</th>
<th>6/12 mo</th>
<th>6MDW (mL)</th>
<th>SGRQ (units)</th>
<th>RV (L)</th>
<th>6/12 mo</th>
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<tr>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Baseline 6MDW was associated with differences that were more prominent with the subsequent 6MDW and SGRQ at 12 months. Other outcomes showed no consistent pattern of association. A bias such as regression to the mean cannot be ruled out in this analysis.

4727 Charities evaluation of collateral ventilation versus HRCT assessment, in predicting clinical outcomes following endobronchial valve therapy (EBV) in COPD patients

Studies suggest EBV insertion in heterogeneous COPD is most effective in patients with no collateral ventilation (CV)–ve involved at the targeted lobe.

Aim: To determine whether Charities evaluation could predict clinical outcomes in COPD pts having EBV insertion and who were assessed as having a complete fissure by HRCT.

Methods: A prospective parallel group study with all pts screened with HRCT. Destruction scores were determined for each lobe, tissue integrity was assessed in both lungs. Only pts with >10% differential in destruction scores and complete fissures (for the targeted lobe) were enrolled. All had lung function tests, 6 min walk, differential V/Q, and SGRQ scoring at baseline/30/90 days after EBV placement. Pts had Charities testing of CV prior to EBV placement, but EBV was placed irrespective of the Charities result.

Results: 49 pts were screened. 9 had intact fissures on HRCT assessment and went onto Charities testing and EBV placement. All had EBV placed in the left upper lobe and lingula. 7 pts were CV–ve on Charities: 2 were CV–ve in the CV–ve group, went on to EBV. FEV1 [mean(SD)] increased from baseline 0.69(0.15) to 0.93 (0.19) L, p<0.025, at 90 days. TLC decreased from 6.55 (1.28) to 6.00 (1.11) L, p<0.01. SGRQ scores at 90 days were also significantly lower -43.2(10.5) vs 61.2 (8.7) p<0.01. The two patients in the CV+ve group had no change in lung function.

Conclusion: When used as a supplement to HRCT, Charities assessment of CV predicts improvement in lung function and clinical outcomes in pts with severe COPD undergoing EBV therapy. Charities should be incorporated into decision pathways relating to EBV insertion.

4728 Pneumothorax as a predictor of beneficial outcome following endobronchial lung volume reduction

Introduction: Patients developing significant target lobe volume reduction (TLVR) following endobronchial valve (EBV) treatment experience great improvement in clinical outcome measures. A prospective multicenter study confirmed an improvement in FEV1, SGRQ and 6MWD in patients with a TLVR >20%.

Objective: To evaluate the impact of the pneumothorax on outcome following EBV treatment.

Methods: Retrospective analysis of a multicenter trial evaluating the impact of the pneumothorax on outcome following EBV treatment. All patients underwent chest x-ray the same day of EBV implantation for exploration of pneumothorax. 30 days following valve implantation, TLVR assessed by high resolution computed tomography (HRCT) and clinical outcome measures (FEV1, SGRQ, 6MWT) were evaluated.

Results: 96 emphysema patients received EBV therapy, of which 41 patients experienced a TLVR >350 mL. In total, 8 patients (8.3%) experienced a pneumothorax following EBV placement. TLVR values were available for 6 out of the 8 patients. All 6 achieved TLVR >350 mL cut off for the study. The mean TLVR as well as the improvement in FEV1 was greater in the group of patients who experienced a pneumothorax (p=0.06; mean TLVR -227.3 mL, mean % FEV1 23.8(±10.6) compared to those who did not (n=35; mean TLVR -122.1 mL, mean % FEV1 22.3±24.01). All patients required chest drainage and recovered within 3–14 days.

Conclusion: The event of pneumothorax seems to be a predictor of a great outcome following EBV therapy.
6Pulmonology, University Hospital, Tuebingen, Germany; 6Pneumologie, Maison Blanche CHU, Reims, France; 4Pulmonary Diseases, Asklepios, Gauting, Germany; 5UKT Internal Medicine, University Hospital, Tuebingen, Germany; 4Thorax Klinik, Universitätsklinikum, Heidelberg, Germany; 5UKT Internal Medicine, University Hospital, Tuebingen, Germany; 6Pneumologie, Krankenhaus vom Roten Kreatz, Stuttgart, Germany; 8Pulmonology, CHU Strasbourg, France; 9Pneumologie, Hopital Pasteur, Nice, France; 11Pulmonary Medicine, University Medical Center, Groningen, Netherlands.

The Lung Volume Reduction Coil (LVRC, PneumRX USA) is a bronchoscopic device for the treatment of emphysema. A previous pilot study showed safety and feasibility in severe upper-lobe heterogeneous emphysema. In this multicenter study (NCT0122089, NCT01328899) we investigated whether LVRC is safe and effective for the treatment of upper- and lower-lobe heterogeneous and homogeneous emphysema.

Methods: 71 subjects underwent two separate bronchoscopic treatments using LVRC Coils under anesthesia using fluoroscopy (142 procedures). Over 1350 LVRC Coils were placed with median 10 Coils (range 5-15) placed per procedure in 48±24 minutes. Safety was evaluated by recording all SAEs and AEs; effectiveness was measured by SGRQ, pulmonary function and exercise testing through 6 months.

Results: 71 subjects (42F/29M, 62±8 yrs), FEV1: 29±6.6%, RV: 247±50%, FEV1/ FVC: 0.71±0.19, 6MWD +42m (/Δ1 20.2 and Δ1 20.0 and 13.1% respectively. In the 4 RLL patients, ΔFVC was 22.9% ±22.8 and 23.6% ±15.8. ΔSGRQ was -7.5 points ±19.1 and ±7.5 at 6 months in LLL and RLL respectively.

In the VENT subgroup, 26 patients had heterogeneous emphysema of ≤15% with a mean change in FEV1 at 12 months of 15.4% ±2.51 compared to 31.±28.8 in the 35 patients with a score >15%. In the Chartis subgroup, 14 had a score of ≤15% and showed a mean improvement in FEV1 of 15.9% ±16 at 30 days compared to 26.4% ± 27.9 in the 20 patients with a score >15%.

Conclusion: A clinical relevant response can be obtained after LVRC in lower lobes and in patients who are not highly heterogeneous.

For the remainder of the text, please refer to the original document. The text is not included here due to its length and complexity.
Results: In vitro, acute exposure of AEC to hypoxia (0.5% O2 for 1 h) rapidly decreased transepithelial Na+ transport as assessed by equivalent short-circuit current Ieq and the amiloride-sensitive component of Na+ current across the apical membrane, reflecting ENaC activity. Hypoxia reduced the expression of α-, β-, and γ-ENaC proteins in the plasma membrane, with no change in intracellular expression. Hypoxia-induced inhibition of amiloride-sensitive Ieq was rapidly reversed by the β2-agonist terbutaline, and was fully prevented by preincubation with proteasome inhibitors. In vivo, hypoxic exposure (8% O2 for 24h) reduced amiloride-sensitive alveolar fluid clearance by 69% in wild-type mice without changing the expression level of ENaC proteins in the distal lung, but had no significant effect in homozygous mutated Liddle mice.

Conclusion: These data strongly suggest that decreased cell surface expression of ENaC subunits under hypoxic condition is related to Ned44-2-mediated endocytosis of ENaC and subsequent degradation in the proteasome.

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Conclusion: These data strongly suggest that decreased cell surface expression of ENaC subunits under hypoxic condition is related to Ned44-2-mediated endocytosis of ENaC and subsequent degradation in the proteasome.

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IL-17C is expressed in respiratory epithelial cells under inflammatory conditions

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Background: IL-17 is a cytokine that comprises a group of five IL-17 subtypes (IL-17A to F). IL-17 directly activates epithelial cells leading to the expression of inflammatory mediators and antimicrobial factors. Recent studies showed that IL-17A/F is released by professional immune cells such as CD4+ T cells and macrophages whereas IL-17C is expressed by epithelial cells. It was the purpose of this study to examine the expression of IL-17 in respiratory epithelial cells infected with bacterial pathogens.

Methods: Bronchial epithelial cells were exposed to smoke and infected with bacterial pathogens. Mice were exposed to smoke and colonized with H. influenza.

Expression and release of IL-17 (A to F) was measured by ELISA and qRT-PCR. IL-17C was detected in human bronchial tissue by immunohistochemistry.

Results: Bacterial pathogens such as P. aeruginosa and H. influenzae induced the expression and release of IL-17C in human bronchial epithelial cells (HBECs). The same was true for ligands of Toll-like receptors 3 and 5 (flagellin, polyI:C).

Conclusion: IL-17C expression may play an important role in epithelial response to bacterial pathogens and may thus provide beneficial effects on epithelial barrier function.

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Synthetic response of stimulated respiratory epithelium: modulation by prednisolone and iκK2 inhibition

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Background: The airway epithelium plays a central role in wound repair & host defense & is implicated in the immunopathogenesis of asthma. Whether there are intrinsic differences between the synthetic capacity of epithelial cells derived from asthmatics & controls & how this mediator release is modulated by anti-inflammatory therapy remains uncertain.

Aims: We sought to examine the synthetic function of epithelial cells from different locations in the airway tree from subjects with & without asthma & to determine the effects on synthetic activity of epidermal growth factor (EGF) & TLR3 ligands in response to EGF & TLR3 stimulation.

Methods: Primary epithelial cells were derived from nares & bronchial lung tissue of healthy controls & patients with asthma & COPD. The synthetic response of epithelial cells was determined by measuring cytokine and antimicrobial factor release.

Results: The synthetic activity of epithelial cells was significantly increased in patients with asthma & COPD compared to healthy controls. The synthetic activity of epithelial cells was significantly increased in patients with asthma & COPD compared to healthy controls. The synthetic activity of epithelial cells was significantly increased in patients with asthma & COPD compared to healthy controls.

Conclusion: The synthetic activity of epithelial cells is increased in patients with asthma & COPD compared to healthy controls. This finding may have implications for the pathogenesis of asthma & COPD.

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Corticosteroids improve airway epithelial regeneration and restore oxidative stress-induced epithelial barrier dysfunction

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Background: The airway epithelium plays an emerging role in the pathogenesis of respiratory diseases. Its barrier function may be defective in asthma and COPD.

Aims: To study the protective effect of inhaled corticosteroids budesonide (BUD) on different aspects of epithelial integrity, including cell-cell contact formation, regeneration upon wounding and barrier function during mucociliary differentiation at the airliquid interface (ALI).

Methods: We studied the effect of BUD (10^-5 to 10^-4 M) on epithelial resistance and expression of factors of the innate immune system such as antimicrobial peptides and proinflammatory cytokines under basal conditions and upon wounding. BUD significantly improved baseline resistance and significantly increased epithelial barrier function during mucociliary differentiation at the airliquid interface (ALI).

Conclusion: BUD improves the restoration of epithelial cell-cell contacts upon wounding in 16HBE cells. Oxidative stress induced a transient defect in 16HBE cell monolayer integrity upon wounding and barrier function during mucociliary differentiation at the airliquid interface (ALI).

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AN01 expression and activity in cystic fibrosis

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Defective CFTF function in the airway epithelium is responsible for cystic fibrosis (CF) patient lung disease. CFTFR represents the most important pathway for apical chloride (Cl-) secretion in human bronchial epithelial cells. Calcium activated Cl- channels (CaCCs) are also an important pathway of Cl- secretion. In 2008, three independent teams suggested that AN01 (Anoccamine 1) also called TMEM16a could be a CaCC candidate. Mice lacking AN01 exhibit a defect in epithelial Cl- transport and pathology similar to CF.

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The main aim of this study is to characterize ANO1 protein in CF vs non CF context. For this study, we used different CF and non CF models whose cell lines, mice, and lung explants from CF and non CF patients. Our results show that ANO1 expression and activity are significantly decreased in CF compared to non CF models.

ANO1 is expressed at plasma membrane of bronchial epithelial cells and there is no difference in localization between CF and non CF cells. To understand the differential expression between CF and non-CF cells/tissues we will investigate mRNA expression that could modulate ANO1 protein.

We conclude that decreased ANO1 activity in CF cells could be explained by decreased ANO1 ARNm and protein expression and may contribute to the worsening of ionic imbalance and decrease lung function. All of these results lead us to think that this Cl- channel could be a potential pharmacological target for the treatment of cystic fibrosis patients.

4739 Cystic fibrosis epithelial cells are primed for apoptosis as a result of increased Fas

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Apoptosis is a physiological process essential for homeostasis of epithelial organisation and function. Cystic fibrosis (CF) lung disease is characterised by chronic infection and inflammation and previous work suggests that apoptosis is dysfunctional in the CF airways with conflicting results. In addition, controversy exists regarding how CFTR misfolding contributes to apoptosis. In this study, we evaluated the relationship between CFTR mutation and apoptosis in CF airway epithelial cells. Basal activity of the executioner caspase, caspase-3, was significantly increased in CF tracheal and bronchial epithelial cell lines and primary bronchial epithelial cells compared to non-CF controls. In addition, activity of the upstream initiator caspase, caspase-8, was significantly increased in CF epithelial cells compared to controls, suggesting involvement of extrinsic apoptosis signalling, which is mediated by the activation of death receptors, such as Fas (CD95). Increased levels of Fas were evident in the brushing samples, and neutralization of Fas significantly inhibited caspase-3 activity in CF epithelial cells compared to untreated cells. Furthermore, activation of Fas significantly increased caspase-3 activity and apoptosis in CF epithelial cells compared to control cells. Overall, these results suggest that CF airway epithelial cells are more sensitive to apoptosis via increased levels of Fas and subsequent activation of the Fas death receptor pathway. Further work will delineate the mechanism underlying increased Fas expression in CF epithelial cells.

495. Prevalences and characteristics of obstructive airway disease

P4740 COPD prevalence in Romania and possible influence of social and household characteristics

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COPD is a very important public health issue at individual and society level alike. Knowing the prevalence of COPD is extremely useful in health services planning, but using an early detection tool is crucial for life duration and quality of life of the patient. We aimed to estimate the prevalence of COPD in Romanians aged 40+ in relations to certain social variables and specific household exposures. A cross-sectional survey was performed using a stratified sample of 9638 subjects aged 40+. Using a pre-screening questionnaire, 51% of the responders were identified as being at risk for COPD (4930). 2000 subjects, randomly selected, were invited to perform a spirometric evaluation (at least 3 spirometry tests per patient, according to ATS/ERS standards). Smoking subjects (current or former) with a FEV1 ratio lower than 0.7 were considered as having COPD. Social variables considered were geographical region, rural/urban, education, occupation, income category. Specific household exposures were way of cooking and source of household heating.

We found a COPD prevalence of 9.7% (±2.18) (15.7% and 3.9% in males and females). Median age of COPD subjects was 56 and 46 years in males and females. No significant correlations were found with geographical region, urban/rural distribution, education, job and income category, both for males and females. No significant correlations were found for source of heating and cooking.

Conclusions: Our study showed that around half of the general population aged 40+ meets the criteria for being at risk for COPD (around 5 million people). In the risk group, COPD prevalence reached to 9.7%. Social and household variables seemed not to be associated to COPD.

P4741 High prevalence of COPD symptoms in the Tunisian population contrasting with low awareness of the disease

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Introduction: In Tunisia, the estimated prevalence of COPD was low compared with America and Europe and the disease is certainly under diagnosed. We have estimated the prevalence of COPD in the city of Sousse, following the BOLD protocol.

Methods: We surveyed a representative random sample of 807 aged adults 40+ selected from the general population and have collected information on respiratory history and symptoms, risk factors for COPD and health status. Post-bronchodilator spirometry was performed for assessment of COPD. COPD and its stages were defined according to GOLD guidelines. Population weighted prevalence of COPD were computed allowing for survey design.

Results: 661 subjects were included in the final analysis. The response rate was 90%. The estimated population prevalence of GOLD Stage 1 and stage 2 or higher COPD were 7.8% and 4.2%, respectively (LLN modified stage 1 and stage 2 or higher COPD prevalence were 5.3% and 3.8%, respectively). COPD was far more common in men, increased with age and exposure to tobacco smoke. Prevalence of stage 1+ COPD was 2.3% in <10 pack years smoked and 16.1% in >20 pack years smoked. Only 3.5% of participants reported doctor-diagnosed COPD.

Conclusions: In this Tunisian population, the prevalence of COPD is higher than reported before and higher than self-reported doctor-diagnosed COPD. The implications for disease diagnosis and management in clinical practices might have a public health impact. In subjects with COPD, age seems to be a much more powerful predictor of lung function than smoking. LLN, Lower Limit of Normal; BOLD, Burden of Lung Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
COPD was diagnosed if FEV1/FVC was lower than 0.7 after a bronchodilator test.

**Results:** COPD prevalence in the Canary islands was 7.3% (IC 95%, 5.5-9.5%) being higher in male than female (8.7% CI 95%, 5.8-12.7% vs 6.3% CI 95%, 4.7-8.4% p <0.005). COPD prevalence classified by GOLD showed a 1.1% in stage I, 5.0% in stage II, 1.1% in stage III and 0.3% in stage IV. The level of undiagnosis was 63.5% and undertreatment reached 71.6%.

**Conclusions:** The Canary islands have a lower COPD prevalence than the rest of Spain as a whole, with a lower severity in spite of having a high smoking prevalence. This finding could be related to the specific climatic characteristics of the Canaries.

P4743

**Prevalence of COPD by disease severity in men and women in relation to smoking in northern Vietnam**

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**Background:** The prevalence of COPD and its risk factor pattern varies between different areas of the world. The aim of this study was to investigate the prevalence of COPD by disease severity in men and women and risk factors for COPD in northern Vietnam.

**Methods:** From all 5782 responders to a questionnaire survey, a randomly selected sample of 1500 subjects was invited to a clinical follow-up study. The methods included a structured interview using a modified GA2LEN study questionnaire for registration of symptoms and possible determinants of disease. Spirometry was performed before and after bronchodilatation. The age distribution of the sample was 23-72 years.

**Results:** Of 684 subjects attending, 565 completed acceptable spirometric measurements. The prevalence of COPD defined by the GOLD criteria was 7.1%; in men 10.9% and in women 3.9% (p=0.002). Of those 3.4% had a mild disease, 2.8% a moderate and 0.9% a severe disease. In ages >50 years, 23.5% of men and 6.8% of women had COPD. Among smokers aged >60 years (all men), 47.8% had COPD. None of the women with COPD had been smokers. Increasing age, smoking and male sex were the dominating risk factors, although male sex lost its significance in a multivariate setting.

**Conclusions:** The prevalence of COPD among adults in northern Vietnam was 7.1% and was considerably higher among men than women. The prevalence increased considerably with age. Increasing age and smoking, the latter among men only, were the most important determinants of COPD.

P4744

**Prevalence characteristics of COPD in never smokers**

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**Background:** COPD can be recorded among non-smokers due to different causes other than smoking.

**Methods:** This study was performed in the Chest Department, Menoufia University, from April 2009 to August 2011, on 300 COPD patients, 230 men (76.66%) and 70 women (23.34%). The mean age was 60±7.5±35.5 years. History was taken and exposure to risk factors for COPD was assessed by a prewritten questionnaire.

**Results:** Out of the 300 COPD patients, 120 (40%) were never smokers and 180 (60%) were ever smokers. Women made up 41.7% of the never smokers and 11% of the ever smokers. Never smokers were significantly older than smokers (65.0±5.03 years vs 56.3±5.67 years p < 0.001) and were more likely to be women [41.7% vs 11% (P < 0.001)]. Never smokers made up 40% of all COPD cases: 78% of GOLD stage II and 45.5% of GOLD stage III cases. Among never smokers, 58.3% and 41.7% fulfilled the criteria for GOLD stage II and III respectively. Never smokers had more occupational exposure to organic and inorganic dust and irritant gases [41.7% vs 27.7%, P < 0.05], more biomass exposure [41.7% vs 6%, P < 0.001], less education [75% vs 41.7%, P < 0.001], more exposure to passive smoking [75% vs 22.2%, P < 0.001]. When compared with never smokers with GOLD stage II, never smokers with GOLD stage III were older in age, have a higher female percentage, lower BMI, more occupational exposure, more biomass exposure, less education, more exposure to passive smoking. Independent predictors of COPD in never smokers were old age, female sex, occupational exposure, biomass exposure and low educational level.

**Conclusions:** This study revealed that never smokers constitute a significant proportion of the Egyptian COPD patients.

P4745

**Higher than expected prevalence of alpha-1-antitripsin deficiency (AATD) may not necessarily impact on airflow, gas exchange or acute exacerbation rate (AER)**

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AATD is estimated to occur in 1-3% of COPD patients and is believed to accelerate disease. To determine its prevalence in a community practice and impact on disease progression, all patients with COPD, >10 pack-year smoking history and a post-bronchodilator FEV1/FVC < 0.70 were offered testing for AATD. Spirometry and diffusing capacity (DLco) were measured respecting ATS criteria, and serum AAT levels were assayed. Of 323 patients, 291 (90%) accepted screening. 44 (15%) had low serum AAT levels (AATD mean 0.76g/L ± 0.05 vs. non-AATD 1.57 ± 0.03). Age (74±1 years vs. 72±1, smoking history (63±pack-years±3 vs. 45±3), FEV1 (63±predicted±4 vs. 61±4) and FEV1/FVC (54±4 vs. 54±1) were similar. 40 AATD and 187 non-AATD patients had DLco measured and were similar (64±predicted±4 vs. 64±2). Annual AER and prior spirometry was available in 44 AATD and 217 non-AATD and prior DLco in 39 AATD and 167 non-AATD subjects. Annual AER (1±0.06fections/year±1 vs. 1.2±0.01 over 4±years±0.1) and annual decline of both FEV1 (18±ml/year±19 vs. 3±6 over 6±years±0.3) and DLco (0.60± lost/mmHg/year vs. 0.5±0.1 over 6±years±0.3) were similar. In this population, AATD prevalence was 5 times greater than previously reported, yet no difference in FEV1, and DLco decline, or AER was observed. Whether this lack of difference is due to strict smoking cessation, medication compliance, aggressive management of exacerbations or a predominance of heterozygotes remains to be determined.

P4746

**A new paradigm for classification of disease severity and progression of COPD**

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**Background:** The current classification scheme for COPD uses lung function to classify disease severity and monitor disease progression. This scheme does not capture other important components of the disease process, nor does it allow for improvement of disease status.

**Methods:** We evaluated existing data to develop a classification scheme for COPD using measures beyond lung function, including respiratory symptoms, exacerbation history, quality of life assessment, comorbidity, and body mass index. We then applied this classification to data from the Lung Health Study, calculating a score for study subjects in year 1 and year 5 of the study, along with the difference between year 1 and year 5.

**Results:** We developed a 4 point scale ranging from 1.00 (mild) to 4.00 (very severe). In year 1 of the study, the mean COPD score was 1.76 (standard deviation (SD) 0.35), in year 5 it was 1.82 (SD 0.38). The mean difference from year 1 to year 5 was an increase (worsening) of 0.06 (SD 0.37), and a range from -1.0 to 1.6. The COPD score at year 1, year 5, and the difference between these scores were all predictive of mortality at follow-up. For example, the 14.0% of subjects whose score improved by at least 0.25 between year 1 and 5 had decreased mortality compared to those with stable scores (between -0.25 and 0.25, hazard ratio 0.6, 95% confidence interval 0.4, 0.8). Conversely, those whose score worsened by 0.75 or more points had increased mortality (HR 1.7, 95% CI 1.2, 2.5).

**Conclusions:** A COPD score that includes components in addition to lung function and allows for both improvement and worsening of disease may provide additional guidance to COPD classification, management, and prognosis.
P4747 Identifying a 'frequent exacerbator' phenotype in a cohort of COPD patients
(AEACO study)
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Background: Exacerbations are a major cause of morbidity and mortality in patients with COPD.

Objectives: To determine whether it is possible to identify a sub-group of 'frequent exacerbators', i.e. COPD patients who experience a high number of exacerbations every year, and to compare characteristics to that of non-frequent exacerbators.

Methods: In this French prospective observational study, respiratory physicians (n=132) included 835 COPD patients followed over 4 years. Sociodemographic data, clinical history, symptoms, lung function data and treatments were initially recorded. COPD clinical features, pulmonary function tests, treatments and the onset of exacerbations were recorded by the investigators at follow-up visits. Patients also completed exacerbation diaries. The KmL method was used to identify frequent and non-frequent exacerbators. This analysis was conducted in 464 patients with complete exacerbation-related data.

Results: 2 groups with homogeneous numbers of exacerbations were identified. The 1st group consisted of 114 (24.6%) patients who were frequent exacerbators (mean, 3.5 exacerbations/patient/year; SD: 1.3). The 2nd group consisted of 350 patients (75.4%) who experienced fewer exacerbations (mean, 0.9 exacerbations/patient/year; SD: 0.7). Frequent exacerbators were found to have a higher dyspnea score, a lower FEV1 (% predicted vs 50.3% P<0.0001) and reported more impaired daily activities (38% vs 18%, p < 0.0001), more frequent chronic cough (p < 0.01) and sputum production (p < 0.001) more frequently. Their slope of FEV1 decline was steeper.

Conclusion: Frequent exacerbators appear to belong to a distinct, clinically relevant, COPD phenotype.

P4748 Distribution of a COPD population based on the GOLD assessment framework
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Background: GOLD 2011 proposed a new COPD assessment framework based on: 1. Risk of future adverse health events, using FEV1 <50% and/or history of ≥2 exacerbations in the previous year to identify patients at high risk; 2. Symptom level using either COPD Assessment Test (CAT™) or modified Medical Research Council Dyspnoea Scale (mMRC). This analysis focuses on the GOLD symptomatic cut-off for high symptoms of CAT ≥10 or mMRC ≥2.

Methods: Data from 1041 EU COPD patients (38.5% from primary care) in the 2011 Adelphi Disease Specific Programme were used providing CAT and mMRC scores, spirometry and the previous year’s exacerbation history.

Results: One third (32.9%) of all patients had ≥2 exacerbations in the preceding year (79.5% had an FEV1 ≥50, almost all (97.7%) were on maintenance treatment. The correlation between CAT and mMRC scores was moderate (r=0.55). Within each mMRC Grade, there was a wide distribution of CAT scores. The mMRC categorised more patients as having low symptoms (51.2%) than the CAT (10.0%). The mMRC categorised 13.4% of patients as having low symptoms and high risk (FEV1 <50% and/or ≥2 exacerbations in the preceding year). The CAT categorised only 0.7% of patients with this paradoxical picture.

GOLD Group Symptoms Risk Using CAT (% of patients) Using mMRC (% of patients)
A Low Low 9.3 37.8
B High Low 48.5 20.1
C Low High 0.7 13.4
D High High 41.5 28.8

Conclusion: There was a modest concordance between CAT and mMRC. The mMRC cutpoint score of ≥2 (“I have to stop for breath when walking at my own pace on the level”) for high symptoms appears to classify too many patients as having low symptoms. Use of MRC Grade ≥1 as the cut point should be explored.
P4753 COPD subtypes most likely to benefit from inhaled corticosteroids (ICS) during the exacerbations: \textit{Cluster analysis}.

\textbf{Methods:} We re-analysed two, pooled 1-year clinical trials (SCO40023, SCO100250) of 1,543 subjects with a COPD exacerbation history who were randomised to salmeterol/fluticasone propionate (SFC) or salmeterol alone (SAL). Cluster analysis maximised treatment differences between groups on major annual exacerbation rates. A negative binomial regression model was used, adjusting for baseline FEV1 predicted, reversibility stratum (≥12% and ≥70mL), time on treatment, and region. Data included lung function, demographics, COPD history, St George's Respiratory Questionnaire (SGRQ), and 19 medication classes. 

\textbf{Results:} Three distinct COPD clusters were identified based on diuretic use and reversibility of exacerbations (Cluster 1, no diuretic or with diuretic use; Cluster 2, with diuretic use; Cluster 3, no diuretic use). Patients in Cluster 1 had lower exacerbation rates with SFC vs. SAL (0.95 vs. 1.7 and 1.1 vs. 1.7 per/yr, respectively). Patients in Cluster 2 had higher exacerbation rates with SFC vs. SAL (1.1 vs. 1.7 per/yr, respectively). Patients in Cluster 3 had lower exacerbation rates with SFC vs. SAL (1.3 per/yr) and less severe obstruction compared to Cluster 1 (median FEV1: 38% vs. 32%). 

\textbf{Conclusions:} The greatest ICS benefit on exacerbations was in two COPD clusters: 1) patients with diuretics as well as more treatment for co-morbidities and 2) patients with ≥12% bronchodilator reversibility. Cluster analysis results may aid physicians in implementing personalised medicine. (Funded by GSK; WEUSK/GP5831).

\section*{P4754} 

\textbf{Association between serum clara cell secretory protein (CC-16) levels and asthma-related phenotypes among adults from the EGEA study} 

\textbf{Methods:} A total of 2,04,912 patients visited 7400 GPs, Gen Ps and Ps in India on 13,225 GPs, Gen Ps and Ps from 22 states and 5 union territories across India were randomly selected from 880 cities and towns and invited to participate in a 1-day point-prevalence study. On 1st Feb 2011 those doctors who agreed to participate kept a record of all symptoms and diagnosis for which patients visited their clinic or hospital. 7710 doctors consented and clean data was obtained from 7400 doctors (65% GPs, 17.4% GenPs and 17.6% Ps). Data was transferred into Epi-Info software and simple descriptive analysis was performed. 

\textbf{Results:} A total of 2,04,912 patients visited 7400 GPs, Gen Ps and Ps in India on 1 day. Amongst these, 16,783 patients visited a doctor for a diagnosis of asthma or COPD accounting for the highest number of visits (8.2%). Systemic hypertension (HT), anemia, diabetes and eczema accounted for 7.8%, 5.5%, 4.8% and 2.3% of the visits respectively. These observations were generally uniform across India, with no disease hot or cold spot regions. 

\textbf{Conclusion:} In this study, the above figures to around 15,00,000 registered GPs, GenPs and Ps in India, 3.5 million (m) patients visit a doctor every day in India for OADs, followed by 3.3 m for HT, 2.3 m for anemia, 2 m for diabetes and 1 m for eczema.
P4756

Time trends (1985-2011) in asthma and rhinitis in Italian general population samples
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Aim: To estimate trends in the prevalence of asthma, asthma-related symptoms and risk factors such as allergic rhinitis and smoking.

Methods: Three surveys were carried out on general population samples living in Pisa, Italy; in 1985-88 (PI1,n=3267), 1991-93 (PI2,n=2604) and 2009-2011 (PI3,n=1619). Subjects filled in standardized questionnaires on respiratory symptoms, asthma, rhinitis and smoking habits. In PI1 and PI2 the same questionnaire was administered, whilst in PI3 the IMCA2 questionnaire, with different wording of the questions (particularly about rhinitis), was used. To compare the disease/symptoms prevalence within the samples the same age range (18-97 yrs) was selected. Comparison of variables across studies was performed by Pearson Chi-squared test.

Results: Both the prevalence of asthma diagnosis and current asthma attacks show a trend to increase. Current rhinitis increased from PI1 to PI2 and doubled from PI2 to PI3. Current smoking significantly decreased among the three surveys.

P4757

The prescribing patterns for asthma in general practice setting: Adherence to GINA guidelines
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Background: General practitioners (GPs) are the first healthcare professionals whom asthma patients refer to for their symptoms.

Aim: To assess drug prescription for asthma by GPs and to evaluate prescriptive adherence to GINA guidelines (GL).

Methods: 107 GPs throughout Italy provided data on 995 asthmatic patients (45% males, mean age 43.3±17.7 yrs).

Results: 48.5% of patients had intermittent (48.5%) or mild persistent asthma (25.3%); 61% had co-morbid allergic rhinitis (AR). More frequently, prescribed medicines were a combination of inhaled corticosteroids (ICS) plus long-acting β2-agonists (LABA) (55%), and short-acting β2-agonists (SABA) as mono-therapy or in combination with ICS (46%). In general, prescriptive appropriateness was higher for patients with only asthma (25%) than for those with asthma+AR (16%). Regardless of concomitant rhinitis, the lowest adherence to GL was found in the mild persistent asthma category (11%), whilst the highest was in the severe persistent group (56.3%).

Conclusion: In general, we found low adherence of GPs to GINA GL recommendations, with a trend to over-treatment of intermittent asthma; conversely, more appropriate therapeutic regimens were applied for severe asthma.

P4758

Estimated steps from motion detectors worn at the wrist, waist and ankle in COPD patients
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Increased walking activity is desirable in COPD patients, but its direct measurement presents a problem in slow-moving individuals. Accordingly, we tested the effectiveness of a tri-axial accelerometer in estimating steps in patients with COPD. Devices were simultaneously worn on the dominant side on the wrist, waist, and ankle. Estimated steps were compared to visually-counted steps in 14 patients (FEV1 52±22%). Step counting was performed at three walk speeds during endurance shuttle testing: 1) at the lowest shuttle walk speed (1.78 km/hr), 2) at 85% of maximal (3.18±0.53 km/hr), and 3) at mid-way between these extremes (2.50±0.33 km/hr). The graphs (3 observations per patient) demonstrate the relationships between estimated steps from the 3 locations and visually counted steps. The diagonal line is the line of identity.

The devices significantly predicted counted steps (r²= 0.57, 0.46 and 0.65 for wrist, waist and ankle locations, respectively, p < 0.0001 for all). However, the wrist and waist devices underestimated visually-counted steps at all walk speeds (-137±76 and -167±80 steps, respectively) although less-so at higher speeds, while the device on the ankle came closer: -55±57 steps (all, p < 0.0001). In summary, the accelerometer on the ankle appeared to be more accurate and precise as a step-counter in COPD patients.

P4759

Validity of activity monitors for physical activity assessment in patients with chronic obstructive pulmonary disease
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Rationale: Physical inactivity (PA) and symptoms during PA are hallmarks of COPD.
P4760 Performance of activities of daily living as a predictor of respiratory hospitalization for patients following an exacerbation of COPD
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Purpose: To evaluate the rehospitalization rates for patients with COPD using performance of activities of daily living (ADLs) as a metric marker.

Methods: The Discharge, Assessment, and Summary @ Home (D.A.S.H., Klingensmith HealthCare, Ford City, PA, United States) program is a respiratory therapy-driven home care program based for patients with COPD who are using supplemental oxygen following discharge from the hospital following a COPD exacerbation. The program includes the performance of four patient selected ADLs (e.g. walking the four points of the home, loading the dishwasher) on days #1, #7, and #30 post-hospitalization. Oxygen saturation is maintained above 90% using a SmartDose Oxygen-delivery system. Each ADL is measured as either fully completed or not completed.

Results: 68 patients were recruited in four centres each wore simultaneously four out of six available activity monitors validated in chronic conditions (Lifecorder Plus, ActiWatch Spectrum, RT3, Actigraph GT3X, DynaPort MoveMonitor and SenseWear Armband) during waking time for 14 consecutive days. AEI was measured (0.9; Total Energy Expenditure (TEE) [DLW]-resting metabolic rate) and the validity of the monitors was evaluated by correlations between AEI and monitors outputs and through multiple regression analysis using TEE as the dependent variable with total body water (TBW) plus several PA monitors outputs as independent variables.

Results: Except for the Lifecorder Plus and the RT3, the remaining four monitors met the validation criteria. Actigraph GT3X and DynaPort MoveMonitor explained the majority of the TEE variance not explained by TBW (53% and 79% respectively) and showed significant correlations with AEI (p=0.63 p<0.0001, r=0.55 p=0.0001, respectively).

Conclusions: The present findings should guide users in choosing valid activity monitors for research or for clinical use in patients with chronic diseases such as COPD.

Funded by: The Innovative Medicine Initiative Joint Undertaking (IMI IU # 11S011)

P4761 Effects of a 3-week inpatient pulmonary rehabilitation (PR) on activity parameter in patients with COPD
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Rationale: Physical activity (PA) level in patients with COPD is markedly reduced in comparison to elderly healthy people. The aim of this study was to investigate the effect of a 3-week inpatient rehabilitation program (PR) on activity parameter measured by SenseWear®.

Methods: Forty patients with COPD, stage III-IV (age: 62±5y; BMI: 26±5kg/m²; FEV1: 56±30%pred.) were included in this prospective trial. PA was measured by SenseWear® Armband in all patients for 3 days at the beginning and at the end of inpatient PR. Additionally, quality of life was requested by SF36 questionnaire and each patient performed a 6-minute walking test (6MWT) (after treatment) pre and post PR.

Results: 6MWD improved significantly following PR (+391 ±95% CL, +69 to +8) p=0.001. We observed an increase in mental score of SF36 (+5.10 ±2.8, p=0.01). No significant differences between PA parameter pre and post PR were found: total energy expenditure (+35.27±139kal, p=0.49), steps per day (+293±1419, p=0.20), metabolic rate (-0.01±0.28, p=0.78), duration of PA more than 30fold basic metabolic rate (+4.9±4.7, p=0.63) were seen. There was no significant difference in PA data between 24 hours calculated as the mean of 3 days compared to the PA data of the first 24 hours of the 3 day measurement.

Conclusions: These data show that there are no relevant changes in PA following inpatient PR. Although exercise capacity and quality of life are improved. We hypothesize that an inpatient setting predetermines the daily amount of PA that is not similar to the activity chosen in daily life at home. We conclude that PA measurement may not be appropriate as an outcome parameter for an inpatient PR.

P4762 The usefulness of pedometry in patients with chronic obstructive pulmonary disease
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Introduction: Effort tolerance and daily physical activity (DPA) is predictive of quality of life and survival in COPD patients, but still remains difficult to assess on their real life.

Aim: How to relate pedometry with other classical parameters commonly used in pulmonary rehabilitation (Respir Med).

Methods: DPA has been evaluated by pedometry to 74 patients with COPD, age 63.55±8.73 (12 stage II, FEV1=0.16±7.78%; 29 stage III, FEV1=0.39±0.67; 30%; 33 stage IV, FEV1=0.23±1.7±8.18%). Monitoring for a period of 7 days has been done before and 6 months after a PR of 3 weeks.

Results: Values have been widely dispersed with a maximum of 17420 and minimum of 964 steps/24hrs. Average values acquired: lowest in COPD stageIV, still with the highest increase over 6 months of PR +636 steps/24hrs (2476.32±2104.12 vs 3112.63±2088.46 steps/24hrs, p < 0.02); in COPD stageIII the increase of DPA was +579 steps/24hrs over 6 months (5627.44±3135.15 vs 6224.32±2105.19, p < 0.04); in COPD stageII was the lowest increase +540 steps/24hrs (8724.33±2908.34 vs 9264.16±2405.18, p < 0.13), probably because the subjects belonging to this stage had the best preserved DPA.

Conclusions: DPA decreased opposite COPD stage; it is fluctuant with every subject, dependant of clinical status, weather and daily schedule. Wearing pedometers is very easy and motivational, provided that patients realize that they are being "watched".
COPD, there is limited available information on those phenotypic factors that determine real-life daily physical activity.

**Aim:** The objective of this pilot study was to examine the impact of baseline lung dysfunction, exercise capacity and quadriceps muscle strength on daily walking movement intensity (WalkMI), walking energy expenditure (WalkEE) and average muscle force (QuadsMF). Physical activity was measured over 14 consecutive days using the ActiPoint MoveMonitor triaxial accelerometer.

**Methods:** 20 COPD patients (age: 66±10; FEV1: 48±15%predicted; FMMI: 18±3) were assessed using an incremental walk test, the 6MWT and quadriceps muscle force (QuadsMF). Physical activity was measured over 14 consecutive days using the ActiPoint MoveMonitor triaxial accelerometer.

**Results:** WalkMI was related to 6MWT (r=0.44, p=0.05) and inversely related to dyspnea sensations during the 6MWT (r=−0.56, p=0.009). WalkEE was positively related to peak oxygen uptake (r=0.57, p=0.009), peak work rate (r=0.59, p=0.006) and FEV1 (β=−0.52, p=0.017) and inversely related to dyspnea sensations during the 6MWT (r=−0.53, p=0.017). QuadsMF adjusted by body weight (r=0.42, p=0.046) and inversely related to peak oxygen uptake (r=0.57, p=0.009), peak work rate (r=0.59, p=0.006) and FEV1 (β=−0.52, p=0.017)

**Conclusions:** Strategies to enhance whole body endurance capacity and locomotor muscle strength would ameliorate daily physical activities along with dyspnea sensations in patients with COPD.

Funded by the Innovative Medicine Initiative Joint Undertaking (IMI JU #115011).

**P4765**

**Reasons to be physically active differ from reasons to be sedentary in COPD:**

**A qualitative analysis**

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The daily physical activity (DPA) level in COPD patients is low, notwithstanding its beneficial effects. For the development of successful prevention and management programs it would be helpful to gain insight in the reasons why COPD patients are physically active or sedentary. The aim of the study is to assess this in a qualitative way.

115 COPD patients (68% male, FEV1/forced expired volume in one second 58±28, age 65±9 years) were interviewed in-depth. Furthermore, DPA (tri-axial accelerometer), lung function and dyspnea (MRC-scale) were determined. Answers were categorized according to the Groningen Codebook. Afterwards descriptive analysis using k-means cluster analysis was performed.

The cluster analysis shows 2 clusters, one cluster with a high DPA level (n=52) and the second with a low DPA level (n=60) (figure 1). A high DPA level was related to being physically active because of fun, because of having a continuous active lifestyle in the past, the number of reasons mentioned to be physically active and self-efficacy. A low DPA level was related to being sedentary because of bad weather influencing health, financial constraints, bad health and shame to be physically active.

**P4766**

**Muscle phenotypes in COPD patients: An exploratory cluster analysis**

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Peripheral muscle dysfunction is a key outcome in chronic obstructive pulmonary disease (COPD) and has been well characterized by reductions in fiber cross-sectional area (CSA) and type I fiber proportion (p<0.05). Reduced fiber CSA and increased protein carbonylation were found only in the most severe cluster of patients (p<0.05). Yet, clusters of patients had the same age (64±8.8 yrs vs. 60±9.0 yrs; p=0.87). Last, an algorithm including 6-minute walking distance, ventilatory threshold, and body mass index accurately classified 57% of the individuals according to fiber atrophy and/or type I fiber regression. These clusters may indicate distinct COPD phenotypes, as they are related to clinical outcome (muscle fiber biologic mechanism and time course) may have differed in the two clusters of COPD patients. Decision trees may improve the identification of COPD patients with distinct muscle features.

Background: Although quadriceps Type I muscle fibre proportion is reduced in patients with COPD, there is conflicting evidence as to whether quadriceps muscle endurance is impaired. We therefore performed a systematic review and meta-analysis of studies comparing quadriceps endurance in COPD to healthy controls.

**Methods:** Studies comparing quadriceps endurance between patients with COPD and healthy controls were identified using six databases (1946-2011) and grey literature. Full text articles were obtained after two researchers independently reviewed the abstracts. Weight standardized mean difference (WSDM) with 95% confidence intervals were calculated by a random effects model for measures of quadriceps endurance.

**Results:** Data were extracted from 17 studies involving 565 patients with COPD and 353 healthy controls. The outcome measurements involved a mixture of techniques. Quadriceps endurance was greater in the controls compared with COPD (WSDM =−1.46 [−0.84 to −2.09]; p<0.001). This relationship was similar both when non-solitonal versus solitonal techniques (p=0.26) or when sustained versus dynamic contractions (p=0.43) were used to measure quadriceps endurance. There was significant heterogeneity between studies.
Validity of the six-minute stepper test in patients with COPD

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Cardio-respiratory fitness assessed by peak oxygen uptake (VO2peak) is an independent predictor of mortality in obesity. We investigated whether VO2peak measured during corridor walking tests was similar to that measured by an incremental treadmill (ITM) test in obesity.

Methods: Individuals with a BMI ≥30 were recruited from a sleep clinic. All patients had treated Obstructive Sleep Apnea. Patients with chronic lung or heart disease were excluded. Participants completed an ITM test; the gold standard to determine VO2peak; two-six minute walk tests (6MWT) and two incremental shuttle walk tests (ISWT) on three separate days in a randomised order.Expired gas analysis was performed during all tests. The difference between the peak parameters for the two corridor tests compared to the ITM was assessed by Dunnett test.

Results: 16 patients completed the study: 8 male, mean [SD] age 58 [12] y, BMI 36.1 [7.6] kg/m2. The results of the second walking test were used. Table 1 shows the peak parameters for the three tests.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ITM</th>
<th>ISWT</th>
<th>6MWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 (ml/min)</td>
<td>2266 [478]</td>
<td>2017 [561]</td>
<td>1778 [340]*</td>
</tr>
<tr>
<td>VCO2 (ml/min)</td>
<td>2636 [695]</td>
<td>2210 [714]</td>
<td>1676 [471]*</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>82 [25]</td>
<td>73 [26]</td>
<td>56 [13]*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>134 [30]</td>
<td>142 [27]</td>
<td>127 [21]</td>
</tr>
</tbody>
</table>

*Significantly different to ITM (p<0.01). VCO2 = carbon dioxide output, VE = minute ventilation, RER = respiratory exchange ratio.

The limits of agreement for VO2 peak between the ITSM and the ISWT was 730 m/min.
P4773
Long-term adherence to exercise after pulmonary rehabilitation: What are the motivating factors and barriers?

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Introduction: Adherence to exercise after PR is known to be low, but motivation/barriers to exercise in this population are unclear. This study aimed to investigate motivation and barriers to exercise post PR.

Method: A postal survey was sent to 112 (38%) participants who completed >50% of a PR program in the previous three years. Collating demographics, physical activity level, exercise information and participants’ views of their motivation (21 items) and barriers (14 items) to exercise, quantified along a 5-point Likert scale.

Results: 51.8% (n=58) responded; mean age 71.72, MRC dyspnoea 2.86 and co-morbidities 90.1%, COPD=87.9%. Individual’s motivation and barrier mean were calculated, but did not correlate, mean barrier did correlate with; MRC (p=0.003), co-morbidities (p=0.001) and intent to exercise (p=0.001). The most frequent (always/everytime) motivating reasons were: I want to improve my fitness=82.7%; I want to be physically fit=80.4%; I exercise for health concerns=72.6%. Barriers were: shortness of breath=58.4% and lack of energy=52.2%. Significant differences in motivation/barriers were identified between exercisers (> once a week most weeks co-morbidities and non-exercisers, but not time since completion of PR. Preferred options to motivate exercise were: weekly PR group 47.4% and repeat PR yearly 42.1%, those with a higher motivation (p=0.039) or lower barrier (p=0.011) opted for the weekly PR group significantly more.

Conclusion: This study quantified motivation/barriers to exercise post-PR identifying many items that significantly differed depending on exercise level: these do not change significantly over time and may predict long-term exercise preference.

P4774
Effect of pulmonary rehabilitation on erythrocyte oxidative stress and antioxidants in COPD patients

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Background and objective: Recent studies suggest that pulmonary rehabilitation (PR) is essential in the management of COPD. However, the effect of PR on oxidants and antioxidants in erythrocytes is only partially understood. The aim of this study was to evaluate whether PR improves not only exercise capacity and health-related quality of life (HRQoL), but also the oxidant/antioxidant imbalance in erythrocytes.

Methods: Twelve stable COPD patients participated in PR for 8 weeks. A pulmonary function test, 6-minute walking test (6MWT), shuttle walk test (SWT), and the St. George’s Respiratory Questionnaire (SGRQ) were administered before and after PR. Blood was collected prior to and after PR for analysis of thiobarbituric acid-reactive substances (TBARS), superoxide dismutase (SOD), Cu-Zn-SOD, glutathione peroxidase (GPX), and total glutathione (GSH).

Results: After PR, exercise capacity was improved (6MWT: 399.5±28.6 vs 455±31.7 m, P<0.01; SWT: 335.6±45.9 vs 373±47.1 m, P<0.01). There were reductions in the SGRQ total, symptoms and activity scores, indicating a clinical improvement, but no significant difference in TBARS pre and post PR. Erythrocyte CAT activity and GSH were significantly increased after PR (CAT: 158±6±4 vs 174±4±6 μkat/l, P<0.05, GSH: 4.9±0.7 vs 5.6±0.7 μmol/l, P<0.05), but there were no differences in the erythrocyte SOD and GPX activities and the Cu-Zn-SOD concentration.

Conclusion: The current study suggested that PR improved exercise capacity and HRQoL, and upregulated antioxidant capacity, resulting in no further increase with repeated exercise. PR improved exercise capacity and health-related quality of life (QoL), and inflammation.

P4775
Introduction: In obesity, the ISWT VO2 pk more closely reflects ITM VO2 pk than the 6MWT VO2 pk, but is not predictive in an individual.

P4776
Farming environment during infancy and lung function at age 31 – Prospective birth cohort study in Finland

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Aims: Investigate the prospective associations between farming environment during infancy and lung function in adulthood has not been studied earlier.

Methods: Childhood in a farming environment may protect from obstructive-type lung disease in adulthood. The prospective association between farming environment during infancy and lung function in adulthood has not been studied earlier.

Results: While CRP decreased in both groups (p<0.05), we found a significant increase in the 6-MWT (p<0.005) and a significant decrease in the CAT (p<0.05) in the PTG group only (table 2).

Conclusion: In patients hospitalised due to an exacerbation of COPD, the addition of active muscle contraction with the Galileo system results in beneficial effects on QoL and exercise capacity.

947. Air pollution: from the particles in town to the pollutants in the countryside
P4777

Latitude variation in the prevalence of asthma and allergic rhinitis in Italy: Results from the GEIRD study

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Background: Earlier studies have pointed out a great variability in the prevalence of asthma and asthma-like symptoms in different geo-climatic areas.

Aim: To test the association between latitude and prevalence of asthma and allergic rhinitis.

Methods: In the frame of Gene-Environment Interaction in Respiratory Diseases study, a postal screening questionnaire on respiratory health and exposure to environmental factors was administered to 18,357 randomly selected subjects aged 20–44 years in 7 centres: 1 in Northern (Trento, Pavia, Verona), 2 in Central (Ancona, Perugia) and 2 in Southern Italy (Salerno, Sassari).

Results: 10,494 (57.2%) subjects responded to the questionnaire. The prevalence of self-reported doctor-diagnosed asthma and allergic rhinitis in the lifespan was 10.2% and 26.9%, respectively, and was significantly different across the centres (p < 0.05). After adjusting for sex, age, potential risk factors for respiratory disease and allergic reactions, the prevalence of asthma (OR: 1.07 per 1° latitude decrease; p < 0.001) and asthma-like symptoms (wheezing, chest tightness, asthma attacks: OR ranging from 1.04 to 1.06; p < 0.05) and allergic rhinitis (OR: 1.03, p=0.04) showed a significant north-to-south trend. Similarly, a 1°C increment in temperature was significantly associated with asthma (OR: 1.10, p < 0.001) and asthma-like symptoms (OR from 1.07 to 1.10, p < 0.05), but not with allergic rhinitis (OR=1.02, p=0.190).

Conclusion: The prevalence of asthma and allergic rhinitis increased moving southwards in Italy, suggesting that prolonged exposure to different geo-climatic conditions may affect the onset of asthma and allergic respiratory diseases.

P4779

Association between daily levels of air pollution and school absences in the proximity of a cement plant in Italy

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Background: Emission of dust represents the main hazard associated with cement production and may cause adverse respiratory health effects to the population living nearby.

Aim: To evaluate the association between daily levels of PM2.5 and a morbidity indicator (school absenteeism) in children aged 7-14 years attending a school within 2 km from a cement plant in Fumane (Northern Italy).

Methods: Data on absences of students (average: 461 students/year) and daily concentrations of PM2.5 from a fixed monitoring station placed in the schoolyard were collected for 3 school years (541 school days from November 2007 to June 2009). The association between average level of pollutants from Lag 0 to Lag 4 and school absences confirmed the presence of a statically significant association with PM2.5 levels (RR: 1.016; 95% CI: 1.003-1.029 for each μg/m3 increase).

Conclusions: Daily PM2.5 levels are associated with school absences, a proxy indicator of short-term morbidity, in children who attend schools in proximity to a cement plant. Primary prevention interventions aimed at reducing air pollution in the area are recommended.

P4780

Lung function and respiratory symptoms of Brazilian sugarcane cutters exposed to biomass burning

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Brazil is the largest producer of ethanol from sugarcane in the world and part of this production is still manually harvested and for this, it needs to be burned. This action releases toxic gases that cause lung damage. The aim of this study was to evaluate the lung function and frequency of respiratory symptoms of sugarcane cutters exposed to biomass burning. We evaluated twenty-three male sugarcane cutters (age=25.4±7 years, BMI = 24.8±3 kg/m2), non-smokers, from Sugar and Ethanol Company located in Brazil. Evaluations were performed in the pre-harvest and harvest. Lung function was assessed by spirometry and respiratory symptoms by questionnaire. Data normality was tested by the Shapiro-Wilk test, and comparison of spirometric values in the two periods was performed using the paired t-test. To compare the qualitative variables we used the Goodman test. The level of significance was p=0.05. In the pre-harvest spirometric values were: FVC (4.4±0.57), FEV1 (93.8±1.43), FEV1/VC (3.9±0.47), FEV1% (96.3±13.3), FVC/FEV1 (89.4±5.55) and FVC/FEV1% (104.8±1.22). In the harvest of we found the following values: FVC (4.5±0.85), FEV1 (94.5±14.1), FEV1 (3.9±0.47), FEV1% (90.3±13.3), FVC/FEV1 (83.6±7.85) and FVC/FEV1% (94.4±10.14). There was a statistically significant decrease in FEV1% (p<0.033) and FVC/FEV1 (p=0.002) after harvest. The prevalence of difficulty of breathing when there is dust and/ or climate change increase after harvest. Our results suggest that six months of harvest leads to airway obstruction and increases respiratory symptoms in these workers.

P4781

Dampness, mould and endotoxin in primary schools and lung function in children: The international HIITEA study

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Respiratory health effects in relation to moisture in homes are well recognised, but little is known on effects of dampness in school environments. We have previously reported a higher prevalence of respiratory symptoms in pupils from moisture damaged schools. Here we aim to study associations between dampness and visible mould in school buildings, endotoxin exposure and lung function in children.

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We included 15 Spanish, Dutch and Finnish primary schools with and 10 without moisture, dampness and visible mould based on reports and inspections. Endotoxin in settled dust was measured in 237 classrooms. Acceptable forced spirometry tests were done in 2736 children aged 6-12 years. Associations between measured log-transformed endotoxin levels and lung function were assessed by multiple linear regression adjusted for gender, age, height, home moisture, ETS, parental education, technical, school and (for endotoxin analyses) school moisture status. In the Netherlands and Finland, FEV₁ and FEF25-75 tended to be higher in children attending damaged schools or classrooms with higher endotoxin levels. FEV₁ was 39% (95% CI 5-72%) higher in Dutch children attending damaged schools and in Finland FEV₁ significantly increased with increasing endotoxin exposure. In Spain, FEF25-75 tended to be somewhat lower, but not statistically significant, in relation to school moisture status and increased endotoxin levels. Our findings do not provide consistent evidence for adverse effects of moisture damage in the school environment on lung function in children. Heterogeneity across different geographical areas may be related to climate, ventilation characteristics and type of school building.

P4782 Fate of inhaled ultrafine carbon particles after one week; human exposure using a novel aerosol with 111Indium

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Particulate air pollution, such as nanosized particles <100 nm in diameter, has negative health effects. But, there is still limited knowledge regarding the fate of inhaled particles in the human body. Controlled exposure conditions provide information about the biological pathways of particle pollutants, such as deposition and retention, in human body. Recently we have developed a method for labelling ultrafine carbon particles with an indium isotope (111In), and generating an aerosol, which enables long-term deposition and retention studies in humans (Sanchez-Crespo, et al. 2011: 111Indium-labelled ultrafine carbon particles..." Inhal Toxicol 23(3): 121-128). In the present study ten healthy volunteers were exposed for the aerosol (particle size range 58-124 nm) and followed for seven days. One volunteer was followed for totally 29 days. One week after the exposure, pulmonary particle retention was 92%. There was no elimination of particles from the body via urine. The total in vitro leaching of 111Indium was 0.3%, which indicates a stable bonding between the labelling have higher levels of activity. Conclusions: We conclude that measurements with indium-111 enables longer follow-up studies as a novel tool in ultrafine particle tracking.

P4783 Particulate air pollution on systemic inflammatory response: Roles of monocytes and neutrophils

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Research has increasingly demonstrated the detrimental effects of air pollution on systemic human diseases. However, there has been little examination of the pattern and scope how neutrophils and monocytes respond to the inhalants. We exposed C57BL/6 mice to ambient fine particulate matter (PM2.5) in a timely manner to investigate the roles of neutrophils and monocytes. C57BL/6 mice were exposed to PM2.5 or filtered air 6 hours a day, 5 days a week for up to 3 weeks in Columbus, OH in a versatile aerosol concentration enrichment system. The measurements were conducted at days 5, 14, and 21 for circulating inflammatory biomarkers via magnetic beads, leukocytes rolling and adhesion in mesentry via intravital microscopy, inflammatory responses in the lung and visceral adipose tissues via flow cytometry and immunohistochemical staining (IHS), and inflammatory chemotactic responses via Boyden chamber. We found that both rolling and adhesion leukocytes were increased in mesentry, especially at days 14 and 21. Circulating MCP-1, IL-6, and TNFα were elevated, especially at day 5. There were increases in Ly6G (neutrophil) and F4/80 (monocyte) expression from lung bronchoalveolar lavage by flow cytometry and lung and visceral adipose tissues by IHS, especially F4/80 expression throughout the entire course. Boyden chamber assay also indicated that lung and visceral adipose tissues were "inflamed", especially monocytes/macrophages after PM2.5 exposure. We concluded that, in this murine model of inhalational exposure to ambient PM2.5, the murine monocytes respond rapidly to chemokines locally (in the lung) and systemically (in visceral adipose tissue), which may not be accompanied by neutrophils.

P4784 PM10 is associated with an increase in day-by-day respiratory variability in asthma

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Rationale: Whilst particulate air pollution is well recognized as a contributor to greenhouse gas emissions and thus plays a vital role in global warming, exposure is also detrimental to cardiovascular and respiratory health. The environmental impact of switching to more sustainable fuels is well accepted; however there is little evidence of potential health benefits that may result from such an approach. Here we examined cardiovascular and respiratory effects after inhalation of biodiesel blend and petrodiesel exhaust.

Methods: 16 healthy subjects were exposed to petrodiesel exhaust and biodiesel blend (30% rapeseed methyl ester (RME30) blended with petrodiesel) for 1h, standardized for PM mass concentration of 300 μg/m³. Vascular somatomotor function was assessed with forearm venous occlusion plethysmography, using acetylcholine, bradykinin, sodium nitroprusside and verapamil. Additional cardiorespiratory measurements were also performed throughout.

Results: Infusion of all vasodilators caused a dose-dependent increase in forearm blood flow (P<0.01 for all), which was similar following both exposures (P>0.05 for all), but attenuated as compared to filtered air exposures from previous studies. Results: Diesel exhaust inhalation is known to impair vascular endothelial function, which is linked to an increase in cardiovascular events. This study demonstrates that replacing 100% petrodiesel with RME30, a commercially available mixture, results in similar adverse effects, and suggests there are unlikely to be any health gains in switching from petrodiesel to RME30. We suggest that these adverse health effects should be taken into consideration alongside environmental concerns when assessing future developments.
P4786
Respiratory effects in a chamber study of diesel exhaust exposure in healthy volunteers
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Background: In previous chamber studies of diesel exhaust exposure by the Umea group, volunteers were exposed to particle mass concentrations (PM) of 300 μg/m³ for 1 hour. Clear effects were found in bronchial biopsies and BAL, but not in crude lung function tests.

Aim: To examine whether exposure to diesel exhaust at 300 μg/m³ for 3 hours would cause symptoms, signs and lung function changes.

Methods: Eighteen healthy subjects were exposed twice to diesel exhaust at 300 μg/m³, and twice to clean air (<3μg/m³), in a double-blind cross-over design, at least one week apart. NO₂ levels were about 1.4 ppm. Before and after exposure measures of respiratory function and symptoms were performed. Symptom scores were assessed before and after, and after 15, 75, and 135 minutes of exposure. Generalized Estimating Equation models were used to analyze changes from baseline, adjusted for exposure sequence.

Results: Symptom scores for eyes and throat were higher during diesel exhaust exposure than during filtered air after 75 and 135 minutes. Signs of irritation in upper airways were more common after diesel exhaust exposure. PEF increased during filtered air exposure, but decreased during diesel exhaust, with a statistically significant difference after 75 and 135 minutes. There were no such differences for spirometry.

Discussion and conclusion: Increased symptoms and signs from eyes and upper airways were to be expected, while a decrease of PEF has not been reported previously. Repeated PEF measurements during exposure may be statistically more powerful than spirometry before and after exposure. Symptoms, signs, and lung function changes were found at exposure levels much lower than occupational limit values.

P4787
Effect of NO₂ on inflammatory response in subjects with asthma
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Patients with asthma may be more susceptible to NO₂. Our aim was to investigate whether repeated exposure to realistic indoor concentrations of NO₂ enhances inflammatory response in the airway of subjects with asthma. Participants were 19 non-smoking subjects with intermittent asthma and airway hyperresponsiveness during methacholine challenge. The study had a double-blinded, crossover design. On day 1, subjects were exposed to either 200 ppb NO₂, 600 ppb NO₂, or purified air for 30 min, and on day 2, to the same pollutant, for 2 x 30 min. The order of exposure to the two concentrations of NO₂ and air-only was randomized and exposures were separated by 2 weeks. Markers of inflammation were measured in sputum daily, 6 hours after the first (on Day 1) and the third exposure (on Day 2) and 48 h after the first exposure (Day 3) and compared to baseline. The effect of NO₂ on bronchial responsiveness to methacholine was tested at baseline and on Day 3. Exposure to 200 ppb or 600 ppb NO₂ had no direct effect on respiratory function either during or after the exposure sessions. Compared to baseline, the variation in the percentage of eosinophils in induced sputum after exposure to NO₂ was -2% after air, +16% after 200 ppb NO₂, and +7% after 600 ppb NO₂. Linear association between the variation and the level of exposure was significant (p=0.01). Exposure to NO₂ did not cause any change in lung function and no NO₂-related effect on responsiveness to methacholine was found. NO₂ exposure had a significant and dose-related effect on the eosinophilic inflammatory response of patients. These data suggest that exposure to NO₂ might enhance the eosinophilic activity in sputum in subjects with intermittent asthma.

P4788
Noise exposure during sleep and risk of OSAS: A population-based study
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Objective: To determine the association between chronic arsenic exposure through drinking groundwater and risk of obstructive sleep apnea syndrome (OSAS) in a representative sample from the Pakistani population.

Methods: A time series of daily cardiopulmonary ERV/HAs between the years 2003 and 2009 was made from hospital registar data. Three-day moving averages of exposure variables PM10, nitrogen dioxide (NO₂), O₃, and weather variables were calculated. The ERV/Ha counts were regressed on the exposure variables with Generalized Additive Models assuming Poisson distribution, and time trend adjustment using Cubic splines. The relative increase in number of events per interquartile range (IQR) increase in pollutant level was calculated from the model coefficients with a 95% confidence interval (CI).

Results: Mean daily number of ERV/HAs was ten, 76% were cardiac and 60.8% were not. Intercorrelations are low, a large fraction of particulate matter with aerodynamic diameter ≤ 10(μm) (PM10) is from natural sources, and ozone (O₃) peaks in early in spring. This study aimed to study short-term associations between pollution levels and daily emergency room visits and hospital admissions (ERV/Ha) for cardiopulmonary causes.

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**P4791**
**Measuring the health of the 2012 European green capital, Vitoria-Gasteiz:**

"The impact of air pollution and weather conditions on COPD"

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**Background:** On October 21, 2010, the European Commission designated Vitoria-Gasteiz European Green Capital 2012. The air that the citizens breathe received the highest score given to any city. Only 65 km far away from Vitoria-Gasteiz, Bilbao is the second industrialized region of Spain, behind Barcelona.

**Aims:** To compare the impact of air pollution and weather conditions on COPD in two cities from the Basque Country, very close by distance, but with a different environmental scenario.

**Methods:** Between January 2010 and December 2010 in Santiago Hospital (Vitoria-Gasteiz) and Basurto Hospital (Bilbao) all admissions for COPD exacerbations were retrospectively evaluated. The daily average values of NO2 and Ozone (both oxidant air pollutants), and meteorology data were obtained from the Basque Meteorological Agency.

**Results:** Measuring air quality, in Vitoria-Gasteiz the NO2 exposure average was low. In contrast, in Bilbao, ozone concentration was >100 μg/m³ several times over the year.

**Conclusions:**
- NO2 (Vitoria-Gasteiz) 28 μg/m³; 0-78 μg (mean annual) 40 μg/m³ (maximum daily mean of hour)
- Ozone (Bilbao) >100 μg/m³ 100 μg/m³ maximum daily mean of hour

Pearson correlation for COPD exacerbations rate and air pollution was: Ozone: 0.75 (p<0.01), NO2: 0.72 (p<0.01). The weather correlation was not significant, but there was an inverse relation between higher NO2 levels and lower temperatures, r=-0.74 and NO2: 0.73 (p<0.01). The weather correlation was no significant, but there were no significant differences in the distribution of genotypes of polymorphisms of GSTT1 null patients and healthy controls, and in lung cancer GSTT1 null polymorphism was found to significant associated (OR=0.47; 95% CI=0.30-0.73;p<0.001). But GSTM1 null polymorphism was not significant associated with lung cancer patients. In subgroup analysis in age, we found GSTM1 N/P polymorphism significantly associated between age 50–60 years for COPD (OR=0.21; 95%;CI=0.07-0.60; p=0.03), but in case of Lung cancer none of GSTT1/M1 null polymorphism were associated (p=0.07).

**Conclusion:** We can conclude that the GST1 null polymorphism was associated with COPD. We also observe that GSTT1 null polymorphism was associated between age group 50-60 years COPD patients but not in case of Lung cancer. So we can conclude that aging have affect of COPD not in lung cancer patients.

**P4794**
**Proteinase activated receptor-1 (PAR-1) polymorphisms and susceptibility to exacerbations in COPD**

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**Introduction:** COPD is a condition of global importance, characterized by accelerated lung function decline and an abnormal inflammatory response. Exacerbations (i.e. episodes of acute deterioration of respiratory health) account for much of the morbidity and mortality in COPD. The reasons why some patients are more susceptible to exacerbations is poorly understood, but familial clustering suggests that there may be a genetic basis. Proteinase activated receptor-1 (PAR-1) activation leads to the generation of several inflammatory mediators involved in COPD and our unpublished data have shown that functional polymorphisms of PAR1 are protective in sarcoidosis.

**Aims & objectives:** The aim of this study was to investigate whether PAR1 polymorphisms are associated with COPD exacerbation frequency (ExF).

**Methods:** Two PAR1 SNPs (rs2277744 and rs32934) and a 13bp indel (rs11267092) were genotyped in 136 infrequent and 67 frequent exacerbators.

**Results:** The genotypic distributions of all polymorphisms were in Hardy-Weinberg equilibrium. The rs2277744 SNP showed a statistically significant association with ExF: Frequency of the minor allele was 0.47 in infrequent and 0.37 in frequent exacerbators (OR 1.5, 95%CI 1.0-2.4, p=0.04). Considering exacerbations as a continuous variable, the presence of the minor allele was associated with a significantly lower exacerbation rate (3.03 vs 1.98 exacerbations/year, MWU p=0.04).

**Conclusions:** Taken together with our previous studies showing that the presence of the minor allele at SNP rs2277744 increases PAR1 expression, these data suggest that this SNP may confer a degree of protection against exacerbations in COPD by increasing PAR1 expression.

Funded by the BLF.

**P4795**
**Heterozygosity for F2R2V in ABCA3, lung function and COPD in 64,000 individuals**

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**Background:** There is increasing evidence for a close relationship between aging and chronic inflammatory diseases: COPD is a chronic inflammatory disease of the lungs, which progresses very slowly and the majority of patients are therefore elderly. In this study, we assess whether age in metabolism of phase 2 enzyme gene polymorphisms GSTT1 & GSTM1 in northern Indian COPD and lung cancer patients.

**Material & methods:** In this case study only, we have enrolled 422 study subjects (218 lung cancer & 204 COPD). COPD enrolled after spirometry evaluation and lung cancer patients confirmed by Histopathology. All genotyping were done by PCR-RFLP method.

**Results:** GSTM1 null was found to be significantly higher in COPD patients as compared with healthy controls (OR=2.08; 95%;CI=1.40-3.09; P=0.0001), but there were no significant differences in the distribution of genotypes of poly- morphisms of GSTT1 null patients and healthy controls, and in lung cancer GSTT1 null polymorphism was found to significant associated (OR=0.47; 95%; CI=0.30-0.73;p<0.001). But GSTM1 null polymorphism was not significant associated with lung cancer patients.

**Conclusion:** We can conclude that GSTM1 null polymorphism was associated with COPD. We also observe that GSTT1 null polymorphism was associated between age group 50-60 years COPD patients but not in case of Lung cancer. So we can conclude that aging have affect of COPD not in lung cancer patients.

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CI 3.3-11.4). In elderly, NO2 was associated with an increase of 3.4% (95% CI 0.1-6.8). We found no associations with PM10.

**Conclusion:** In this study, O3 was associated with cardiopulmonary ERV/HAs. NO2 was associated with ERV/HAs in the elderly.
associated with chronic lung disease in childhood, but frequency of chronic lung disease due to ABCA3 mutations in the general population is unknown. We tested the hypothesis that individuals heterozygous for ABCA3 mutations have reduced lung function and increased risk of COPD in the general population. We resequenced 760 individuals and identified three novel (H86Y, A320T, A1086D) and four previously described (P292G, P766S, S1262G, R1474W) in ABCA3. We genotyped the entire Copenhagen City Heart study (n=10,043) to assess the clinical importance of these variants. To validate our findings we genotyped an additional 54,395 individuals from the Copenhagen General Population Study for the E292V mutation. In the Copenhagen City Heart Study E292V heterozygotes had 5% reduced FEV1% predicted (t-test: p=0.008) and 3% reduced FVC % predicted compared with noncarriers (p=0.04) and an increased odds ratio for COPD of 1.9 (95% CI: 1.1-3.1) is in contrast, the A1086D mutation was associated with increased FEV1% predicted (p=0.03) and FVC % predicted (p=0.008) in the Copenhagen City Heart Study. None of the other ABCA3 mutations associated with lung function or COPD risk. In the larger Copenhagen General Population Study, and in the two studies combined, E292V heterozygotes did not have reduced lung function or increased risk of COPD (p>0.11), while this was the case for the positive controls, surfactant protein B (SPPB; 121ins2 heterozygotes and α1-antitrypsin ZZ homozygotes). Our results indicate that partially reduced ABCA3 activity due to E292V is not a major risk factor for reduced lung function and COPD in the general population.

Conclusion: TSPYL-4, NT5DC1 genes polymorphism are associated with susceptibility to COPD and pulmonary function in a southern Chinese Han population.

P4798 Genetics of detoxification and oxidative stress pathways in COPD

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We hypothesized that occupational factors might affect the relationship between genetic predisposition and the risk of chronic bronchitis. Cases were 122 workers with a confirmed diagnosis of occupational chronic bronchitis and controls were 166 healthy workers matched to cases by age, sex and industrial exposure time. 55 SNPs were genotyped by PCR-RFLP. Significant association with occupational chronic bronchitis risk were observed with VDBP 1307C→G, Padj=0.0066, OR=2.54 (95%CI 1.60-4.04), IL8 -210A→G (Padj=0.0016, OR=2.87 (95%CI 1.86-4.69), ADAM33 1394C→G (Padj=0.0004, OR=3.95 (95%CI 2.64-6.04), IL2-447A→G (Padj=0.0008, OR=3.66 (95%CI 2.38-5.69), NQO1 869C→T (Padj=0.0008, OR=3.75 (95%CI 1.35-6.72), UGT2B7 2146C→T (Padj=0.0021, OR=2.34 (95%CI 1.35-4.04), CYPA1 2461delT (Padj=0.0041, OR=2.08 (95%CI 1.27-3.49), CYTP2C19 1293C→T (Padj=0.0046), VDBP 1307C→A (Padj=0.0258), CYPA1 3798T→C (Padj=0.0457).

The formation of occupational chronic bronchitis in workers is determined not only by the composition of harmful dusts and duration of exposure but also the individual characteristics of the organism. The disease occurs predominantly in healthy workers matched to cases by age, sex and industrial exposure time. 55 SNPs were genotyped by PCR-RFLP. Significant association with occupational chronic bronchitis risk were observed with VDBP 1307C→A, 1296G→T (Padj=0.0066, OR=2.54 (95%CI 1.60-4.04), MMPI 519A→G (Padj=0.0001, P=0.0205, 95%CI 1.10-2.80). The MMP12*−519A/A genotype carriers in children had a significantly increased risk of chronic lung disease (OR=4.49; 95%CI 2.33-8.81 for adults). The MMP1*−519A/A genotype were identified as a risk for chronic lung disease (OR=3.64; 95%CI 1.76-7.68 for children, OR=4.49; 95%CI 2.33-8.81 for adults). The MMP1*−519A allele carriers in children had a significantly increased risk of chronic lung disease (OR=1.75; 95%CI 1.10-2.80) The MMP1*−22A/A genotype was identified as a risk for chronic lung disease in children (OR=1.75; 95%CI 1.10-2.80) but not for adults. The genotype and allele frequencies of other MMP genes do not significantly differ in groups. The results of our study suggest the genetic polymorphisms in degradation pathway genes may play a significant role in the development of chronic lung disease.

P4799 New degradome markers in children and adults with chronic lung disease

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The degradome protease a large group of enzymes that act in the extracellular environment have been associated with multiple physiological and pathological processes in lung tissue. Through protein degradation and turnover proteases play an essential role in lung tissue remodeling and repair during the inflammatory response and may be important in the development of chronic lung disease. In our case - control study we investigated common genetic mechanisms of susceptibility to chronic lung disease in children and adults. We analyzed MMP genes in 220 children with chronic respiratory diseases and 230 control and in group of 362 adults with COPD and 483 control, respectively. The following genotypes were detected: MMP1*−519A/A, MMP2*−735C/T, MMP3*−1293C:7632T:9893C of the CYP1A1, 930AG+GG of CYBA associated with increased MDA level, decreased FEV1% and CAT activity and decreased MDA and decreased LS in patients (p<0.05). Gene polymorphisms affecting the function of proteins cause imbalance of detoxification and oxidative-stress pathways thereby contributing to pathogenesis.

Cigarette-smoking, although, is the most important risk factor, but only a small percentage of smokers develop symptomatic COPD. Does that mean the genetic predisposition plays a pivotal role? To address this query, we investigated polymorphisms on several genes but restrict here to cyclochrome P450 1A1 (CYP1A1), CYP1A2, N-acetyl transferase (NAT) and micromesial epoxide hydrolase (mEPHX) of detoxification and cyclochrome b-245 alpha (CYBA), glutathione-S-transferase P1 (GSTP1) of oxidative stress pathways in a case-control design. We present data on haplotypes, gene-gene interactions and correlations with clinical and biochemical levels.

Haplotypes 462Val:3801C, 462Val:3801T of CYP1A1, −1293C:9893C, −1293C:9893G and −1293C:7632T:9893C of the CYP2E1, 930G:2424 of CYBA (p=0.05), 105V-114V of GSTP1 (p=0.001) and 1138H:131H of mEPHX (p=0.05) were over-represented in patients. The same allele-associated genotype-combinations between genes, GSTP1, CYBA and NAT2*6 and NAT2*7 alleles were prevalent in patients (p<0.01). Patients have significantly elevated malondialdehyde (MDA) level and decreased catalase (CAT), glutathione peroxidase (GPx), activities, glutathione (GSH) level (p=0.01). Genotypes, 462IleVal:Val:Val, 3801T+C of CYP1A1 and 930A+GG of CYBA associated with increased MDA level, decreased FEV1% and CAT activity and decreased GSH levels in patients (p<0.05). Gene polymorphisms affecting the function of proteins cause imbalance of detoxification and oxidative-stress pathways thereby contributing to pathogenesis.

P4800 Longitudinal analysis of airway epithelium of COPD subjects reveals unique inflammatory gene networks up-regulated over time

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Introduction: The goal of this study was to determine temporal changes in regulatory gene networks in the small airway epithelium of subjects with COPD. Methods: Small airway epithelial (SAE) cells were collected at bronchoscopy
Fahri Akbas
Investigation of the role of miRNAs as a biomarker in chronic obstructive pulmonary disease (COPD)

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COPD as a complex disease with genetic and environmental compound, is one of the leading cause of death in worldwide. miRNAs have role in gene expression as responsible gene's down-regulated by blocking miRNAs after transcription, translation inhibition and breaking of mRNA. Aim of the study is definition a biomarker that are based on the measurement miRNA level of plasma, is specific to COPD. 20 COPD and 10 healthy control cases were included in this study. The median age was 59±6.6 and 55±5.2 years for controls and COPD, respectively. miRNA specific quantitative real-time-PCR based miRNA (miR-qRT-PCR) detection has been used. Free PCR Array Data Analysis Software has been used for data analysis. As a result of the study, two miRNA were significantly upregulated (miR-7 and miR-30a) and seven different miRNA were significantly downregulated in COPD patients (miR-9, miR-20a, miR-26b, miR-28-3p, miR-34c-5p, miR-100, miR-101).

As a conclusion, this is the first study using QRT-PCR Array method to investigate the association between serum miRNAs and COPD. Upregulation of miR-7 and miR-30a might be potential biomarkers for early diagnosis of disease.

P4802
Cell-cell variation in expression of blaCTX-M-14

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Background: Cell-cell variation in expression of their gene in isogenic population is frequently observed in isogenic culture which is recognized as one of the reasons for phenotype heterogeneity. The aim of this study is to investigate the heterogeneous resistance level in genetically identical cells which was originated from cell-cell variation in expression of blaCTX-M-14. Methods: The transcriptional region of CTX-M-14 with or without the entire coding sequence of CTX-M-14 which were amplified from clinic strain isolated from patients with lower respiratory tract infection were subcloned to upstream of green fluorescent protein (GFP) gene to regulate expression of GFP followed by standard method. Applying flow cytometry measurement (FCM) to analyze the expression pattern of blaCTX-M-14 in single cell using GFP as the report genes. The expression pattern of cells after cultured with different ceftriaxone concentrations ranging from 0µg/ml to 240µg/ml was also analyzed. Using the E-test method to measure the MIC to ceftriaxone.

Results: Variation in GFP expression from cell to cell was seen (The fluorescence intensity of different cells vary largely) ranging from 106 to 109). The resistance level to ceftriaxone was positively correlated with the expression level, with increment of the extracellular ceftriaxone concentrations, the proportion of cells with more GFP abundance increasing. We also found the epigenetic resistance phenotype mediated by the heterogeneous expression was non-strictly inheritable and have a transient property.

Conclusions: Heterogeneous expression of antibiotic genes other than nucleotide alterations in genetically identical cell may be one of the reasons for diverse antibiotic resistance level.

P4803
Polymorphisms of genes involved in extracellular matrix remodeling, xenobiotic metabolism, antioxidant pathways and chronic lung disease in children

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We performed a candidate gene association study of 43 polymorphisms in genes coding genes functioning in extracellular matrix remodeling, xenobiotic metabolism and antioxidant pathways in 257 children with severe chronic lung disease (CLD) and 335 controls. The frequencies of wild type/wild type genotype of CYP2F1 (c.14,15insC) gene were significantly higher in CLD patients than in the healthy control group (Padj=0.00001; OR=3.16 2.10-4.77). Association with CLD and CYP1A1 gene polymorphisms (3798T>C and 2454A>G) in additive model (Padj=0.0003; OR=1.32 1.21-1.45) and (Padj=0.001; OR=1.54 1.08-2.21) was also found. The patients with CLD showed significantly elevated frequencies of the GSTT1 gene deletion (Padj=0.003; OR=1.98 95% CI 1.16-3.89). The GSTT1 (313A>G) polymorphism was associated with CLD (for AA genotype Padj = 0.0046, OR=1.65 1.17-2.34). Regression analysis showed that CAT (-262C>T) C allele was associated with a 1.84-fold increase (95% CI 1.22-2.65; Padj=0.0009) and NQO1 (-1156C>T) T allele was associated with a 1.89-fold increase (95% CI 1.90-3.02; Padj=0.0006) in additive model. Association with CLD and MMP9 (+1171 A>A), MMP12 (+82A>G), MMP3 (+660A>G) and TIMP3 (-1296T>C) gene polymorphisms in dominant model was found (Padj=0.0013, OR=2.75 1.43-5.31; Padj=0.007, OR=1.83 1.16-2.89; Padj=0.017, OR=1.54 1.08-2.21; Padj=0.033, OR=1.48 1.11-2.10). Consequently, CYP2F1, CYP1A1, CAT, GSTT1, NQO1, MMP3, MMP9, MMP12 and TIMP3 genetic polymorphisms probably play a substantial part in susceptibility to severe pulmonary inflammation in children with CLD.
Results: A significant case-control difference was observed for the presence of null GSTM1, (61.8% vs. 55.0%, P = 0.04). No difference was observed in the frequency of GSTT1 Null genotype and COPD susceptibility. (54.8% vs. 55.0% OR 1.28, CI 0.87-1.84, P = 0.28) For GSTP1 polymorphism we found that Subjects homozygous variants Val/Val were at increased risk of developing COPD (OR 2.58, CI 1.2-4.8) as compared to heterozygote variants Ile/Ile (OR 1:29 CI 0.7-2.14). Also, the mutant allele frequency (Val) was significantly higher in patients as compared to controls and the difference was found to be statistically significant. (OR: 1.8 CI: 1.4-4.2; P Value = 0.001)

Conclusion: that subjects with GSTM1 null allele and GST P1 homozygous isoallelic genotypes are at higher risk of COPD and are significant indicators of susceptibility to chronic obstructive pulmonary disease in Indian population.

P4805
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 responsible for AATD is the Z mutation. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ERS and ATS guidelines advocate the routine testing of AAT in all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as for those diagnosed with COPD, our results suggest that FLCN haplo-insufficiency in the lung may knock-downed.

P4806
Lung fibroblast function in patients with Birt-Hogg-Dube syndrome
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Objective: To clarify the mechanism of lung cyst formation, we isolated lung fibroblasts from patients with BHDS and analyzed their function because they are principal cells responsible for the production and maintenance of extracellular matrix.

Methods: Lung fibroblasts were isolated from lung tissue obtained from patients with BHDS (n=10) and lung cancer (n=7). Lung fibroblast function was evaluated by chemotaxis to fibroblast and three dimensional (3D)-gel contraction assay.

Result: We confirmed that lung fibroblasts express FLCN mRNA, but there was no difference in expression level between control and BHDS fibroblasts. BHDS fibroblasts showed reduced chemotaxis as compared with control fibroblasts (p<0.001). But there was no significant difference in contraction of 3D-collagen gels between two groups (p>0.1726). Expression of fibronectin, transforming growth factor (TGF-β) and type I collagen was significantly reduced in BHDS fibroblasts as compared to control fibroblasts when evaluated by real-time PCR. In support of these results obtained from primary cultured fibroblasts, normal fetal lung fibroblasts (HFL) exhibited reduced chemotaxis when FLCN expression in HFL-1 was knocked-down.

Conclusion: Our results suggest that FLCN haplo-insufficiency in the lung may cause fibroblast dysfunction leading to impaired tissue repair.

P4807
CCDC103 encodes a novel cilia dynein arm factor that is mutated in primary ciliary dyskinesia
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Primary ciliary dyskinesia (PCD) is a genetically heterogenous disorder charac-terized by chronic destructive respiratory tract disease. In about 50% of cases it is associated with situs inversus, because embryonic cilia play a critical role in establishing organ left-right asymmetry. Zebrafish schmalsans mutants exhibit characteristic features of ciliopathy caused by a mutation in ccdx 103; in electron microscopy cilia lack inner (IDIA) and outer (ODA) dynein arms.

Screening individuals for CCDC103 (the human ccdx 103 ortholog) identified ten patients with mutations. We found homozygous loss-of-function mutations in six siblings and one patient, who had no family history of ciliopathy, revealed a 3 bp frame shift (c.833_834delG) predicting a premature termination of translation. In four affected individuals a homozygous transversion (c.A461C; p.H154P) was identified. The affected individuals exhibited typical clinical findings for PCD. Three patients had situs inversus totalis, one had situs inversus abdominalis and two dextrocardia. High-speed videomicroscopy (HSV) of patient OP-1192II (c.833_834delG) showed ciliary immotility with only residual flickering. In contrast, in two patients with the p.H154P variant, HSV showed reduced beat amplitude and coordination and few immotile cilia. In patient OP-1192II, immunofluorescence microscopy demonstrated distal ODA deficiency. Immunofluorescence microscopy of ODA component DNALI1 showed cilia immotility with only residual flickering. In contrast, in two patients with the p.H154P variant, HSV showed reduced beat amplitude and coordination and few immotile cilia.

Our findings indicate that CCDC103 mutations cause PCD in humans. Whereas the loss-of-function mutation results in ciliary immotility and distal ODA deficiency, the p.H154P variant presents as a hypomorphic mutation.

P4808
Recessive HYDIN mutations cause primary ciliary dyskinesia without situs abnormalities
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Primary ciliary dyskinesia (PCD) is a genetically heterogenous disease character-ized by reduced muco-ciliary clearance. This is caused by defects in cilia motility. Impaired sperm flagella motility contributes to male infertility. In about 50% of cases PCD is associated with situs inversus or more rarely situs ambiguous as a result of embryonic cilia dysfunction leading to randomization of left-right body asymmetry. 70 years ago the hy3 mouse carrying hydin mutations has been described. These mutations lead to an abnormal composition of the central pair (CP) apparatus. Clinically, these mice suffer from lethal hydrocephalus. Now we report HYDIN mutations in human PCD patients without hydrocephalus and normal body composition.

By using a homologygous mapping strategy we identified a novel PCD locus on chromosome 16q21-q23 across the HYDIN locus. In three affected siblings genomic analyses showed homozygous c.3985G>T HYDIN mutations affecting the evolutionary conserved splice acceptor site of exon 27. We confirmed aberrant splicing with early stop of translation by cDNA analysis. High-speed videomicroscopy (HVM) of respiratory cells showed a reduced bending capacity. Sperm motility was markedly decreased with only 8% of sperm showing minimal progressive motility. Transmission electron microscopy (EM) appeared normal in most cross sections. 9 + 0 cilia and 8 + 1 cilia composition were found very rarely. EM tomography showed absence of the CP apparatus C2b projection resembling findings in Hydrocephalic mice. Our results expand the knowledge on PCD genetics. Careful diagnostic evaluation is obligate in this PCD variant as HVM and EM findings are subtle.

882s
P4009
Clinical characteristics and determinants of exacerbation in Japanese patients with COPD: Hokkaido COPD cohort study results
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Introduction: Exacerbations are one of the major factors that may influence natural history of COPD. However, little is known about clinical characteristics and determinants of exacerbation of COPD in a Japanese population.

Aims: To examine characteristics and determinants of exacerbation in Japanese patients with COPD in a 5-year observational cohort study.

Methods: A total of 279 patients with COPD participated in the Hokkaido COPD cohort study (AIRCCM 2012) and 268 subjects (GOLD 1, 26%; GOLD 2, 45%; GOLD 3, 24%; GOLD 4, 5%) who had clinical data of multiple visits were analyzed for this analysis. Exacerbation was defined in four ways: symptom criteria, requiring prescription change (prescription criteria), requiring antibiotics treatment (antibiotics criteria), and requiring hospital admission (admission criteria). Exacerbation frequency was observed over a period of 5 years.

Results: Exacerbation frequency was 0.24±0.47/yr (symptom criteria), 0.20±0.43/yr (prescription criteria), 0.13±0.28/yr (antibiotics criteria), and 0.06±0.19/yr (admission criteria). Cox proportional hazard model showed that an increase in SGRQ total score was significantly associated with short exacerbation-free period defined by all criteria and a decrease in body mass index (BMI) was also associated with short exacerbation-free period defined by antibiotics and admission criteria. Subjects who experienced hospital admission >1/yr tended to have rapid annual decline in FEV1 (p<0.07).

Conclusion: While exacerbation frequency is low in our cohort subjects, poor health-related quality of life and low BMI are independent risk factors for the development of exacerbation of COPD.

P4010
Is controlled oxygen therapy in COPD patients presenting in acute respiratory failure sub-optimal prior to commencement of NIV?
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Introduction: Controlled oxygen delivery with target oxygen saturations is a key aim in managing COPD patients in respiratory failure.

Aims: This audit assessed if controlled oxygen therapy is utilised on these patients on admission to hospital and prior to NIV in line with British Thoracic Society guidance.

Methods: In a district general hospital, case notes for twenty patients with COPD requiring NIV between April 2011 - February 2012 were analysed retrospectively. VO2, SpO2 and arterial blood gas values (pH, PaO2, PaCO2 and HCO3) were calculated on patients requiring NIV between April 2011 - February 2012 were analysed retrospectively. VO2, SpO2 and arterial blood gas values (pH, PaO2, PaCO2 and HCO3) were calculated on admission to hospital and prior to NIV in line with British Thoracic Society guidance.

Results: Oxygenation on admission and immediately prior to NIV

Conclusion: While exacerbation frequency is low in our cohort subjects, poor health-related quality of life and low BMI are independent risk factors for the development of exacerbation of COPD.

P4011
Impact of diabetes in patients admitted with acute exacerbation of COPD
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Background: In patients admitted with acute exacerbation of COPD (AECOPD), the presence of concomitant diabetes has been shown to prolong the length of stay (LOS) and increase the risk of death. However, it is not clear if this impacts on readmission rates.

Methods: A retrospective study of consecutive patients admitted with AECOPD in an acute teaching hospital.

Results: 67 patients (45% male) with a mean (SD) age of 72 (12) years and % predicted FEV1 of 55 (20) were included in the study. 15 (22%) of them had concomitant diabetes with a mean (SD) HbA1C of 6.8 (1.3).

Baseline characteristics and outcome parameters

Conclusion: The presence of DM might have an impact on readmission rates following a hospital admission with AECOPD. Prospective studies with larger sample size are needed to evaluate this further.

No significant difference in LOS or mortality within one year was noted between the two groups. However, there was a trend for increased readmission rates in the following year in patients admitted with AECOPD and concomitant diabetes.

Conclusions: Our study suggests that the presence of DM might have an impact on readmission rates following a hospital admission with AECOPD. Prospective studies with larger sample size are needed to evaluate this further.

P4012
The prognostic value of elevated levels of troponin T (Tn T) and heart-type fatty acid binding protein (H-FABP) in hospitalized COPD patients with acute respiratory failure (ARF)
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Aim: To evaluate the diagnostic and prognostic value of heart injury biomarkers (H-FABP and Tn T) in COPD patients with ARF.

Methods: We enrolled 80 hospitalized patients with COPD (65.6±18.9 years, PaO2 53±8±7.2 mm Hg). All patients underwent a complex diagnostic investigation including chest X-ray, blood gases, echocardiography, measurement of serum Tn T, H-FABP, BNP-fragment.

Results: The main causes of ARF were bacterial infection (BI)-43.7%, pneumonia-23.6%, acute decompensation of chronic heart failure (ADCHF)-12.5% and acute myocardial infarction (AMI)-11.3%. The H-FABP levels were increases in 92.5% of all cases. Patients with AMI had the highest levels of H-FABP than patients with BI (967.7 [453.7-2916.6], 2358.1 [1060.5-4809.2], 1939.6[982.2-2361.1] vs 4637.3[306.8-1013.2] pmol/L, p<0.05, respectively). There were significant differences between other groups. The Tn T levels were elevated (0.5 pmol/L) in 21.3% of all cases without significant differences between groups. BNP-fragment levels were higher in patients with pneumonia, ADCHF, AMI than in patients with BI (p<0.05 for all, respectively). The area under ROC curve for the prediction of hospital mortality were increased for BNP-fragment (0.827), for H-FABP (0.809). Survival was worse in patients with elevated Tn T (>0.5 mg/L) than in patients with Tn T <0.5 mg/L (log-rank test, p<0.01).

Conclusion: In COPD patients with ARF the serum levels of Tn T and H-FABP were significantly elevated without documented acute coronary syndrome and were the strong predictors for all-causes hospital mortality.

P4013
Regulation of ghrelin on appetite in patients with acute exacerbations of chronic obstructive pulmonary disease
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Background: Patients with COPD are usually complicated with malnutrition, which is partly caused by reductions of appetite and food intake, especially...
in acute exacerbations. Recent studies reported the key roles of ghrelin in appetite stimulation and energy homeostasis. However, the association between the orexigenic function of ghrelin and appetite reduction in AECOPD remains unclear.

Objectives: To investigate the secretion, acylation of ghrelin, and its association with appetite reduction in patients with AECOPD.

Methods: Thirty-six patients with AECOPD and 23 healthy adults were enrolled. Total and acylated ghrelin, obestatin, simplified nutritional appetite questionnaire (SNAQ) scoring, and calorie intake were compared in patients between in exacerbations and in remissions. Further more, the same indexes were also compared between AECOPD patients and healthy controls.

Results: Total ghrelin level in patients was significantly higher in exacerbations than remissions (627 ± 234.9 vs. 500.8 ± 181.0 pg/ml, p < 0.001), while the SNAQ score and calorie intake were significantly lower (10.8 ± 2.3 vs. 14.3 ± 1.8, p < 0.001; 663.5 ± 188.3 vs. 1031.4 ± 188.9 kcal, p < 0.001, respectively). The proportion of acylated ghrelin, the SNAQ score, and calorie intake of patients were significantly lower than controls (10.6 ± 6.7% vs. 15.0 ± 5.9%, p < 0.005; 10.7 ± 2.1 vs. 15.4 ± 1.2, p < 0.001; 647 ± 141.6 vs. 1257 ± 280.8 kcal, p < 0.001, respectively).

Conclusions: A higher ghrelin level in AECOPD indicated increased secretion of ghrelin, but its role in stimulating appetite was compromised. Moreover, the decreases in appetite reduction was noted in patients, which might be a cause for appetite reduction in AECOPD.

P4814
Cardiac biomarkers and outcome in patients with acute exacerbation of chronic obstructive pulmonary disease
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Purpose: Cardiac biomarkers are associated with prognosis in patients with chronic obstructive pulmonary disease (COPD). The optimal time point for biomarker analysis remains uncertain. We thus compared prognostic implications of admission and discharge concentrations with outcome after acute exacerbation of COPD.

Methods: This was a prospective study in patients hospitalized with acute exacerbation of COPD. We measured NT-proBNP and troponin T (TnT) concentrations at admission and discharge. Hospitalizations and deaths were recorded for 6 months after discharge.

Results: We included 127 patients (70% ± 10 years, 70% men, GOLD III/IV 87%). Left ventricular ejection fraction was < 50% in 11% (9 patients) and 96 (76%) patients had significant obstructive limitations. Total and discharge concentrations of NT-proBNP and TnT were elevated in 76 (60%) and 35 (28%) patients, respectively. By discharge, this decreased to 46 (38%) and 24 (19%) patients. During follow-up, 44 (35%) patients were rehospitalized and 10 (8%) died. Kaplan-Meier curves analysis showed association between TnT at discharge andrehospitalizations (log-rank test 5.74, p = 0.017). In a Cox model of proportional hazards adjusted for age, gender, GOLD stage, and left ventricular function, only TnT at discharge remained associated with rehospitalizations (hazard ratio 2.89, 95% confidence interval 1.13-7.36). No associations between admission and discharge concentrations of NT-proBNP, TnT and death were found.

Conclusions: Cardiac biomarkers are frequently elevated in patients hospitalized for acute exacerbation of COPD. Discharge TnT was predictive ofrehospitalizations whilst none of the biomarkers predicted death during 6 months.

P4815
Predicting hospital readmission in patients discharged following acute exacerbations of COPD (AECOPD)
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Background: Readmission rates following hospitalisation for AECOPD are high. The ability to accurately identify patients at a high risk of readmission could help clinicians effectively direct resources and interventions.

Objective: To identify predictors of readmission in patients surviving hospitalisation for AECOPD.

Method: Clinical data from consecutive patients surviving hospitalisation for AECOPD were collected. All variables associated (p < 0.10) with outcome (readmission to hospital, or death at home without readmission, within 90 days of discharge) on univariate analysis were entered in to a multivariate logistic regression model, exacerbations whilst none of the biomarkers predicted death during 6 months.

Impact of patient nutritional status on acute exacerbation of COPD
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Introduction: Nutritional status has to be considered in the course of COPD. In fact, both obesity and malnutrition influences quality of life of patients with COPD and has a prognostic value.

Aim: Evaluate the impact of patient nutritional status on acute exacerbation (AE) of COPD.

Patients and method: Retrospective study including patients hospitalized for AE of COPD between 2009 and 2010 in our department. Nutritional status was evaluated by body mass index (BMI). Patients were divided into four groups regarding their BMI (BMI < 18; 18 ≤ BMI < 24; BMI ≥ 25; BMI ≥ 25; IMC ≥ 25; IMC ≥ 25; IMC ≥ 30). Number of AE/year, duration of hospitalization and use of systemic corticosteroids were also determined.

Results: Fifty patients were enrolled with a mean age of 64 years. Mean value of BMI was 23.5 ± 6.9 kg/m². 50% of patients had COPD stage III and 28% had COPD stage IV. Considering all patients, mean value of AE/year was 1.5, mean duration of hospitalization in AE was 15.49 days and use of systemic corticosteroids was necessary in 66% of cases. Compared to patients with normal BMI (G2), those with malnutrition (G1) had more severe AE: longer duration of hospitalization (35,48days vs14,54days) and frequent use of corticosteroids (83, 33% vs 64,28%). Patients suffering from obesity had similar number of AE/year as patients from G2, but the use of corticosteroids was more frequent (85,71% vs 64,28%).

Conclusion: We emphasize on the evaluation of nutritional status in COPD as a major parameter to consider in the management of this disease.
P4818
Can acute phase proteins predict survival in ventilated patients with acute exacerbation of COPD
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Background: Factors determining in-hospital mortality of patients ventilated with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are not precisely understood.

Purpose: The aim of this study was to assess the correlation between acute phase proteins [High sensitivity C-reactive protein (CRP) and prealbumin (PA)] and mortality in ventilated patients with COPD.

Methods: We evaluated 336 COPD patients with AECOPD and on invasive mechanical ventilation. Detailed clinical evaluation was done daily. Concentration of CRP and PA was measured on admission, 3rd, 8th and 16th day.

Results: During the study; 237 patients were discharged and 99 died. The difference between the two groups in CRP and PA was significant at admission, 3rd, 8th and 16th day. In non survivors; there was a significant increase in CRP values with a significant decrease in PA with time (P<0.001). In-hospital mortality was significantly associated with lower arterial oxygen tension, higher carbon dioxide arterial tension, lower arterial oxygen saturation, lower body mass index and longer hospital stay.

Conclusions: CRP levels in patients who died was significantly higher on admission, 3rd, 8th and 16th day. A fall in CRP levels on follow up indicated a significantly better prognosis. An increase in the prealbumin level was observed in survivors.

Clinical implications: Persistently high CRP and low prealbumin in COPD patients is associated with poor prognosis. A non-invasive treatment of systemic inflammation and malnutrition may improve prognosis. Prediction of survival status may be enhanced by considering arterial oxygen tension, albumin, body mass index, duration of hospitalisation.

P4819
A comparison of specific health-related quality of life questionnaires to predict COPD exacerbations
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Objectives: Compare the specific health-related quality of life (HRQoL) instruments, St George respiratory questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ), Clinical COPD Questionnaire (CCQ) and Airways Questionnaire 20 (AQ20) to predict COPD exacerbations.

Methods: A group of 49 COPD patients who completed SGRQ, CRQ, CCQ and AQ20 were followed for 2 years. Emergency visits and hospitalizations were collected. We also assessed sociodemographic, clinical and pulmonary function data. The chi-squared, t test, and Mann-Whitney U were used to compare differences between groups. Multivariate logistic regression was performed for all variables showing statistically significant differences. A p-value < 0.05 was considered significant.

Results: The mean (SD) age was 65.9 (8.4) years and the mean FEV1 was 59.1 (19.5 %) of predicted value. In the univariate analysis only CCQ questionnaire showed differences for patients with emergency visits in the first year. Significant differences were seen in the scores of the CCQ total score SGRQ and all subscales, except SGRQ symptoms, and the scale disease control of CRQ between the group with hospitalization in the first year. In the logistic regression model, the CCQ questionnaire finally proved to be independent predictor of emergency visits during the first year (OR: 1.06; 95% CI, 1.00 to1.11; p=0.036). Other variables significantly associated were BMI (OR: 0.87; p<0.04) and prior hospitalizations (OR: 1.79; p<0.01).

Conclusions: Among a wide range of HRQoL questionnaires only the CCQ are independently associated with a higher risk of emergency visits for COPD exacerbations the first year of follow-up.

P4820
30-days mortality in patients admitted with COPD
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Introduction: The aim of this study was to describe 30-days mortality after hospital admission of COPD patients.

Methods: This is a retrospective study of all patients with the diagnosis of COPD as a primary diagnosis or co-diagnosis admitted to a tertiary pulmonary treatment unit, Department of Respiratory Medicine, Gentofte Hospital, Denmark in 2010.

Results: 67 (15.1 %) died out of 442 patients admitted with COPD within a period of 30 days after hospital admission, compared to 10% at the national level, odds ratio 1.51 (1.99). Mean age was 82.2 years, 55.2% were women and average BMI was 20.7. They had an average admission rate at 2.89 admissions in a period of 12 months prior to the inclusion date. Out of the 67, 23 (34.3%) received non-invasive ventilation (NIV) or respirator treatment at the respiratory unit or the intensive care unit. In 4 (5.9%) cases COPD was neither the cause of admission nor the cause of death, in further 18 (26.9%) cases COPD was not the cause of admission and 5 (7.5%) patients was wrongly diagnosed with COPD.

Conclusion: The 30-days mortality is significantly higher at Department of Respiratory Medicine at Gentofte Hospital. Possible explanations are a selection of hospitalization of more severe cases of COPD since the department has a unique outgoing COPD-treatment unit, which treats the milder exacerbations at home. Furthermore a mortality increase due to a selection of high risk patients with complications, comorbidities and pulmonary cancer in a tertiary unit. In conclusion, the crude 30-days mortality needs further data interpretation if to be used as a measure for quality of treatment for patients admitted with COPD.

P4821
Influence of COPD exacerbations on health related quality of life
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Background: An exacerbation is the most important adverse event in the progression of chronic obstructive pulmonary disease (COPD). Exacerbations appear to accelerate the decline in lung function that characterises COPD, resulting in reduced physical activity, poorer quality of life and an increased risk of death.

The aim of this study was to investigate the influence of chronic obstructive pulmonary disease exacerbations on health related quality of life (HRQL).

Methods: 152 consecutive patients with COPD were enrolled into the study. Demographic data, smoking status, self-assessed severity in a questionnaire (Medical Outcomes Study Short Form (SF-36) and the St. George Respiratory Questionnaire (SGRQ)).

Results: The cohort consisted of 90 patients with 2 or less exacerbations per year, mean age 53±3.2 years and 62 patients with 3 or more exacerbations, mean age 55±3.8. In frequent exacerbators COPD was more severe: the mean FEV1% was 34.2±2.1% versus 52.3±2.9%, p < 0.05. Grade of impairment of HRQL was higher in frequent than infrequent exacerbators: SGRQ (73.6±5.1 versus 57.1±6.6, p<0.01) and SF-36 (30.2±1.5 versus 41.1±1.2, p<0.01). Pearson correlation coefficient analysis demonstrates in COPD patients a significant positive correlation between the rate of exacerbations and the total scores of the SGRQ (r=0.61, p<0.01) and SF-36 (r=0.54, p<0.01).

Conclusion: Compared with infrequent exacerbators, frequent exacerbators in our study were characterized at baseline by more severe COPD and more severe deterioration of the health related quality of life.

P4822
Nutritional status of COPD patients with complete respiratory failure on long term home oxygen therapy
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Objectives: This study aimed in assessing nutritional status in patients with the advanced COPD, treated with long term home oxygen therapy.

Material and methods: A group of 49 patients with COPD, mean age 67 year, were included into the study. 43 patients smoked cigarettes in the past (91.5%). Body composition evaluation with bioelectrical impedance analysis (BIA) were performed in all patients. Body Mass Index (BMI) and Fat-Free Mass Index (FFMI) were calculated. FEV1 and FVC were measured. Life quality was assessed with St. George Respiratory Questionnaire (SGRQ).

Results: 17.7% of patients were diagnosed as overweight, in 22.3% the body weight was normal, 61.9% of patients were overweight or obese. FEV1 value was the lowest in overweighted patients, and the highest in overweight and obese patients. Strongly positive correlation between FEV1 and FFMI: r=0.45, p<0.01, was also noted. Statistically significant differences between SGRQ total score and frequency of the undertaken physical activity were seen in patients. Who performed moderate exercises, e.g. walking once a week only, lower life quality was statistically significantly (SGRQ Total Score=77.6) in comparison with the patients, who performed physical exercise thrice a week at least (SGRQ Total Scores=67.7) at p<0.04.

Conclusions: 1. Normal body weight was noted in 22.3% of patients with advanced COPD. Overweight and obesity are seen statistically significantly more often than underweight.

2. Respiratory system function are worse in patients diagnosed with malnutrition than that in patients that are overweight and obese.

3. Quality of life in patients more physically active is better than ones with lower physical activity.
P4823 Reducing hospital admission in COPD exacerbation by urgent oxygen provision and home monitoring of capillary blood gases
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Current NICE guidance recommends hospital admission when SpO2 < 90% but with supplemental oxygen many such patients might be managed at home provided that worsening hypercapnia and respiratory acidosis is excluded. As part of the NHS Lung Improvement Programme, Sunderland Urgent Care Team (South Tyneside NHS Foundation Trust) set up a six month Pilot to reduce emergency hospital admission by introducing measurement of capillary blood gases (TcABGs) and the urgent provision of oxygen to manage what would have been an admission into a treatable condition at home. Following a clinical assessment, a team of advanced nurse practitioners guided by an operational protocol measured TcABGs in a group of patients with AECOPD who’s SpO2 was in the range 85-90%. Suitable patients were provided with oxygen cylinders delivering oxygen in the range of 2-6 L/min and monitored until oxygenation improved (SpO2 > 90%) and there was clinical recovery. Initially, urgent oxygen provision and ABG measurement proved problematic but 25 patients were recruited. 4 were excluded for breaching protocol (2 TcABGs failed, 1 was acidic (pH 7.29) and chose to remain at home, 1 had no follow up data). 4 were admitted (2 acidic, 2 hypoxic on LTOI). The remaining 16 hypoxic (SpO2 86±1) patients improved (SpO2 93±2) with urgent oxygen provision and were managed safely at home but 1 became non-compliant. Initial visit times lasted 186±80.7 mins with between four and twelve follow up visits until recovery. With urgent oxygen provision, careful selection of patients, hospital admission can be avoided even in moderately hypoxic patients with exacerbations of COPD.

P4824 Comparison of different dosage nebulised budesonide in COPD exacerbation
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Objective: To compare the efficacy and safety of different dosage nebulised budesonide (BUD) in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD).

Design: Randomised, double-blind, parallel-group trial.

Patients and interventions: A total of 64 patients who had moderate to severe acute exacerbations of COPD and required hospitalisation were enrolled in the study. The patients were randomized into three groups. Group 1 received systemic (intravenous) prednisolone 40 mg daily (n=28), group 2 received 4 mg NB daily (n=20), group 3 received 8 mg NB daily (n=16). Airway obstruction [forced vital capacity (FVC), forced expiratory volume 1 second (FEV1)] was evaluated at admission and discharged. Arterial partial pressure of oxygen (PaO2), carbon dioxide (PaCO2), pH, and oxygen saturation (SaO2) were evaluated at 24 and 48 hours, and at day 10.

Results: There were no significant differences between groups at baseline. In groups, differences were significant for FVC, FEV1, PaO2, and SaO2 (p<0.001), but not for PaCO2 and pH, in comparison with their baseline values. There were no significant differences between groups for all parameters at all time periods. While blood glucose exhibited an upward trend only group 1 (8 patients), oral anti-coagulant therapy was discontinued in groups, differences were significant for FVC, FEV1, PaO2, and SaO2 (p=0.000), but not for PaCO2 and pH.

Conclusions: Nebulised budesonide is effective and safety in the treatment of COPD exacerbation. There is no significant difference in terms of efficacy and safety between 4 mg and 8 mg nebulised budesonide.

P4825 COPD: Acute exacerbation (AE) and hospitalization rate (HR) in patients with different serum surfactant protein D (SPD) level
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† Internal Medicine, DMA, Dnipropetrovs, Ukraine; ‡Laboratory, DMA, Dnipropetrovs, Ukraine

Aim: To evaluate whether and in which extent SPD have influence on the AE and hospitalization rate in patients with COPD.

Study population: 26 patients with stable COPD, GOLD stage II-IV, made the study sample.

Methods: SPD was evaluated in serum by ELISA (Hyctyl Biotech, Netherlands) for all patients. AE (including AE, required systemic corticosteroids (SCS) and any-}

thobitic (AB) prescription) and HR during 12 months were evaluated retrospectively by analysis of patient’s medical documentation.

Results: In accordance with SPD level all patients were divided on two groups: 12 patients with SPD >600 ng/ml (Group I) and 14 with SPD <600 ng/ml (Group II). Both groups were similar regarding to sex, age, FEV1, smoking status and basic therapy. One or more AE during the year were found in 7 (58.33%) patients of Group I and 12 (85.71%) of Group II. The data from patient’s medical documentation analysis are presented in the table 1.

Conclusions: 1. COPD patients with high SPD had higher AE rate and required and more frequent both SCS and AB prescription. 2. SPD did not influence on HR in patients with COPD, GOLD stage II-IV.

P4826 Relation between metabolic syndrome and acute exacerbation of COPD
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Dorra Gerb, † Ines Akrou, † Hela Hassene, † Wided Ben hamad, † Hela Kammoun, † Dalinda Belhabih, † Mohamed Lamine Megdiche. † Ibn NAFIS, Abderrahmane Mami Hospital, Ariana, Tunisia

The concept of COPD as a systemic disease has been widely accepted in the past several years. However, to date, rare studies have analyzed correlation between exacerbations of COPD (ECOPD) and Metabolic Syndrome (MetS). The aim of this study was to examine if presence of MetS increases the frequency, duration and severity of ECOPD.

Methods: Patients with COPD were prospectively enrolled and followed between January 2008 and December 2011. Medical records, pulmonary function tests, chest X-rays, laboratory test results were gathered to establish the presence of COPD and MetS. Patients were divided in two groups; with and without MetS. The ECOPD was defined as worsening of symptoms requiring increased use of rescue medications and/or need for either systemic steroids or antibiotics or that led to emergency room visit or hospitalizations during 36 months follow-up. A total of 100 patients, 60 with MetS and 40 without. The mean exacerbation of COPD frequency was 2 in MetS group versus 0.7 in the control group during the follow-up period (P < 0.001). Mean duration of each exacerbation was 8±1.5 days in patients with MetS versus 5.5±1.3 days in patients without. Acute respiratory failure was more frequent in patients with MetS than control with significant difference. Serum C-reactive protein (r = 0.3, P = 0.001), fasting blood glucose (r = 0.6, P < 0.001), and triglycerides (r = 0.61) were positively and significantly correlated with exacerbation frequency. This study demonstrates an association between ECOPD and its duration and severity with the MetS. The inflammatory state induced by common cytokines may explain the linkage between the two conditions.

500. The best of pharmacology treatment for asthma and COPD

P4827 Acute dose- and time-dependent effects of budesonide on airway blood flow in asthma
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Inhaled corticosteroids (ICS) have been shown to decrease airway blood flow (Qaw) via a non-genomic action on airway vascular smooth muscle contraction. We have previously shown a dose-dependent decrease in Qaw with a single inhalation of 360, 720 and 1440 μg budesonide (BUD) in moderate-to-severe asthmatics where Qaw decreased transiently from 12 to 21% after all doses (p=0.05 vs baseline and placebo).

Objective: Here, we have investigated the effects of repetitive BUD inhalations on Qaw in moderate-to-severe asthma patients on regular ICS use.

Methods: The 18 subjects enrolled were told to abstain from ICS for at least 36 h before the experiment. Inhalation of 720 μg BUD was given 4 times, separated by 30 min. Qaw, FEV1, blood pressure, heart rate and oxygen saturation were measured before each inhalation and 30, 90, 150, 210 and 270 min after the last dose. A soluble, inert gas-uptake method was used to measure Qaw.

Results: Baseline mean Qaw was 61.3±3.15 μL/min (per mL of lung anatomical dead space) and FEV1 2.3±0.3 L. Numerically, mean Qaw progressively decreased after each BUD inhalation. At 30 min after the last dose, mean Qaw was 28% below baseline (p<0.05) and remained 11% below baseline after 270 min. There were no statistically significant changes in FEV1, PEF 25-75%, PEF, oxygen saturation and mean blood pressure.

Conclusions: In moderate-to-severe asthma patients on regular ICS use, repeated inhalations of high BUD dose have a cumulative acute vasoconstrictive effect in the airway suggesting an acute non-genomic action that increases vasoconstrictor tone. This effect could decrease airway non-genomic action and the vascular clearance of concomitantly inhaled bronchodilators from the airway.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>AE (Mean, cases per year)</th>
<th>AE with SCS (Mean, cases per year)</th>
<th>AE with AB (Mean, cases per year)</th>
<th>HR (Mean, cases per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.04±0.27</td>
<td>1.01±0.18</td>
<td>0.75±0.22</td>
<td>1.02±0.47</td>
</tr>
<tr>
<td>2</td>
<td>2.35±0.34</td>
<td>2.17±0.35</td>
<td>1.98±0.54</td>
<td>1.6±0.34</td>
</tr>
</tbody>
</table>

*p<0.01; p=0.05; p>0.05.
Budesonide reverses IL-13-induced airway hyper-responsiveness but has little effect on β2 agonist response in human small airways

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IL-13 modulates airway smooth muscle sensitivity to contractile stimulus. Steroids and α2 agonists decrease current from a control level of 1.4 ± 0.2 pA to 51.8 ± 1.9 pA; in pig type II AEC, an increase from 23.6 ± 3.2 to 173.2 ± 7.4 pA was observed, and in rat AEC, from 10.7 ± 3.8 pA to 66.2 ± 5.3 pA

These results show that AP301 activates ENaC in type II AEC from dog, pig and rat. To our knowledge, this is the first cell-based analysis of the oedema-clearing effect of AP301 observed in the porcine model of pulmonary oedema. Furthermore, the results validate the dog and pig models in preclinical assessment of AP301.

P4831
MEMP1972A, an anti-ε1 prime monoclonal antibody, reduces serum IgE in healthy and allergic rhinitis subjects

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Background: MEMP1972A, a humanized monoclonal antibody specific for the M1 prime epitope of membrane IgE, depletes M1 prime-expressing IgE-switched B cells, IgE memory B cells and IgE plasmablasts. MEMP1972A is in development for the treatment of allergic rhinitis. Aim: To evaluate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of MEMP1972A in healthy and allergic rhinitis (AR) subjects.

Methods: Two Phase I, randomized, controlled trials investigated the safety, tolerability, PK and PD of MEMP1972A in (1) healthy adults (n=31 MEMP1972A, n=14 placebo [PB]) and (2) AR subjects (n=24 MEMP1972A, n=12 PB [NCT01160861]). In healthy adults, MEMP1972A was given as single escalating doses of 0.003–5 mg/kg intravenous (IV) or 3 mg/kg subcutaneous (SC). In AR subjects, monthly doses were given for 3 months at 1.5 and 5 mg/kg IV and 3 mg/kg SC.

Results: MEMP1972A was well tolerated, and the exposure of serum neutralizing antibodies to MEMP1972A was low. The terminal half-life of MEMP1972A was 20–21 days and mean clearance was 2.2–2.7 mL/day/kg. MEMP1972A administration led to a dose dependent reduction in serum IgE in both studies. In healthy adults, a single dose of MEMP1972A at 3 and 5 mg/kg IV significantly reduced serum IgE by ~25% relative to baseline at Day 85, with no significant reductions observed in the PB, lower IV or 3 mg/kg SC cohorts. Monthly doses of MEMP1972A at 5 mg/kg IV or 3 mg/kg SC in AR males reduced serum IgE by ~25% relative to baseline at Day 85. Serum IgE reductions were sustained for 6 months.

Conclusion: MEMP1972A was well tolerated and reduced serum IgE in adults with or without allergic disease.

P4830
ENaC-activating effect of AP301 in type II alveolar cells isolated from dog, pig and rat lungs

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The synthetic peptide, AP301, mimics the TIP, or lectin-like, domain of human TNF-α (Lucas, R. et al Science 1994; 263:814-817). TNF-α and AP301 activate ENaC in porcine type I alveolar epithelial cells (AEI) by activating a PAR2 receptor (MEMP1972A) and reduces current from a control level of 1.4 ± 0.2 pA to 51.8 ± 1.9 pA; in pig type II AEC, an increase from 23.6 ± 3.2 to 173.2 ± 7.4 pA was observed, and in rat AEC, from 10.7 ± 3.8 pA to 66.2 ± 5.3 pA.

Ventilation strategies excepted, no specific therapy presently exists for treatment of pulmonary permeability oedema, ALI or ARDS. AP301, currently undergoing clinical trials, is being developed as a therapy for these conditions and is also being developed for the treatment of allergic rhinitis. AP301 has also been shown to improve alveolar liquid clearance and lung function in a porcine model of ALI.
Conclusion: IgE is a potent inducer of pro-inflammatory extracellular matrix components in the human airway wall and its effect can be prevented by Omalizumab. Thus the anti-IgE antibody drug may reduce airway remodelling in long term therapy.

P4833 The effects of extraline beclomethasone/formoterol on hyperinflation and airway geometry in COPD patients

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Aim of this study was to assess the effects of extraline beclomethasone/formoterol treatment on lung hyperinflation and airway geometry in COPD. Data of lobar volume (%pred) and specific lobar airway volumes (siVaw) at FRC and TLC were obtained with functional imaging in 25 COPD patients (GOLD II 1.4, III 7, IV 4) pre- and 4h post-bronchodilator (post BD) both at baseline and after 6 months of treatment. A post BD drop was observed for both functional residual capacity (FRC) and TLC lobar volumes at baseline (FRC: -10%, p<0.01, TLC: -2%, p<0.01) and after 6 months (FRC: -12%, p<0.01, TLC: -2%, p<0.001) as index of reduced hyperinflation. siVaw did increase 4 hours after administration at both time points (+10%; p<0.01, and +8%; p<0.001).

P4834 Formoterol reduces asthmatic airway smooth muscle cell proliferation through p27 (Kip) which is supported by steroids

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Background: Airway remodelling in asthma is partly due to increased airway smooth muscle (ASM) mass. We and others reported earlier that steroids alone do not significantly reduce proliferation of ASM cells isolated from asthma patients. Objective: Here, we investigated the anti-proliferative signalling pathway of formoterol combined with three different steroids on ASM cell proliferation control.

Methods: Proliferation was determined by cell count 3 days after stimulation. Drugs were used at concentrations 1nM – 1microM. Protein expression (p21, p27) was determined by immuno-blots and -staining. Cyclic AMP was inhibited by DDA pre-incubation.

Results: Serum induced proliferation was reduced by steroids (dexamethasone, fluticasone, budesonide) in ASM cells of healthy controls but not of asthma patients. Formoterol dose dependently reduced cell proliferation by maximal 25% in both asthma and control ASM cells and this was paralleled by p27(Kip) activation in asthma ASM cells only. In combination the inhibitory effect of formoterol increased to 52% by dexamethasone, to 69% by budesonide and to 76% by fluticasone in healthy cells. In asthmatic ASM cells the combined rug’s effect was 47%, 52% and 56% respectively. Inhibition of proliferation of asthmatic ASM cells by formoterol occurred through cAMP and p27(Kip), which were both increased by the addition of steroids. The anti-proliferative effect of the combined drugs in control ASM cells involves p21(Waf1) and in asthmatic cells by p27(Kip). This effect was consistently augmented by SQ22556 and reproduced by forskolin in both systems. Our results suggest that formoterol-2 inhibited tracheal ring contraction induced by carbachol. The anti-inflammatory effect remained unaltered following epithelium removal or pretreatment with L-NAMe, but it was clearly sensitive to 9-(tetrahydro-2-furyl) adenine (SQ22556), an adenylic cyclase inhibitor. Formoterol-1 inhibited apoptosis of T cells treated with JMF2-1 in vitro was assessed by flow cytometry. The spasmolytic effect of JMF2-1 was assessed on isolated rat tracheal rings. Intracellular levels of cAMP from T cells and airway smooth muscle cells treated with JMF2-1 were detected by radioimmunooassay. We found that JMF2-1 inhibited tracheal ring contraction induced by carbachol. The anti-inflammatory effect remained unaltered following epithelium removal or pretreatment with L-NAMe, but it was clearly sensitive to 9-(tetrahydro-2-furyl) adenine (SQ22556), an adenylic cyclase inhibitor. Formoterol-1 inhibited apoptosis of T cells treated with JMF2-1 in vitro was assessed by flow cytometry. The spasmolytic effect of JMF2-1 was assessed on isolated rat tracheal rings. Intracellular levels of cAMP from T cells and airway smooth muscle cells treated with JMF2-1 were detected by radioimmunooassay.

We sought to test if JMF2-1 effects are a consequence of increased intracellular cAMP levels in asthma cells. These results may underlie the clinical benefit of combination therapy of LABA and LAMA for patients with COPD.

P4835 Synergistic effects between glycopyronium bromide and indacaterol on a muscarinic agonist-induced contraction in airway smooth muscle

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Rationale: Bronchodilators play an important role in therapy for stable chronic obstructive pulmonary disease (COPD). Anticholinergics and beta2-adrenoceptor agonists are widely used to improve lung function, symptoms, and QOL of patients with COPD. This study was designed to investigate whether combination of anticholinergics and beta2-adrenoceptor agonists is beneficial. Combined effects on airway smooth muscle contraction were examined using glycopyronium bromide (GB), a long-acting muscarinic antagonist (LAMA), and indacaterol, a long-acting beta2-adrenoceptor agonist (LABA).

Methods: For record of isometric tension, the strips of tracheal smooth muscle from guinea pigs were placed in the organ bath and were perfused with the physiological solution at a constant flow rate of 2 ml/min.

Results: One nM indacaterol caused a modest (7.9%, n=18) inhibition of 1 μM methacholine (MCh)-induced contraction of tracheal smooth muscle. GB at 3, 10, and 30 nM caused a concentration-dependent inhibition of 1 μM MCh-induced contraction with values of percent inhibition of 11, 1, 2; 1, 9, and 52.2%, respectively (each n=6). However, when equi-molar of GB were applied in the presence of 1 nM indacaterol, the inhibitory effects of GB (3, 10, and 30 nM) decreased (1 nM) combination were markedly enhanced, with values of percent inhibition of 25.6 (<p<0.05), 46.1 (<p<0.01), and 91.2% (<p<0.001), respectively (each n=6).

Conclusions: Indacaterol synergistically potentiated GB-induced inhibition against cholinergic stimulation in airway smooth muscle. These results may underlie the clinical benefit of combination therapy of LABA and LAMA for patients with COPD.

P4836 Cyclic AMP mediates the anti-asthma properties of the lidocaine analog JMF2-1

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Inhalation of JMF2-1, an analog of lidocaine with reduced anesthetic activity, prevents airway contraction and lung inflammation in experimental asthma models. We sought to test if JMF2-1 effects are a consequence of increased intracellular cAMP levels. These effects may underlie the clinical benefit of combination therapy of LABA and LAMA for patients with COPD. We and others reported earlier that steroids alone do not significantly reduce proliferation of ASM cells isolated from asthma patients. Objective: Here, we investigated the anti-proliferative signalling pathway of formoterol combined with three different steroids on ASM cell proliferation control.

Methods: Proliferation was determined by cell count 3 days after stimulation. Drugs were used at concentrations 1nM – 1microM. Protein expression (p21, p27) was determined by immuno-blots and -staining. Cyclic AMP was inhibited by DDA pre-incubation.

Results: Serum induced proliferation was reduced by steroids (dexamethasone, fluticasone, budesonide) in ASM cells of healthy controls but not of asthma patients. Formoterol dose dependently reduced cell proliferation by maximal 25% in both asthma and control ASM cells and this was paralleled by p27(Kip) activation in asthma ASM cells only. In combination the inhibitory effect of formoterol increased to 52% by dexamethasone, to 69% by budesonide and to 76% by fluticasone in healthy cells. In asthmatic ASM cells the combined rug’s effect was 47%, 52% and 56% respectively. Inhibition of proliferation of asthmatic ASM cells by formoterol occurred through cAMP and p27(Kip), which were both increased by the addition of steroids. The anti-proliferative effect of the combined drugs in control ASM cells involves p21(Waf1) and in asthmatic cells by p27(Kip). This effect was consistently augmented by SQ22556 and reproduced by forskolin in both systems. Our results suggest that JMF2-1 inhibits respiratory smooth muscle contraction as well as T cell survival through enhancement of intracellular cAMP levels. These findings may help to explain the anti-inflammatory and antiastmatic effects of JMF2-1 observed in previous studies.

P4837 Evidence for a non-β2-adrenoceptor (β2AR) binding site in human lung tissue for the long acting β2-agonist (LABA) vilanterol

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Background: Vilastron (VI) is a novel LABA with inherent 24 hour activity in development for inhaled once daily administration in combination with an inhaled corticosteroid for both COPD and asthma. We describe here an additional binding site in human lung tissue distinct from the orthosteric β2AR binding site in an in vitro binding assay.

Methods: Radioligand saturation and competition binding experiments were performed by titration with [3H]VI or [3H]propranolol and human lung parenchyma membranes measured at 37°C (∼100μM Gpp(NH)p with NSB 10μM β2AR antago- nist IC118551). Competition binding with a range of unlabelled β2AR agonists/antagonists was determined (data shown mean ∆SEM, n=4). Statistical differences measured by ANOVA (Bonferroni post-test) with P < 0.05 deemed significant.

Results: Saturation binding data were best fitted to a one affinity site model with Ki values 8.8±0.3 and 9.0±0.1 and Bmax values 0.5±0.1 and 0.4±0.1 pmol/mg for [3H]VI and [3H]propranolol, respectively. IC118551, propranolol, salbutamol, formoterol and carmoterol resulted in inhibition of [3H]VI (△<0.3nM) binding.
Introduction: NVA237 (glycopyrronium bromide) is a long-acting muscarinic antagonist for the treatment of COPD. It is primarily eliminated by the kidneys. Since renal function decreases in elderly and the target population of NVA237 includes elderly patients it is important to investigate the effect of renal impairment (RI) on NVA237 pharmacokinetics.

Methods: Subjects: 8 with mild RI, 8 with moderate RI, 8 with severe RI, 6 with elderly healthy patients. Comparison was made by matching healthy volunteers (HV). Renal function was assessed by the estimated glomerular filtration rate (eGFR). Subjects were randomized to treatment with: NVA237 without acetylcysteine (NAC) or with concomitant administration of NAC to study the pharmacokinetics (PK) of NVA237 following inhalation versus NVA237 administered via the Breezhaler® device. 

Conclusion: In subjects with mild and moderate RI (eGFR >30 mL/min/1.73m²), the mean terminal half-life of NVA237 was estimated to be about 5%. In Part 2 the absolute bioavailability with oral activated charcoal (AC) to study the pharmacokinetics (PK) of the bioavailability of inhaled NV A237 (glycopyrronium bromide-GP) delivered via the Breezhaler® device. 

Results: A moderate increase in NVA237 total systemic exposure (AUCLast) of up to 1.4-fold (on average) was seen in subjects with mild and moderate RI as compared to HVS. An increase of up to 2.2-fold was observed in subjects with severe RI and ERSD. Renal clearance (CLR) of NVA237 was strongly correlated with eGFR. In subjects with severe RI, CLR was reduced by about 80% compared with HVs. NVA237 was partially cleared during hemodialysis with an extraction ratio of 24.3%. NVA237 was well tolerated by HVs and RI subjects. Conclusion: RI had an impact on NVA237 total systemic exposure which was modest in subjects with mild RI and high in subjects with severe RI. The limited effect of severe RI on systemic exposure to NVA237 and the correlation analysis of total systemic clearance versus eGFR suggests that non-renal clearance mechanisms play a role in the elimination of NVA237.

P4838
Small impact of mild and moderate renal impairment on the pharmacokinetics of inhaled NVA237

Conclusion: NV A237 inhaled via the Breezhaler® device is efficiently deposited in human lung parenchyma membranes. In addition, VI binds to a additional binding site, distinct from the functional orthosteric β₂AR binding site shared with salmeterol and indacaterol.

Results: In Part 1, NV A237 400 μg dose of NV A237 delivered via the Breezhaler® device. In Part 2, NV A237 200 μg dose was administered orally to 10 HVs with and without concomitant administration of AC to demonstrate that GI absorption of NVA237 can be blocked. In Part 2 (n=20 HVs) the PK of 200 μg inhaled NVA237 with and without AC were compared to those of an i.v. infusion of 120 μg i.v. Plasma PK data were analyzed by non-compartmental and compartmental methods.

Conclusion: In Part 1 showed that oral AC was effective in blocking the oral absorption of NVA237. Absolute bioavailability of orally administered NVA237 (without AC) was estimated to be about 5%. In Part 2 the absolute bioavailability of inhaled NV A237 was about 40%. About 90% of systemic exposure was due to pulmonary absorption, 10% to GI absorption. About 36% of the inhaled dose was deposited and absorbed in the lungs. The mean terminal half-life of NV A237 was 52.5 h and 57.2 h in the inhalation treatments, 6.2 h after the i.v. dose and 2.8 h after the oral dose.

Conclusion: NVA237 inhaled via the Breezhaler® device is efficiently deposited and absorbed in the lungs. The terminal half-life of NV A237 is much longer after inhalation than after i.v. or oral dosing which points to sustained lung concentrations of NVA237 following inhalation.

P4840
Guafensin suppresses MUC5AC content and secretion in human airway epithelial cell cultures: Comparison with N-acetylcysteine and ambroxol

Conclusion: The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Methods: This study in healthy volunteers (HVs) was designed to investigate the impact of renal impairment (RI) on the pharmacokinetics of NVA237 (glycopyrronium bromide, GP) delivered via the Breezhaler® device. The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Methods: Cells were treated with 1 ng/mL IL-13 for 3d, then treated with GGE, NAC, or Amb (+IL-13). At 3, 8, or 24 h after treatment, cells were analyzed from videos. Apical secretions from 8 and 24 h were analyzed by micro parallel plate rheology.

Conclusion: At 24h, IL-13 decreased MCT rates by 75% but did not affect G' (elastic) or G'' (viscous) moduli. All drugs significantly increased MCT and decreased G' vs. IL-13 alone. GGE (30 μM) increased MCT 2.6-fold at 24h and reduced G'' to 10% of IL-13-only values. NAC reduced G' but increased MCT –2-fold at 30 μM and decreased MCT to below baseline at 100 μM. Effects of Amb were smaller. The reduced MCT for NAC at 100 μM could be due to uncoupling of ciliary beat from mucus. Bonferroni analysis (p<0.05) showed significant advantages for GGE vs. NAC & Amb (MCT) and vs. Amb (rheology, G').

Conclusion: GGE increases MCT via decreased mucus viscoelasticity, which may be a useful property in treating certain respiratory diseases.

P4841
Guafensin alters mucus rheology and improves mucociliary transport in human airway epithelial cell cultures: Comparison with N-acetylcysteine and ambroxol

Methods: The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Results: At 24h, IL-13 decreased MCT rates by 75% but did not affect G' (elastic) or G'' (viscous) moduli. All drugs significantly increased MCT and decreased G' vs. IL-13 alone. GGE (30 μM) increased MCT 2.6-fold at 24h and reduced G'' to 10% of IL-13-only values. NAC reduced G' but increased MCT –2-fold at 30 μM and decreased MCT to below baseline at 100 μM. Effects of Amb were smaller. The reduced MCT for NAC at 100 μM could be due to uncoupling of ciliary beat from mucus. Bonferroni analysis (p<0.05) showed significant advantages for GGE vs. NAC & Amb (MCT) and vs. Amb (rheology, G')

Conclusion: GGE increases MCT via decreased mucus viscoelasticity, which may be a useful property in treating certain respiratory diseases.

P4842
The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Background: Airway mucus hypersecretion is common in many respiratory diseases such as upper respiratory tract infections, asthma and COPD (chronic bronchitic form). Drugs to inhibit mucus production are needed. We showed that guafensin (glyceryl guaiacolate ether, GGE) inhibits unstimulated MUC5AC production in differentiated human airway epithelial cells in vitro (Seagar et al. EXP Lung Res 2011;37:606–14).

Aims: We examined the effects of GGE on MUC5AC secretion and secretion in cells stimulated with IL-13 to produce additional mucus and compared the GGE effects with those of the mucolytic N-acetylcysteine (NAC) and the mucoactive drug ambroxol (Amb).

Hypothesis: GGE would inhibit IL-13-stimulated MUC5AC production.

Methods: Cultures were pre-treated with 1 μg/mL IL-13 for 3d, then treated with 10, 30, 100 or 300 μM GGE, NAC or Amb for 3, 8 or 24 h in the presence of IL-13. The apical surfaces were washed and cells were lysed. MUC5AC content was measured in the washes (secretion) and lysates (content) was assessed by ELISA.

Results: IL-13 increased MUC5AC secretion (2-fold) and content (1.5-fold) over baseline at 24h. GGE significantly inhibited MUC5AC secretion and content in a concentration-dependent manner, with IC50s of ~110 and 150 μM and inhibition was seen at 300 μM GGE of 80 and 90% respectively at 24h. Although NAC and Amb inhibited IL-13-induced MUC5AC production, inhibition was only 20–40% at 24h. GGE concentration-dependence in lowering cell viability was not concentration-dependent. Non-renal clearance mechanisms play a role in the elimination of NVA237.

Conclusion: The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Hypothesis: GGE reduces stimulated mucus viscoelasticity and increases MCT.

Methods: Cells were treated with 1 ng/mL IL-13 for 3d, then with 30 or 100 μM GGE, NAC, or Amb (+IL-13). At 3, 8, or 24 h after treatment, MCT rates were calculated from videos. Apical secretions at 8 and 24 h were analyzed by micro parallel plate rheology.

Results: At 24h, IL-13 decreased MCT rates by 75% but did not affect G' (elastic) or G'' (viscous) moduli. All drugs significantly increased MCT and decreased G' vs. IL-13 alone. GGE (30 μM) increased MCT 2.6-fold at 24h and reduced G'' to 10% of IL-13-only values. NAC reduced G' but increased MCT –2-fold at 30 μM and decreased MCT to below baseline at 100 μM. Effects of Amb were smaller. The reduced MCT for NAC at 100 μM could be due to uncoupling of ciliary beat from mucus. Bonferroni analysis (p<0.05) showed significant advantages for GGE vs. NAC & Amb (MCT) and vs. Amb (rheology, G').
3.8. COPD comorbidities II

P550 Longitudinal changes in detrended fluctuation analysis “alpha” of PEF in COPD
Gavin Donaldson1, Terence Seemungal2, John Hurst1, Urs Frey3, Iadhiga Wissa4, 5, Academic Unit of Respiratory Medicine, UCL Medical School, Royal Free Hospital, London, United Kingdom; 2Department of Clinical Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago; 3Pneumatics, University Children’s Hospital, Basel, Switzerland

Introduction: Detrended fluctuation analysis can assess the “memory” of previous events with the exponent alpha. Alpha is higher in COPD than asthma, responses to pharmacotherapy, and is related to exacerbation frequency, but is not known whether alpha changes with increasing disease severity.

Methods: We examined 230 patients from the London COPD cohort who recorded for at least two years on diary cards daily morning, post-medication PEF measurements made with Mini-Wright PEF meter. Patient characteristics were collected at recruitment to the cohort. The data was divided into yearly intervals, and the alpha and mean PEF in each yearly interval calculated. Random-effects, GLS regression models were used to assess changes over time.

Results: The 230 COPD patients (144M; mean age (SD) 68.3 (8.1) years; FEV1 1.12 (0.47) L; FEV1/FVC predicted 44.6 (16.5); FEV1/PVC ratio 0.45 (11.7). There were 1000 yearly intervals with on average 4.3 per patient (range 2-15). Figure 1 shows a predicted alpha in the first year of 0.93 (95% CI 0.91-0.95) with alpha falling by -0.0008 per year (-0.007 to 0.005; p=0.791). Over the same period PEF fell from the 227 l/min (217 to 236) by -4.3 l/min per year (-5.1 to -3.7; p<0.001).

Figure 1

Conclusion: In COPD patients, PEF declines over time but alpha remains unchanged. These results suggest that alpha is assessing a feature of the airways that is independent of lung function and changes little over time.

890s
Adequate repair of damaged tissue is important for maintaining normal lung function. Changes in this delicate repair mechanism could contribute to pathological processes, such as alveolar destruction (emphysema) and airway fibrosis, in lung diseases including chronic obstructive pulmonary disease (COPD). Transforming growth factor (TGF-β) and bone morphogenetic proteins (BMPs) interactively regulate tissue homeostasis and lung organogenesis. In particular, BMP4 is known to be important for proper lung development. BMP4 is also an important regulator of TGF-β-induced lung fibrosis. The activity of BMP4 is antagonized by the TGF-β-induced protein follistatin-like 1 (Fstl1). Moreover, depletion of Fstl1 was found to be an essential regulator of lung development in mice. We hypothesize that increased Fstl1 contributes to cigarette smoke-induced fibrosis and emphysema in COPD. Interestingly, specific depletion of Fstl1 from the mice endothelium caused thickened alveolar septa and airway fibrosis. In human, Fstl1 is expressed in structural and inflammatory cells of the lung and treatment of primary human airway smooth muscle cells with cigarette smoke extract increases Fstl1 expression. Taken together, these findings suggest that increased expression of Fstl1 due to smoking could lead to structural changes in the lung associated with COPD.

OP/Y/01
Follistatin-like 1: A crucial factor in lung development and a novel regulator of airway remodelling

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The bone marrow contains a number of distinct progenitor cell populations, including endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs) which have the capacity to modulate the course of lung disease. We have investigated whether these populations of stem cells are recruited from the bone marrow to the lungs in two contrasting models of lung disease (house dust mite (HDM) model of allergic airways disease and bleomycin-induced lung fibrosis). We show an increased recruitment of EPCs to the inflamed lung in the HDM model, along with increased peribronchial angiogenesis, and reduced numbers of EPCs in the bone marrow. Blocking either CXCR2 or VEGF inhibited the number of EPCs recruited to the inflamed lung and reduced the associated peribronchial angiogenesis. Further experiments suggest that while VEGF is required for mobilisation of EPCs from the bone marrow into the blood, ELR+CXC chemokines mediate their recruitment into the lungs. We have identified a population of MSCs residing in the naive lung, which are phenotypically different to bone marrow MSCs. In the bleomycin model of pulmonary fibrosis, we have observed a significant elevation in MSC numbers in the circulation and lung tissue and are currently investigating whether this is due to MSC recruitment from the bone marrow. Although the regenerative capacity of MSs has been extensively investigated, their ability to be mobilised from the bone marrow and recruited to the lung following injury has not yet been explored, and the mechanism by which this may be occurring is under investigation.

OP/Y/02
Activation of Wnt/β-catenin signaling promotes lung epithelial repair in emphysema

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Emphysema is characterized by airspace enlargement, tissue destruction and reduced Wnt signaling. Wnt/β-catenin activation attenuated experimental emphysema. Here, we aim to elucidate the mechanism of Wnt/β-catenin-induced alveolar epithelial cell repair in vitro and in vivo. Alveolar epithelial type II cells were isolated from untreated (ATIIc) or elastase treated (ATIIe) C57BL/6 mice at day 3, 7 and 14 with similar purity (>94%) and viability (>92%). ATII cells depicted increased cell numbers (i.e. 6.0±1.6x10⁶ ATIIc vs. 3.9±1.0x10⁶ ATIIe, day14), and significantly reduced expression of the Wnt target genes Axin2, LEF1 and LRP6 (i.e. LRP6 0.29±0.56 ATIIe vs. 0.86±0.56 ATIIc, day7) as determined by qRT-PCR. Freshly isolated ATII cells showed increased apoptotic susceptibility (Annexin V/PI staining). Live imaging of cultured ATII cells revealed altered ATII cell morphology and migratory behavior. Wnt activation of ATII cells by rWnt3a led to increased expression of Wnt target genes (i.e. Axin2 -2.15±0.12 rWnt3a vs. -5.18±0.29 control), epithelial markers SPC, TJP1, and Occludin, and increased proliferative capacity (BrDU). Primary ATII cells exhibited reduced Wnt/β-catenin activity and altered functional capacity. Wnt/β-catenin activation led to increased epithelial marker expression and stabilized ATII cell monolayers. Thus, activation of Wnt/β-catenin is a suitable tool to increase alveolar epithelial cell repair capacity in pulmonary emphysema.

OP/Y/03
Lung tissue engineering: generation and characterization of decellularized lung scaffolds for stem cell differentiation

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The interaction of stem cells with the surrounding matrix environment is crucial for cell fate. The development of biomaterials that recapitulate the in vivo environment is a key component to driving differentiation of pluripotent cells into lung endoderm precursors. We investigate whether decellularized lungs with intact matrix composition can promote the differentiation of embryonic stem cells (ESC) into distal lung epithelial cells. Rat cadaveric lungs were decellularized by sequential tracheal lavages and retrograde pulmonary arterial perfusion using a range of physical, chemical, and enzymatic treatments. Histological staining, immunofluorescence, electron microscopy, and tensile testing have confirmed decellularization and preservation of matrix proteins. Murine ESC (F112x2CD4; Bry/GFP cells) were seeded onto scaffolds following endoderm induction using activin, and analysed for lung lineage marker expression. Seeded ESC maintained FoxA2 expression and adopted an epithelial-like tubular organization. This demonstrates the ability of decellular lung scaffolds to support the adherence, proliferation, and potential differentiation of murine embryonic stem cells. Current studies are analysing their potential as viable scaffolds for the unidirectional differentiation of human endoderm-induced ESC (Hes2 cell line) into distal lung epithelial cells.

OP/Y/04
Recruitment of stem cell populations to the lung with disease

Kate Gowers, Carla Jones, Clare Lloyd, Sara Rankin, NHLI, Leukocyte Biology, London, United Kingdom

Mesenchymal stromal cells identified in tissue from lung-transplanted patients

S. Rolandsson 1, A. Andersson-Sjöland 2, J. Brane 3, L. Eriksson 1, I. Skog 1, L. Hansson 1, L. Björner 1, S. Scheding 1, G. Westergren-Thorsson 1

Background: Chronic rejection expressed as bronchiolitis obliterans (BO) is seen in 50% of lung-transplanted (LT) patients. BO is characterized by extra cellular matrix deposition, where the fibroblast is thought to be a key player. The fibroblast origin is at present not fully known. The fibrocyte is one of the potential origins, and our group has shown that fibrocytes are associated with remodelling in BO. In this study we focused on another origin the mesenchymal stromal cell (MSC).

Objectives: Our aims were to examine whether MSC are present in tissue from LT patients. We wanted to evaluate whether these cells displays characteristics MSC properties such as adherent clonal growth, multi-lineage potential and a characteristic surface marker profile.

Methods: MSC were isolated from biopsies of LT patients and the single cell suspension was seeded in colony-forming unit-fibroblast (CFU-F) assays. Isolated MSC were differentiated towards adipocytes, osteoblasts and chondrocytes. Their surface markers was examined by flow cytometry.

Results: MSC isolated from LT patients formed typical colonies, displayed spindle-shaped morphology and adhered to plastic. Further, cells displayed multi-lineage potential. Analysis of the surface markers showed that MSC showed expression of CD73, CD105 and CD90, but lacked expression of CD45 and CD34. Conclusions: Our study suggests that MSC are present in lung tissue from LT patients. These cells display colony growth, multipotential and a characteristic MSC surface marker profile.
TGF-β superfamily signaling during lung morphogenesis and adult tissue repair

Numerous studies in genetically modified animals have demonstrated the significance of the TGF-β superfamily in lung development and homeostasis. However, the cellular targets and the pattern of BMP, and/or TGF-β/Activin-signalling in the respiratory system still remain poorly outlined. To address this issue, we utilized two different transgenic lines, one expressing eGFP under the control of a BMP-responsive element (BRE-eGFP line) and a recently developed novel transgenic line expressing mRFP under the control of a TGF-β/Activin-responsive element (TβR-I-mRFP line). Crossing of these animals and development of double reporter mice allowed us to simultaneously monitor BMP and TGFβ/Activin signalling in the same tissues. Analysis of these animals unveils a far more complex and dynamic activation pattern for the TGFβ superfamily signalling system during lung development, homeostasis and tissue repair than previously anticipated. These animal models provide a unique opportunity to isolate specific cell populations under the control of these pathways and construct a functional spatiotemporal map for this signalling system in health and disease.

Resident mesenchymal progenitor cells in adult lung maintenance, repair, and fibrosis

Delineation of embryonic lung mesenchyme is essential for branching morphogenesis and epithelial cell specification in the fetal lung. We have recently demonstrated that lung-specific mesenchymal progenitors persist in the human adult lung. These lung-resident mesenchymal stem cells (LR-MSCs) express embryonic lung-specific mesenchymal markers such as Oct4, and are mobilized in response to lung injury via paracrine mechanisms as well as via direct gap junction communications. An increase in LR-MSC population is seen in response to injury such as after orthotopic lung transplantation and likely plays a role in lung repairs. LR-MSCs can also differentiate into myofibroblasts in response to pro-fibrotic factors such as transforming growth factor-β and an altered pro-fibrotic phenotype is noted in LR-MSCs derived from lungs in diseases such as bronchiolitis obliterans or idiopathic pulmonary fibrosis. Mobilization of the LR-MSC population to the airspaces also precedes development of human fibrotic diseases such as bronchiolitis obliterans. Here we investigate the paracrine factors, cell surface receptors and intra-cellular signaling pathways mediating differentiation of these lung-resident organ-resident paracrine mesenchymal progenitors. We demonstrate that ligation of G protein coupled receptor lysophosphatidic acid 1 leads to migration of LR-MSCs via GSK3β phosphorylation and subsequent β-catenin accumulation and nuclear translocation. These data suggest an important role for β-catenin activation in mobilization of tissue-resident mesenchymal progenitors in human adult lungs.

Lung stem cells and their niche

During lung development, Fibroblast growth factor 10 (FGF10) is secreted by the airway smooth muscle cells progenitors in the distal mesenchyme. β-catenin signaling within these airway smooth muscle cell progenitors is essential for their maintenance, proliferation, and Fgf10 expression. Fgf10 acts on the distally located epithelial progenitors to prevent their differentiation and promote their proliferation. We found that this Wnt/Fgf10 embryonic signaling cascade is reactivated in mature airway smooth muscle cells after airway epithelial injury. Furthermore, we found that this paracrine Fgf10 action was essential for airway epithelial repair. After injury, airway smooth muscle cells secreted Fgf10 to activate Notch signaling and induce Snai1 expression in surviving Clara cells, which subsequently underwent a transient epithelial to mesenchymal transition to initiate the repair process. We have therefore identified airway smooth muscle cells as a stem cell niche for the (variant) Clara cells in the lung and established that paracrine Fgf10 signaling from the niche is critical for epithelial repair after injury. These findings also have implications for understanding the misregulation of lung repair in asthma and cancer.

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Chronic obstructive pulmonary disease (COPD) is characterized by fibroblast activation and changes in extracellular matrix (ECM) composition, in which transforming growth factor (TGF-β1) plays an important role. We previously found that TGF-β1 increases the expression of WNT pathway components, notably the Frizzled-8 receptor (FZD8). This was even more pronounced in fibroblasts of COPD patients. Therefore, we studied the functional role of FZD8 in MRC5 human lung fibroblasts. TGF-β1 strongly induced FZD8 expression, which was attenuated by Smad3 inhibition. Importantly, FZD8 silence reduced TGF-β1-induced ECM gene expression and fibroblast activation. The canonical WNT inhibitor Diclectin did not affect these effects, suggesting that FZD8 signals through non-canonical WNT signalling. In support, TGF-β1 induced the expression of non-canonical WNT-5B. Further, the TGF-β1-induced effects were mimicked by WNT-5B stimulation and reduced by WNT-5B siRNA. Collectively, this implies a critical role for autocrine WNT signalling via FZD8 in COPD disease, including bipolar disorder and epilepsy. Reducing the PGP levels might improve treatment in BOS. Using VPA was interesting, as it is used clinically for other indications. Using POP inhibitors to reduce PGP generation seems to be promising treatment in COPD.

Distal airway epithelial cells differentiate into ATI-like cells as suggested by morphological changes as well as increased expression of differentiation markers AQP3, SPC-A, SPC-C in the 3D model. Wnt11 was identified in the model and in human lung explant cultures as one of the main regulators of ATI differentiation. Added Wnt11 increased the expression of ATI markers, while silencing of Wnt11 resulted in elevated levels of EMT markers N-cadherin and S100A4. We conclude that the 3D lung model is applicable for studying epithelial-mesenchymal interactions in the lung. Our finding may mark Wnt11 as a potential therapeutic target in lung regenerative therapy.
The role of TNF-related apoptosis inducing ligand (TRAIL) in interstitial lung disease

Emmet McGrath, Alan Lawrie, Helen Marriott, Paul Mercer.

Introduction: Driving cellular apoptosis as a potential therapy for diseases is of widespread interest. We previously showed a death receptor ligand, TRAIL, accelerates neutrophil apoptosis and other work revealed TRAIL-induced apoptosis of human lung fibroblasts. The aims of this project were to study the role of TRAIL in bleomycin lung injury in wild-type (WT) and TRAIL−/− (T−) mice and in patients with idiopathic pulmonary fibrosis (IPF).

Methods: Mice received intratracheal bleomycin or saline control. Bronchoalveolar lavage (BAL) at 3, 7, 16 and 23 days was analysed by cytospin and hemocytometer for % neutrophils, % neutrophil apoptosis, total number of neutrophils and apoptotic cells. Flow cytometry was also used to analyse apoptosis. Collagen deposition was analysed using a hydroxyproline assay. TGF-β expression and TUNEL positive events were also analysed. Serum and lung tissue from IPF patients/controls were examined for TRAIL expression and concentration. Lung function and survival data were retrieved from patient charts.

Results: BAL analysis revealed significant differences between T− and WT mice, with T− mice showing increased neutrophil numbers and reduced apoptosis. Collagen deposition was statistically greater in TRAIL−/− mice. TGF-β levels were measured and the role of TRAIL in bleomycin-induced fibrosis and collagen mRNA was assessed. TGF-β levels were increased in TRAIL−/− mice. These data suggest TRAIL may have a role in ECM production by ASM and hence, could present new targets for asthmatic airway remodeling.

PP103
FOXO transcription factors regulate innate immune mechanisms in respiratory epithelial cells during bacterial infection

Christothea Reisswenger, Frederik Seiler, Philipp Lepper, Robert Bals, Christian Herr.

Bacterial pathogens are a leading cause of lung infections and contribute to acute exacerbations in patients with respiratory tract diseases. The innate immune system of the lung controls and prevents colonization of the respiratory tract with bacterial pathogens. Here, we show that FOXO transcription factors regulate innate immune mechanisms of respiratory epithelial cells in response to bacterial pathogens such as Haemophilus influenzae and Pseudomonas aeruginosa. Infection with bacterial pathogens led to the activation of FOXO transcription factors in respiratory epithelial cells and have a central role in regulating innate immune functions of respiratory epithelial cells.

PP104
FOXO transcription factors regulate innate immune mechanisms in respiratory epithelial cells during bacterial infection

Christothea Reisswenger, Frederik Seiler, Philipp Lepper, Robert Bals, Christian Herr.

Introduction: FOXO transcription factors regulate innate immune mechanisms in respiratory epithelial cells in response to bacterial stimuli and have a central role in regulating innate immune functions of respiratory epithelial cells.

Methods: Mice received intratracheal bleomycin or saline control. Bronchoalveolar lavage (BAL) at 3, 7, 16 and 23 days was analysed by cytospin and hemocytometer for % neutrophils, % neutrophil apoptosis, total number of neutrophils and apoptotic cells. Flow cytometry was also used to analyse apoptosis. Collagen deposition was analysed using a hydroxyproline assay. TGF-β expression and TUNEL positive events were also analysed. Serum and lung tissue from IPF patients/controls were examined for TRAIL expression and concentration. Lung function and survival data were retrieved from patient charts.

Results: BAL analysis revealed significant differences between T− and WT mice, with T− mice showing increased neutrophil numbers and reduced apoptosis. Collagen deposition was statistically greater in TRAIL−/− mice. TGF-β levels were measured and the role of TRAIL in bleomycin-induced fibrosis and collagen mRNA was assessed. TGF-β levels were increased in TRAIL−/− mice. These data suggest TRAIL may have a role in ECM production by ASM and hence, could present new targets for asthmatic airway remodeling.

Conclusion: The inflammatory and collagen deposition response to bleomycin is increased in T− compared to WT mice. We demonstrated reduced pulmonary and systemic expression of TRAIL in IPF, which correlates with worse pulmonary function and clinical outcome. This data suggests TRAIL may have biomarker/therapeutic benefit in pulmonary fibrosis.
PP106 Sonic Hedgehog signaling in non-small-cell lung cancer
Olga Bredemeyer, 1 Ina Koch, 1 Elisabeth Hennem, 1 Maria-Magdalena Stein, 1 Michael Lindner, 2 Melanie Königshoff, 2 Oliver Eckelberg, 3 Comprehensive Pneumology Center, Helmholtz; Zentrum München, Munich, Germany; 4 Molecularbiologisches Labor, Asklepios Fachkliniken München-Gauting, Gauting, Germany; 5 Department of Thoracic Surgery, Asklepios Fachkliniken München-Gauting, Gauting, Germany

Introduction: Sonic hedgehog (Shh) signaling has been recently identified as key player in human cancers. We sought to elucidate the expression and role of Shh in non-small-cell lung cancer.

Methods: Cell proliferation was investigated using the inhibitory cyclopamine or small interference RNAs (siRNA) against Gli1, Gli2 and Gli3. Expression of Shh-related genes in normal and tumoral tissue was assessed by quantitative real time PCR in 10 patients with adenocarcinoma and 10 patients with squamous carcinoma.

Results: Inhibition of Shh signaling decreases a decrease in the proliferation of A549 adenocarcinoma and H520 squamous carcinoma cells. H520 cells secrete a high level of Shh, which promotes a high level of Gli1, Gli2 and Gli3 expression. The inhibition of Shh pathway results in limited primary human fibroblasts. In the tumoral tissue, Shh, Gli1 and Gli2 RNA levels were found to be increased mainly in patients in stage T1 or T2.

Conclusions: Shh pathway plays a role in lung cancer cell proliferation and its regulation may be determinant for lung cancer progression.

PP108 Decellularized human lung slices as a culture substrate to examine the role of ECM in lung fibrogenesis and regeneration
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Idiopathic Pulmonary Fibrosis (IPF) is characterized by progressive deposition and remodeling of lung extracellular matrix (ECM). Decellularized human lung tissue provides an ECM scaffold with disease-specific, relevant structure and composition. This study was aimed to investigate whether PBP occurs as a result of increased expression of matrix metalloproteinase 1 (MMP-1), MMP-2 and MMP-9 from activated alveolar macrophages.

Methods: In lung tissue samples from 51 patients presenting with PBP to determine the level of expression of MMP-1, MMP-2 and MMP-9. Semi-quantitative analysis revealed decreased expression of MMP-2 and MMP-9 compared to controls. No alteration in MMP-1 expression was observed in comparison to controls.

Conclusions: Increased levels of MMP-2 and MMP-9 may limit the deposition of matrix construct causing a weakness in type IV collagen. This decrease in MMP activity may alter the proteolysis/antiproteolysis balance reflecting defective repair of the extracellular matrix. Sustained production of MMP-1 under these conditions may further contribute, pushing the re-modelling process towards matrix destruction. PBP results in significant expression of matrix metalloproteinases.

Supported by the 7th FP, HEALTH-F2-2007-202224 eurIPFnet

PP110 Macrophage derived metalloproteinases 1,2 and 9 in the development of primary spontaneous pneumothorax
Rachel Norman1, 2, 3, 4, 5, 6, Ruth Morse, 1 Histology, P.E.H. Guernsey, United Kingdom; 2 Histology, Heartlands, Birmingham, United Kingdom; 7 Life Sciences, U.W.E, Brstol, United Kingdom

Primary spontaneous pneumothorax (PSP) is a common clinical problem affecting previously healthy individuals. The pathogenesis is poorly understood but is related to rupture of apical pleural blebs. Enhanced production of alveolar macrophage derived matrix degrading metalloproteinases within the lung is postulated to result in increased breakdown of collagen and elastin causing alveolar destruction, distal emphysema and formation of blebs. The study aims to investigate whether PBP occurs as a result of increased expression of matrix metalloproteinase 1 (MMP-1), MMP-2 and MMP-9 from activated alveolar macrophages.

Methods: In vivo, in A549 cells treated with rTGF-β1, V5/192 mice KO for a/b-C or WT received intrathoracic bleomycin (in-bio-0.07U/mouse) or AdTGFβ1. Results: In vivo, lung from aged untreated a/b-C KO mice are typically normal. a/b-C is overexpressed in fibrotic areas after bleo or AdTGF-β1. By day 21 after bleo/collagen content in the lung is higher in WT (3 fold, p<0.05) compared to KO mice (2/TGFβ1 (ELISA) is lower in the BAL from KO than WT mice (299±185ng/ml, p<0.05).

PP111 a/b-Crystallin is involved in pulmonary fibrosis
Pierre-Simon Bielle, 1 Gwenn Emery, 2 M Kolb, 1 Gauldie, 1 B Crestani, 2 C Garrido, 2 F Camus, 2 P Bonnifait. 1 INSERM U1366, Dijon, France

Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease. We have shown that the small heat shock protein (αHSP) HSP27 is involved in IPF through a role in EMT, a/b-crystallin (α-b-crystallin) another HSP is expressed in lungs, which is inducible by stress and has a role in cell cytoskeleton architecture. The role of a/b-C in fibrosis is unknown.

Methods: A549 cells were treated with rTGF-β1, V5/192 mice KO for a/b-C or WT received intrathoracic bleomycin (in-bio-0.07U/mouse) or AdTGFβ1. Results: In vivo, lung from aged untreated a/b-C KO mice are typically normal. a/b-C is overexpressed in fibrotic areas after bleo or AdTGF-β1. By day 21 after bleo/collagen content in the lung is higher in WT (3 fold, p<0.05) compared to KO mice (2/TGFβ1 (ELISA) is lower in the BAL from KO than WT mice (299±185ng/ml, p<0.05).

PPI102 Primary spontaneous pneumothorax (PSP) is a common clinical problem affecting previously healthy individuals. The pathogenesis is poorly understood but is related to rupture of apical pleural blebs. Enhanced production of alveolar macrophage derived matrix degrading metalloproteinases within the lung is postulated to result in increased breakdown of collagen and elastin causing alveolar destruction, distal emphysema and formation of blebs. The study aims to investigate whether PBP occurs as a result of increased expression of matrix metalloproteinase 1 (MMP-1), MMP-2 and MMP-9 from activated alveolar macrophages.

Methods: In vivo, in A549 cells treated with rTGF-β1, V5/192 mice KO for a/b-C or WT received intrathoracic bleomycin (in-bio-0.07U/mouse) or AdTGFβ1. Results: In vivo, lung from aged untreated a/b-C KO mice are typically normal. a/b-C is overexpressed in fibrotic areas after bleo or AdTGF-β1. By day 21 after bleo/collagen content in the lung is higher in WT (3 fold, p<0.05) compared to KO mice (2/TGFβ1 (ELISA) is lower in the BAL from KO than WT mice (299±185ng/ml, p<0.05).

PP112 Phenotypic characterization of the putative lung cancer stem cells that egress into peripheral blood
Tomasz Skirecki, 1 Graumpyna Hoset, 1; Jerzy Kawiak, 1, Joanna Domagaa-Kulawik, 2; Laboratory of Flow Cytometry, Medical Center of Postgraduate Education, Warsaw, Poland; 3 Allergology and Pneumology, Warsaw Medical University, Warsaw, Poland

Lung cancer (LC) poses high metastatic potential but the exact cell of origin of metastasis is not known, however the LC stem cells seem to be one candidate for the metastasis-founding cell. We aimed to evaluate whether circulating lung cancer cells have phenotype of the cancer stem cells. Expression of stem cell markers (CD133, EpCAM, CXCR4) was analyzed in LC cell lines, tumor samples and peripheral blood (PB) of LC patients (n=39) by flow cytometry. Murine model of metastatic cancer was developed by subcutaneous injection of LC cells into thymi of the NSG mice. Putative LC stem cells (CD133+/EpCAM+) were present in the analyzed cell lines and in 67/tumor samples. All of the CD133+/EpCAM+ cells co-expressed the CXCR4. 2 weeks after injection of the LC cells, the CD133+/EpCAM+ cells were identified in the PB of all animals. PB of 15 LC patients contained the CD133+/EpCAM+ cells.

We confirmed the presence of a subpopulation of the LC stem cells of CD133+/EpCAM+/CXCR4+ phenotype. This subpopulation can be found in the circulation of the mice with locally transplanted LC cells, and in the PB of some LC patients. Interestingly, the number of CD133+/EpCAM- cells was elevated in the metastatic disease, suggesting important role of the non-malignant stem cells in the progress of disease.

Supported by the 7th FP, HEALTH-F2-2007-202224 eurIPFnet

Macrophage activation is an intricate molecular process likely regulated by the cross talk between activating and inhibitory signals. While much is known on receptors that promote macrophage activation, receptors that suppress their functions received scant attention. Paired immunoglobulin-like receptor B (Pir-B) is an immunoreceptor tyrosine-based inhibitory receptor capable to inhibit immune cell function (e.g. chemotaxis, mediator release, adhesion). Nonetheless, the expression and function of Pir-B in pulmonary fibrosis is unknown. In this study, we demonstrate that Pir-B is upregulated in lung myeloid cell subsets following bleomycin administration. Bleomycin-challenged Pir-B-/- mice displayed increased lymphocytic and decreased neutrophilic inflammation, which was correlated with increased levels of macrophage-derived resistin-like molecule α (Relm-α) and MMP12 but not IL-6, CCL2 and KC. Furthermore, Pir-B-/- mice evidenced significantly increased lung fibrosis as assessed by lung histopathology and collagen content in comparison to wild type mice. Consistently, bone marrow-derived Pir-B-/- macrophages displayed increased Relm-α secretion and MMP12 expression following IL-4 activation in comparison with wild type macrophages. These results define a key role for alternatively activated macrophages in pulmonary fibrosis and establish Pir-B as a fundamental regulator of macrophage polarization.
**Conclusion:** Pim1 protects airway epithelial cells from CS-induced damage and proliferative potential after injury. Influenza virus targets putative lung epithelial progenitors and impairs their inflammation. In vivo, this protective effect suffices to prevent CS-induced neutrophilic airway cell death by phosphorylating BAD and increasing the threshold for apoptosis. BAD phosphorylation was determined by Western Blotting.

**Results:** CS exposure induces neutrophilic airway inflammation and increases KC levels in Pim1-KO mice, but not in WT controls. CSE induces a dose-dependent loss of BAD phosphorylation, loss of 4M and necrotic cell death in Beas-2b cells. All of these CSE-induced effects are aggravated by inhibition of Pim1.

**Conclusion:** Pim1 protects airway epithelial cells from CS-induced damage and cell death by phosphorylating BAD and increasing the threshold for apoptosis. In vivo, this protective effect suffices to prevent CS-induced neutrophilic airway inflammation.

**PP114**

**Influenza virus targets putative lung epithelial progenitors and impairs their proliferative potential after injury**

Qing Ruhana Gottschald, Jennifer Quantius, Werner Seeger, Jürgen Lohmeyer, Susanne Herold. Department of Internal Medicine II, University of Giessen Lung Center, Giessen, Germany

Influenza virus can induce severe damage of the alveolar epithelium, leading to pulmonary oedema and respiratory failure. Therefore, an efficient alveolar repair is crucial for recovery. We defined a lung epithelial cell population (EpCAMhigh CD49dhigh CD24low) during influenza infection. These cells were previously described to have progenitor cell characteristics, being resistant to damage and proliferating after injury in lineages. In this population, dual the protease EPAC1 is expressed at high level CD104high and CCSPpos Sca1intCD104high and CD34high, which is located at the level of bronchioles. After influenza infection, this population showed an increased proliferation rate, peaking at day 7 p. i., when compared to other populations of lung epithelial cells. In addition, the progenitor cells were resistant to infection-induced apoptosis. Different influenza virus strains, of high and low pathogenicity, exhibited different degrees of tropism towards putative lung epithelial progenitors and infection of these progenitors decreased their reparative potential which might determine the pathogenicity of influenza viruses during influenza pneumonia.

**PP115**

**Chlorine gas exposure causes rapid coagulation dysfunction in mice**

Storries Zooraghi, Naseem Anjum, Solana Fernandez, Cilina Ann Rodriguez, Karen Ille, Jean François Petit, Sadis Matalon. University of Alabama at Birmingham, United States

**Rationale:** Chlorine is a highly reactive oxidant gas involved in lung injury. Chlorine and its hydrolysis products produce reactive oxygen - chlorine and nitrogen intermediates that damage the bronchial tree and the alveolar epithelium. Severe exposure (high concentrations of chlorine for an extended period of exposure) can lead to ALI/ARDS and also death. Chlorine gas exposure has been documented to have extra-pulmonary damaging effects by promoting systemic endothelial dysfunction via disruption of vascular nitric oxide homeostasis mechanisms (mainly eNOS).

**Aim:** The main objective of the present study is to evaluate the potential effects of chlorine gas exposure to coagulation that is initiated in instances of lung injury.

**Methods:** C57BL/6 mice were exposed to O2 either at 400 ppm for 30 min or at 600 ppm for 45 min, in environmental chambers and then returned to room air. Mice were euthanized 1h post exposure and blood and bronchoalveolar lavage fluid (BALF) was collected for further analysis. In order to assess the native coagulation parameters, we analyzed whole blood using rotational thromboelastometry. We measured native coagulation (NATEM) parameters such as clotting time and kinetics of clot formation (clot formation time). Additionally, we measured thrombin - anti-thrombin complex formation in both plasma and BALF, a surrogate marker of thrombin generation. Mice that were not exposed to chlorine served as controls in all measurements.

**Results:** Our results indicate that mice exposed to chlorine gas had significantly increased clotting time as compared to control animals (p<0.05). In addition, the kinetics of clot formation were altered with animals exposed to chlorine requiring more time to form a clot. The thrombin - anti-thrombin assay showed that in both plasma and BALF of chlorine exposed animals, thrombin was increased as compared to control animals. These effects seem to be Cl2 concentration dependent since all parameters were pronounced in 600-ppm exposures.

**Conclusion:** These findings highlight the extra-pulmonary effects of chlorine gas exposure. The coagulation is perturbed in animals exposed to chlorine gas since there is reduced ability to form clots, despite the fact that thrombin generation is increased.

**PP116**

**The viability of mesenchymal stem cells after nebulization via different types of nebulizers**

Kulagina Nataliya1, Alexander Averyanov1, Anatoly Konoplyannikov2, Oleg Kuznetcov.1,3 Federal Research Clinical Center of Special Medical Care and Technologies of EMBA of Russia, Moscow, Russian Federation; 2Medical Radiological Scientific Center, Obninsk, Russian Federation

**Background:** Numerous experimental studies have proven the effectiveness of endobronchial administration of mesenchymal stem cells (MSCs) in different types of lung pathology. In transition to the clinical researches inhalation is one of the major ways of MSC delivery in lower respiratory tract. There is currently no data on the efficacy of different ways of nebulization on cell viability.

**Aim:** To determine the viability of MSC after nebulization via jet nebulizer and ultrasonic nebulizer.

**Methods:** In the study diluted 1:10 culture of human MSCs (1.1x106 cells in 1 ml) was used. Staining with nigrosine followed by counting the amount of non-viable (stained) cells in the count chamber under a light microscope was used to assess the viability of cells. It’s known that non-viable cells are stained with nigrosine, unlike the viable MSCs. The cells were administered via inhalation with jet nebulizer OMRON NE-C24 and ultrasonic nebulizer OMRON V-17. Duration of nebulization was 5 and 10 minutes respectively.

**Results:** As presented in Table 1 and Table 2.

**Table 1. Ultrasonic nebulizer**

<table>
<thead>
<tr>
<th>Total amount of MSC</th>
<th>Non-stained (viable) MSC</th>
<th>Stained (non-viable) MSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before nebulization</td>
<td>4.4x10⁶</td>
<td>4.1x10⁵ (93%)</td>
</tr>
<tr>
<td>5 min</td>
<td>4x10⁵</td>
<td>1.2x10⁴ (10%)</td>
</tr>
<tr>
<td>10 min</td>
<td>2.2x10⁴</td>
<td>4.4x10³ (20%)</td>
</tr>
</tbody>
</table>

**Table 2. Jet nebulizer**

<table>
<thead>
<tr>
<th>Total amount of MSC</th>
<th>Non-stained (viable) MSC</th>
<th>Stained (non-viable) MSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before nebulization</td>
<td>2.75x10⁶</td>
<td>2.55x10⁵ (93%)</td>
</tr>
<tr>
<td>5 min</td>
<td>1.55x10⁵</td>
<td>9.9x10⁴ (69%)</td>
</tr>
<tr>
<td>10 min</td>
<td>2.5x10⁴</td>
<td>1.85x10³ (74%)</td>
</tr>
</tbody>
</table>

**Conclusion:** 1. Nebulization of MSCs via jet nebulizer leads to retaining of most of the MSCs in a state of vitality. 2. Nebulization via ultrasonic nebulizer causes damage of the main mass of MSC.

**PP117**

**Exploring the role of microRNA miR-200b in normal and abnormal lung development due to congenital diaphragmatic hernia**

Raman Kohlebrarin, Naghmeh Khoshgoo, Barb Iwasiow, Richard Keijzer. Department of Surgery and Manitoba Institute of Child Health, University of Manitoba, Winnipeg, Canada

**Background:** Congenital diaphragmatic hernia (CDH) and pulmonary hypoplasia are poorly understood. No single gene has been indentified and thus epigenetic mechanisms are proposed to play a role. MicroRNAs are regulators of epigenetics. Previously, we identified miR-200b to be changed in CDH. miR-200b plays an important role in EMT/MET in cancer. We aimed to delineate the role of miR-200b during normal and abnormal lung development to CDH.

**Methods:** We used the nitrofen rat model for CDH. Spatial and temporal expression was obtained using rt-PCR and in situ hybridization. In vitro experiments...
using nitrofen, miR-200b mimics and inhibitors were used to characterize the role of miR-200b in EMT/MET. A SMAD luciferase reporter assay was used to relate the expression of miR-200b and TGF-β signalling.

Results: We observed higher expression of miR-200b during late lung development. miR-200b was mainly observed in epithelial cells. Both in vitro and in vivo experiments demonstrated downregulation of miR-200b expression after nitrogen treatment. This was associated with an upregulation of TGF-β signalling.

Conclusions: We demonstrate dynamic miR-200b expression during lung development with changes during abnormal lung development. The relationship between miR-200b, TGF-β signalling and EMT/MET explains some of the lung abnormalities observed in the hypoplastic lungs in CDH.

PP118
Lysosomal leakage in the human fibrotic lung
Lennart Persson1, Linda Vainikka2. 1Division of Pulmonary Medicine, Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden; 2Division of Experimental Pathology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden.

Background: Excess of iron (Fe) is involved in the pathogenesis of lung fibrosis. To protect the respiratory epithelium against Fe-catalyzed oxidative damage Fe is deposited inside lysosomes of lung macrophages (LMs). When challenged by oxidants, lysosomal Fe triggers lysosomal leakage and ensuing cell death promotes inflammation.

Aim: To assess lysosomal leakage/cell death in oxidatively stressed cultures of LMs harvested from patients with lung fibrosis and healthy subjects.

Methods: LMs were harvested from 7 patients with lung fibrosis and 7 healthy subjects without medications. LMs were oxidatively stressed by a stable concentration of H2O2 (120 μM). Lysosomal leakage and cell death were evaluated at the end of the 1 h oxidant challenge and at 10 h after oxidative stress, respectively. LMs were stained for Fe and cellular Fe and GSH were assessed.

Results: LMs from patients with lung fibrosis exhibited significantly more lysosomal leakage and cell death after oxidative stress. GSH was reduced while cellular and lysosomal Fe were increased.

Conclusions: This study provides a rationale for clinical testing using a combination of acetylcysteine, a precursor to GSH, and azithromycin (a weak base that accumulates 1000-fold inside the acidic lysosomes and attenuates lysosomal Fe reactivity) to prevent fibrosis progression.

PP119
Surfactant protein A in chronic extrinsic allergic alveolitis
Marina Stecclowa1, Marina Vasakova1, Peter Palubík2, Milan Paulík2. 1Department of Respiratory Diseases, Thomayer University Hospital, Prague, Czech Republic; 2Department of Immunology, Thomayer University Hospital, Prague, Czech Republic.

Chronic form of extrinsic allergic alveolitis (EAA) may have common features with idiopathic pulmonary fibrosis (IPF). The aim of presented study was to compare serum SP-A concentrations in IPF and chronic EAA patients and detect possible relationships of SP-A levels, bronchoalveolar lavage fluid (BALF) differential cell counts and high resolution computed tomography (HRCT) patterns in both diseases. Thirteen patients with chronic EAA and 7 patients with IPF were enrolled. All subjects underwent evaluation of SP-A serum concentrations, HRCT of the chest and BALF. HRCT alveolar and interstitial scores (HRCTa, HRCTI) were assessed according to Gay S1.

EAA patients had significantly higher HRCT alveolar score then IPF group (p=0.003). Chronic EAA group exhibited positive correlation between HRCTI and BALF eosinophils (p<0.001) (Fig. 1). Serum SP-A concentrations did not differ between both groups.

Our study shows that SP-A serum concentrations do not differ between chronic EAA and IPF patients and thus should be used as a biomarker for IPF detection. Prognostic value of serum SP-A concentrations in chronic EAA patients should be the aim of further studies.

Reference:

PP120
Human chitotriosidase as a prognostic biomarker of sarcoidosis
David Benedetti1, Elena Bargagli1, Nicola Bianchi1, Pasquale Di Sipio1, Rosa Metella Refini1, Maria Grazia Pieroni1, Paola Rottoli1. 1Respiratory Diseases Section, Department of Clinical Medicine and Immunology, University of Siena, Siena, Italy; 2Department of Environmental Sciences, University of Siena, Siena, Italy.

In the present study were evaluated the sensitivity and specificity of Chitotriosidase, a macrophages derived enzyme, in a population of 232 sarcoidosis patients divided according to the Clinical Outcom Status (COS) classification recently proposed by a WASOG task force. Serum chitotriosidase levels were significantly increased in patients than in healthy controls (p<0.0001) and correlated directly with ACE levels (r=0.25, p<0.0001). ROC curve analysis revealed sensitivity value of 88.6% and specificity of 92.8% with a cut-off value of 48.80 mmol/h/ml. Chitotriosidase concentrations were significantly increased in patients with chest XRay stage 3 vs. stage 0 (p=0.02). Significantly higher serum concentrations were found sarcoidosis patients in patients with persistent disease without treatment (COS5 and 6) and in those with symptomatic and persistent sarcoidosis on systemic therapy (class COS 8 and 9) compared to untreated patients with disease remission (COS1). Chitotriosidase resulted a serological biomarker for sarcoidosis easily detectable in serum with adequate sensitivity and specificity that can be proposed in the clinical practice to differentiate patients with a persistent disease requiring a more rigorous follow-up.

PP121
Role of ADAM19 and neuregulin-1 in Muc5ac expression in lungs of cigarette smoke-exposed mice
Lisa Dupont, Guy Joos, Guy Brusselle, Ken Bracke. Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

Mucus hypersecretion is an important feature of COPD, resulting in chronic cough and contributing to dyspnea by obstructing the airway lumen. Signalling through the epidermal growth factor receptor (EGFR) plays a ubiquitous role in the production of mucus. We hypothesize that A Disintegrin And Metalloproteinase 19 (ADAM19) stimulates mucin production by shedding of the EGFR-ligand neuregulin-1. C57BL/6 mice were exposed to air or cigarette smoke (CS) for 4 or 24 weeks. IHC for ADAM19 on lung tissue sections showed intense staining in bronchial and vascular smooth muscle cells, as well as in dendothelium, and a faint staining in bronchial and alveolar epithelial cells. Quantification of ADAM19 protein expression in the airway wall showed a significant increase upon 4 weeks of CS-exposure, but not upon 24 weeks. Accordingly, protein levels of neuregulin-1 were significantly elevated in BAL fluid of mice exposed to CS for 4 weeks, but not for 24 weeks. Finally, pulmonary Muc5ac mRNA expression was significantly increased upon both 4 and 24 weeks of CS-exposure, while we found no differences in the mRNA expression of Muc5b.

These data demonstrate that 4 weeks of CS-exposure leads to increased expression of ADAM19 and enhanced shedding of neuregulin-1. Binding of neuregulin-1 to EGFR may contribute to the increased expression of Muc5ac. However, especially upon chronic CS-exposure, other EGFR-ligands or alternative mechanisms may be involved in mucin production.
PP122
Amniotic fluid derived lung stem/progenitor cells (AFSC) as a novel strategy to ameliorate lung fibrosis through the modulation of pro-fibrotic cytokines in the alveolar milieu
Orquidea Garcia1,2, Gianni Carraro2, Sargis Sedrakyan2, Gianluca Turcatel2, Barbara Driscoll1,3, Laura Perin1,2, David Warburton1,2. 1Systems Biology and Disease Graduate Program, Keck School of Medicine and Ostrow School of Dentistry, University of Southern California, Los Angeles, USA; 2Developmental Biology and Regenerative Medicine Program, The Saban Research Institute, Children’s Hospital Los Angeles, Los Angeles, USA

Following bleomycin lung injury we transplanted AFSC to modulate the inflammatory response and stimulate resident progenitor cells. C57Bl/6J mice, 10 wks old were given 1.5U/kg of bleomycin intratracheally and 1x10⁶ cells IV at either 2 hours or 14 days post bleomycin. Cohorts were sacrificed at 3 or 28 days to measure the acute and fibrotic response. Pre-transplant AFSC showed expression of type I cell (AECI) lineage markers: AQP5, T1a/PDPN, TTF-1/NKX2-1. Acute phase lung lysates indicated an upregulation of TTF-1 in AFSC treated mice. Mice receiving AFSC at 2 hours vs 14 days post bleomycin exhibited a respective 2-fold vs 1.3-fold reduction in hydroxyproline content when compared to non-treated mice. Cytokine analysis of bronchoalveolar lavage showed a significant decrease in CCL2/MCP-1, 3 days after AFSC transplant. Upregulation of TTF-1 following AFSC transplant indicates that these cells continue along or stimulate the AEC cell lineage while modulating a key fibrotic mechanism: CCL2/MCP-1.

PP123
Vitamin D deficiency – a risk factor for the development of acute lung injury (ALI)?
Rachel Dancer, Vijay D’Souza, Shengxing Zheng, David Thickett. Department of Respiratory Medicine, University of Birmingham, Birmingham, United Kingdom

ALI is a final common pathway to insults such as pneumonia, trauma or abdominal sepsis. Patients with severe sepsis have lower levels of 25-OH vitamin D (25-OHD) than healthy controls. We hypothesized that vitamin D deficiency is a risk factor for ALI. The levels of 25-OHD and 1,25-OH vitamin D (1,25-OHD) were measured in 109 patients with and at risk (AR) of ALI and related to lung injury biomarkers. 25-OHD was lower in patients with ALI compared to AR patients p=0.0001 and normal controls p<0.0001. 1,25-OHD levels were lower in patients with ALI compared to AR p<0.001 and ALI patients who survive ITU had higher levels p=0.034. AR patients who went on to get ALI had lower levels than those who didn’t (Fig. 1). AR patients with 25-OHD deficiency (<20nmol/L) had elevated post-op markers of epithelial damage, permeability and systemic inflammation. Microarrays show that 669 genes were significantly altered when primary alveolar type II cells were treated with 25-OHD. To confirm these effects we show that in-vitro culture with vitamin D increases epithelial cell proliferation p<0.001, wound repair p=0.02 and reduces sFasL mediated cell death p<0.001 (Fig. 2). Our data supports a role for vitamin D in the maintenance of alveolar epithelial cell integrity and suggests vitamin D replacement may help prevent ALI in at risk patients. We will start recruitment to a trial of vitamin D replacement in patients at risk of ALI in 2012.

PP124
Chronic allergic inflammation drives pericyte recruitment to the airway wall
Jill Johnson1,Erika Folestad2, Kristian Pietras2, Ulf Eriksson2, Jonas Fuxe2. 1National Heart and Lung Institute, Imperial College London, London, United Kingdom; 2Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Objective: To investigate the contribution of airway microvascular pericytes to airway remodeling in a model of chronic asthma.
Methods: An established model of house dust mite-induced allergic asthma was used to study the contribution of pericytes to remodelling in mouse airways. Immunofluorescent staining was performed on trachea whole-mount preparations to evaluate the recruitment of pericytes to the airway wall following allergen exposure.

Results: Confocal imaging revealed that pericytes detach from blood vessels and accumulate below the airway epithelium, demonstrating that pericytes associated with the airway microvasculature can contribute to airway remodelling in asthma. This process was exacerbated when PDGF signalling was pharmacologically impaired using a PDGF-Ra inhibitor (CP-673451).

Conclusion: The data indicate that pericytes play an important role in the airway remodelling that occurs in asthma.

Even though the detailed mechanisms behind it have mostly remained unclear, the aim of the study was to characterize stromal cells cultured from small volumes of diagnostic bronchoalveolar lavage (BAL) fluid samples. Cells were collected from 98 patients representing distinct pulmonary diseases and the cultured cells were characterized by immunohistochemistry, electron and immunoelectron microscopy, flow cytometry and differentiation tests evaluated by RT-PCR and alkaline phosphatase activity measurements.

The success of the cell culture varied based on the disease of the donor (p=0.003). Morphologically the cultured cells were fibroblasts or myofibroblasts but they expressed also cell surface antigens typical for mesenchymal stromal cells (previously known as stem cells) being positive for CD105 (endoglin), CD90 (Thy-1), CD73 and CD44. Some of the cells showed high differentiation potential into adipogenic and osteogenic lineage (Fig. 1).

We conclude that some but not all stromal cells cultured from BAL fluid have similarities with stem cells, while some of them are fibroblasts and some are myofibroblasts.

PP125

Creation of lung mucosal tissue with human immune cells

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In pulmonary diseases, such as, e.g., infections, asthma, or cancer, abnormal inflammatory reactions lead to tissue destruction and remodelling, often associated with impaired lung function. Here, we describe the establishment of a novel human three dimensional (3D)-in vitro lung model with dendritic cells (DC), which will be used to further our understanding of human lung physiology and pathology in inflammatory pulmonary diseases. The tissue model recapitulates key anatomical and functional features of lung mucosal tissue, including a stratified epithelial cell layer, deposition of extracellular matrix proteins and the production of tight- and adherence- junction proteins. Labelling of fixed tissue model sections and imaging of live tissue models also revealed that DC distribute in close association with the epithelial layer. We also observed that the lung tissue model regulates the capacity of DC to produce the chemokines, CCL17, CCL18 and CCL22, leading to enhanced production of CCL18 and reduced production of CCL17 and CCL22. Furthermore, we use this model system to study human host-pathogen interactions and immune responses in the lung microenvironment in real time. This novel technological platform, we believe, provides an important tool to study immune cell regulation present in the lung and play a role in structural remodelling of the airway wall in asthma.

PP126

Stromal cells cultured from diagnostic bronchoalveolar lavage fluid samples possess stem cell like properties

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Stromal cells have significant role in the pathogenesis of several lung diseases and the airway wall in asthma where they are involved in the formation of the epithelial basement membrane.

Figure 1: Results of osteogenic differentiation test of 30 BAL fluid derived cell samples. The cells were cultured for 2 weeks with osteoinductive medium or control medium after which the activity of alkaline phosphatase was measured. The values form cells cultured with osteoinductive medium were compared to corresponding control cells so that value 100% indicates that no differentiation occurred and values above that indicate differentiation towards osteoblastic lineages.

PP127

Phospholipase D determines the virulence of Aspergillus fumigatus (A. fumigatus) into lung epithelial cells

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A. fumigatus is a airborne fungal pathogen causing serious infections in immunocompromised patients. Phospholipases (PLs) like PLD as important member of the PL family in A. fumigatus, are key enzymes in pathogenic fungi that cleave host phospholipids, resulting in membrane destabilization and host cell penetration. In this study, disruption of the pld gene significantly decreases extracellular and cellular PLD activity of A. fumigatus. The pld gene disruption did not alter conidial morphological characteristics, germination, growth and biofilm formation, but significantly suppressed the internalization of A. fumigatus into A549 epithelial cells without affecting conidial adhesion to epithelial cells. Importantly, the suppressed internalization was fully rescued in the presence of 100μM phosphatidic acid, the PLD product. Indeed, complementation of pld (pldc) restored the PLD activity and internalization capacity of A. fumigatus, whereas A. fumigatus conidia phagocytosed by 3774 macrophages was not affected. PLD inhibition decreased specifically the internalization of A. fumigatus into A549 epithelial cells. Loss of the pld gene attenuated the virulence of A. fumigatus in mice inmunocompromised with hydrocortisone acetate, but not with cyclophosphamide. Thus, A. fumigatus PLD regulates its internalization into epithelial cells and may represent an important virulence factor for A. fumigatus infection.

PP128

Age-related changes in the relative expression of functional genes in mesenchymal stem cells

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Age-associated changes increased susceptibility to a variety of lung pathologies. Recently, mesenchymal stem cells or B-MSCs have emerged as a critical reparative response mechanism to lung injury. We had demonstrated an association, in animal models, between age and an increase in the susceptibility to injury and we had identified functional differences between B-MSCs from young and old mice. In the present study, we examined the consequences of aging in the gene expression. Methods: 3 and 24 months old B6 mice were sacrificed and B-MSC were isolated according to the expression of the surface markers. RNA was obtained after sorting and used for hybridization on Agilent gene expression microarrays. Ingenuity software was used to determine functional enrichment. For statistical analysis we applied significance analysis of microarrays. A q-value of 5, which corresponds to a 5% false discovery rate, was used as a cutoff of statistical significance. Gene validations were performed by RT-PCR.

Conclusion: The present study demonstrates that aging induce a decrease in the gene expression on B-MSC. The mechanisms affected by the decrease on gene expression includecellular trafficking, cellular growth and proliferation.

PP129

Epithelial regeneration in asthmatic patients treated with ultra-low doses of an alkylating drug melphalan

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Asthma and COPD are characterised by airway obstruction, airway remodelling and airway inflammatory reactions leading to tissue destruction and remodelling, often associated with impaired lung function. Here, we establish the establishment of a novel human three dimensional (3D)-in vitro lung model with dendritic cells (DC), which will be used to further our understanding of human lung physiology and pathology in inflammatory pulmonary diseases. The tissue model recapitulates key anatomical and functional features of lung mucosal tissue, including a stratified epithelial cell layer, deposition of extracellular matrix proteins and the production of tight- and adherence- junction proteins. Labelling of fixed tissue model sections and imaging of live tissue models also revealed that DC distribute in close association with the epithelial layer. We also observed that the lung tissue model regulates the capacity of DC to produce the chemokines, CCL17, CCL18 and CCL22, leading to enhanced production of CCL18 and reduced production of CCL17 and CCL22. Furthermore, we use this model system to study human host-pathogen interactions and immune responses in the lung microenvironment in real time. This novel technological platform, we believe, provides an important tool to study immune cell regulation present in the lung and play a role in structural remodelling of the airway wall in asthma.
and inflammation. These changes may be associated with accumulation in the lung of regulatory T cells (Tregs) and Th17 cells. Permanent expression of the surface receptors (IL-2R and IL-23R, respectively) is a common quality of these two cell subsets. Alkylating drug melphalan (MP) used in low non-toxic dose is capable to selectively inactivate Tregs and Th17 cells blocking the signal transmission by these receptors. Patients with severe steroid-dependent asthma were enrolled into the trial. 26 patients were inhaled with low dose of melphalan MP (0.1 mg/day during 5 days). 26 patients (control) besides basic therapy were inhaled with placebo. All patients demonstrated clinical improvement but the results in MP-treated patients were significantly better. Histological and ultrastructural signs of bronchial epitheliun regeneration have been revealed only in MP-treated patients. We observed normalization of goblet cell number, restoration of their ultrastructure, renewal of intercellular bridging, and significant reduction of edema in mucosa. The number of inflammatory cells was markedly decreased. Such restoration of epithelial phenotype may be associated with Treg number normalization; such restored epithelium is known to possess less proinflammatory properties than normal epithelium. There was no difference between MP-treated and placebo-treated patients in this respect. A possible role of Tregs and Th17 cells in asthma pathogenesis is suggested. This study is one of the first clinical trials to demonstrate the interplay of mitochondrial metabolism and inflammation in asthma.

Abstracts of the Tenth ERS Lung Science Conference, Estoril, Portugal – March 30–April 1, 2012

PP130

Clara cells contribute towards the resolution of cigarette smoke induced-inflammation

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Introduction: COPD is characterized by chronic bronchitis and emphysema. The cause is cigarette smoke (CS) which triggers inflammatory response in lung. The precise mechanism of inflammation is yet unknown. Naphthalene (NA), a CS particle injures Clara cells (CC) due to their abundance of cytochrome P-450 monooxygenases. The objective was to chemically knockout CC by NA to investigate their involvement in inflammatory process in response to CS.

Methods: CS was applied for 3 days in NA pre-treated (†) or saline-treated (S) mice. Giems staining for BAL count, HE staining for histology and immunohistochemistry for CC staining were performed. CC number was assessed by stereology.

Results: Mice exposed to NA-CS invoked higher recruitment of inflammatory cells in BAL fluid compared with NA or saline treated mice alone. They also had less regeneration of CC. Furthermore, after 5 days of smoke cessation, macrophage and neutrophils in BAL of NA-CS group remained significantly higher compared to NA-only or CS-only treated mice.

Conclusion: CC contributed additionally to inflammation in Clara cell exfoliated lungs and further, delayed airway epithelial cell regeneration.

PP131

Mitochondrial metabolism controls lung fibroblast activation in vitro and in vivo

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Background: Fibroblasts exhibit an extraordinary capacity to undergo fibroblast-myofibroblast activation in association with diseases such as pulmonary fibrosis. Little is known regarding the role of mitochondrial function in fibroblasts biology in general and phenotypic switching in fibrosis in particular.

Aims and objectives: To demonstrate the interplay of mitochondrial metabolism with fibroblast/myofibroblast activation.

Methods and results: We demonstrate that stimulated primary lung fibroblasts with the proinflammatory cytokine TGFβ1 results in an enhanced mitochondrial membrane potential (∆ψm). Moreover, proliferation, ECM deposition, and motility of these cells are increased compared to fibroblasts with low ∆ψm. Interestingly, TGFβ1-stimulated cells displayed increased expression of proinflammatory markers (IL-1, TNFα and Cox-2), demonstrating fibroblast-myofibroblast activation. To further corroborate these findings, we sorted primary lung fibroblasts for high and low resting ∆ψm (∆ψm(H/L)). While ∆ψm(H) fibroblasts are morphologically indistinguishable, they demonstrate increased myofibroblast activation compared to ∆ψm(L) fibroblasts. Finally, total cell homogenates derived from fibroblasts, myocytes- or teratoma-treated mice demonstrated increased ∆ψm compared with cell homogenates from saline-treated mice.

Conclusion: Our data suggest that mitochondrial metabolism plays an important role in the phenotypic activation of lung fibroblasts, both in TGFβ1 stimulated cells in vitro and bleomycin-induced fibrosis in vivo.

PP132

Scribble is required for normal epithelial cell-cell contacts in the mammalian lung

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Exploiting our knowledge of lung development may lead to novel therapeutic approaches to enhance the lungs’ intrinsic repair mechanisms. In Drosophila, Scrib is essential for apica- basal (A/B) polarity, but in mammals, perturbation of Scribble leads to defects in planar cell polarity (PCP). We investigated the function of Scribble in lung. We find that the lungs of Scribble mutant mice, Circletail (Ctc), are abnormally shaped with fewer airways. Many airways lack a visible lumen. The PCP pathway is perturbed in Scribble mutant lungs whereas A/B polarity appears unaffected. Scribble is expressed in both adherens and tight junctions of lung epithelium and time-lapse imaging reveals that Scribble localization is perturbed in mutant lung epithelium. Cytoskeletal organisation is also visibly disrupted. Using organotypic cultures as a model of de novo cyst formation, we show that Scribble is required for proper epithelial arrangement and lumen morphogenesis in mammalian lung development.

PP133

Down-regulated let-7b and mir-126 in tumors and surrounding tissue correlate with high microvessel density and poor survival outcomes in non-small-cell lung cancer patients

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32 squamous lung carcinoma, 18 lung adenocarcinoma and 45 healthy individuals were included. let-7b and mir-126 expression were detected by real-time RT-PCR. Expression of these miRNAs in tissue from early stages of lung cancer patients (tumor, tumor surroundings and healthy lung tissue) was compared. Expression of anti-angiogenic let-7b and miR-126 were significantly lower in tumor tissue and surrounding compared to both healthy lung tissue of diseased patients and control. There was no difference between tumor and tumor surrounding tissue. High let-7b expression and mir-126 expression were highly associated with both better progression-free and overall survival. High micro-vascular density was negatively associated to let-7b and miR-126 expression and highly associated with poor outcome. Our results confirm a possible role of these two miRNAs in lung cancer angiogenesis and suggest the potential new target antiangiogenic lung cancer therapy.

PP134

Effects of stem cells of healthy or acute lung injury donors of recipient injury mice

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We aimed to investigate the effects of BMDMCs from healthy and ALI donors in experimental model of ALI. For this, 55 female C57BL/6 mice were randomly assigned into four groups. The control group received saline. ALI mice received E. coli LPS intratracheally (ALI-LP) or intraperitoneally (ALI-Ip). After 24, 48 and 72h whole BMDMCs from all groups were subjected to co-culture with bone-marrow units-fibroblastoid (CUF-F) and flow cytometry. After cell characterization, all animals were treated with saline or BMDMCs (v:v) obtained from healthy and ALI donors at 24h. In ALI, CUF-F assay showed a predominance of non-stromal cells over fibroblastoid colony. In ALI-LP, an irregular CUF-F morphology was observed. In ALI, monocytes and T lymphocytes were increased and hematopoietic precursor cells reduced. At day 7, mortality rate was higher in ALI groups, and after BMDMC therapy reduced. BMDMCs attenuated lung mechanics, neutrophils, alveolar collapse, as well as fibers content. Additionally, reduced the levels of cytokines in lung tissue independent of cell origin. BMDMCs reduced the inflammatory and fibrogenic processes, improving lung mechanics; nevertheless, BMDMCs from ALI animals were less effective at reducing the inflammatory process compared to those originated from healthy donors.

PP135

Post-exposure antioxidant treatment decreases airway hyperplasia and hyperreactivity due to chlorine inhalation in rats

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We assessed the safety and efficacy of combined intravenous and aerosolized antioxidant therapy to attenuate chlorine gas-exposed airway alterations when administered post-exposure. Adult male Sprague-Dawley rats were exposed to air or 400 ppm chlorine (at concentrations likely to be encountered in the vicinity of...
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The ability to produce respiratory epithelial cell types offer new therapeutic options to treat pulmonary diseases. We therefore aimed at identifying key factors which drive the differentiation of murine pluripotent stem cells (mPSCs) into airway epithelial Clara and branching epithelial type II (ATII) cells. Keratinocyte growth factor (KGF) is known as a strong growth factor at least for primary ATII cells and glaucoma cells and also stimulate a factor that may be the maturation of primary lung epithelial cells. In the present study we were able to identify a synergistic effect of KGF and glaucoma cells in lung epithelial cells by qRT-PCR, microarrays, immunostaining and electron microscopy.

PP139
Key factors for the differentiation of pluripotent stem cells into lung epithelial cells
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Rationale: Cigarette smoke is the major cause of COPD/emphysema but the etiology of these diseases is still unknown. Both β-catenin and CAAAT/enhancer binding protein alpha (C/EBPα) are key regulators of cell proliferation, with β-catenin being a negative regulator of C/EBPα. Thus decreased β-catenin signaling may be involved in the paracrine tissue destruction leading to emphysema.

Objectives: Investigate the effect of cigarette smoke on the expression of β-catenin, C/EBPα and cell proliferation in primary human lung fibroblasts.

Results: Cigarette smoke significantly down-regulated β-catenin expression which coincided with increased C/EBPα levels (inverse ratio) and thereby decreased primary lung fibroblast proliferation.

Conclusion: Cigarette smoke reduces lung fibroblast proliferation through β-catenin dependent up-regulation of C/EBPα. This mechanism may underlie the impaired tissue repair in COPD which leads to parenchymal destruction in the lung of COPD/emphysema patients.

PP141
LRIG1 regulates cadherin-dependent contact inhibition directing epithelial homeostasis and preinvasive squamous cell carcinoma development

Epidermal Growth Factor Receptor (EGFR) pathway activation is a frequent event in lung cancer with over-expression one of the earliest abnormalities in the bronchial epithelium of smokers and present in all stages of preinvasive cancer. Mutations in EGFR itself are rare and the mechanisms regulating EGFR pathway activation remained elusive. Leucine-rich immunoglobulin repeats-1 (LRIG1), an inhibitor of EGFR activity, is one of 4 genes identified that predict patient survival across solid tumor types. We hypothesize that tissue homeostasis is maintained via strong endogenous regulation of EGFR signaling by the inhibitor LRIG1 and its loss is the key step in the initiation of preinvasive lung cancer.

Abstracts of the Tenth ERS Lung Science Conference, Estoril, Portugal – March 30–April 1, 2012
Our experiments show that deletion of LRG1 is sufficient to promote murine airway hyperplasia. In vitro, LRG1-deficient cells display loss of contact inhibition, whereas re-expression of LRG1 in human lung cancer cell lines impairs growth. We find that LRG1 forms a ternary complex with EGF and E-Cadherin at the cell surface. This complex modulates the activity of the EGFR and downstream pathways. We also show that loss of heterozygosity at the LRG1 locus as well as down-regulation of LRG1 gene expression are early events in the development of preinvasive human squamous lung cancer.

Our findings imply that lung cancer development is driven by a change in the amplitude of EGF signaling governed by the loss of contact inhibition.

PP142
Endothelial progenitor cells and the endothelin system
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Bone-marrow-derived endothelial progenitor cells (EPCs) might play a key role in the formation of new vessels. Endothelin-1 (ET-1) is known to modulate different stages of neovascularisation. We investigated a potential link between the ET system and EPCs in pulmonary hypertension (PH).

EPCs were isolated from Sprague-Dawley rats and rat pulmonary artery (palECs) endothelial cells served as positive control. ET-A and B receptor expression and detection of prepro-ET and ET converting enzyme (ECE) mRNA were performed by RT-PCR.

In calcium (Ca2+) flux assays EPCs loaded with FURA-2 were exposed to ET-1 [10-7M and 10-8M]. For selective inhibition of receptor subtypes, EPCs were pre-incubated with ETR (BQ123) or ETRB (BQ788) antagonists for 20 min before stimulation with ET-1. ETRB and BQ788 strongly inhibit EPCs expression of ET receptor subtypes. Both pre-pro-ET and ET-encoding mRNA could be detected in EPCs. In Ca2+ flux experiments addition of ET-1 elicited a significantly increased intracellular Ca2+ flux which could be inhibited by BQ123 (90%) and BQ788 (45%).

We proved for the first time the expression of both ETR and ETRB and detected mRNA of prepro-ET and of ECE on EPCs. We also found that ET-1 activates Ca2+ flux in EPCs. In summary, our data reveal for the first time a link between EPCs and the ET system.

PP143
Soluble curcumin-cyclodextrin complexes display an anti-proliferative effect on bronchial epithelial cells
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Introduction: Epithelial cells from lung allografts have been shown turning into fibroblasts through epithelial mesenchymal transition (EMT) and participate in obliterative bronchiolitis.

Methods: CycloDEXtrins have been used as an excitant to form complexes rendering curcumin soluble.

Results: In vitro, curcumin-cyclodextrin complexes reduced cell proliferation whereas proliferation rate was increased in epithelial cells from Lewis Lung carcinoma. Lungs of C57Bl/6 mice were engrafted with Lewis Lung carcinoma and mice were treated daily by an oral administratio n of curcumin-cyclodextrin complexes or control. The incidence and size of obliterative bronchiolitis were significantly decreased in epithelial cells from Lewis Lung carcinoma.

Conclusion: Our data demonstrate that curcumin, when given orally in a soluble complex with cyclodextrin reduces epithelial cell proliferation, increases cell apoptosis in vitro and reduces lung tumor size and incidence in vivo. Our data strongly suggest that curcumin controls cell cycle suggesting potential applicability in lung cancer and in other diseases where the epithelium undergoes proliferation and EMT.

PP145
Repair of cigarette smoke-induced loss of barrier function: Role of AKAPs
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Cigarette smoke causes epithelial damage, which may contribute to the development of COPD. Epithelial barrier is maintained by the cell-cell contact molecule E-cadherin. Interestingly, AKAPs (A-kinase anchoring proteins, particularly AKAP9), which coordinate cAMP signaling in the cell, are known to associate with E-cadherin. Therefore, we hypothesized that AKAPs play a critical role in maintaining epithelial barrier function and integrity, e.g. upon damage by cigarette smoke. To this aim, we studied the effect of cigarette smoke extract (CSE) on electrical cell-substrate impedance sensing (IECS) and on the expression of E-cadherin in human bronchial epithelial cells. CSE markedly reduced the epithelial barrier function (IECS) and caused delocalization of E-cadherin from cell-cell contacts. These processes were completely prevented by disruption of AKAP complexes using HS31. Interestingly, CSE reduced AKAP expression, while reexpression of the expression of AKAP9 and AKAP12 (which are not associated with E-cadherin) nearly unaffected. In conclusion, AKAPs contribute to CSE-induced disruption of the human bronchial epithelial barrier by translocation of E-cadherin from the cell membrane.

Financial support: NAF, grant 3.2.09.034; Rosalind Franklin Fellowship.

PP146
Phenotypic profiling of invading lung fibroblasts in 3D cell culture models
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Rationale: Fibroblasts exhibit an extraordinary capacity to undergo phenotypic changes during development and disease, both in vitro and in vivo. These changes include altered motility, migration or activation. Enhanced migratory capacity of primary lung fibroblasts (f) in f patients was found in vitro, but the underlying mechanisms remain elusive. The aim of this study was to decipher morphological, molecular and functional differences between invading (i) and non-invading (n-i) f in 3D cell culture models.

Methods/Results: We established a high-content 3D invasion model, enabling the separation of i from n-i f allows the comparative analysis of parameters like morphology, invasion depth and protein/mRNA expression levels. Analysis revealed two significantly distinct subtypes. 7.6% of untreated f invaded the collagen matrix. Invasion was augmented by TGFß and EGF treatment. Gene expression analysis of one sample demonstrated significantly different expression profiles. Several markers, previously reported to be associated with i f, were also upregulated. We identified an early stage of invasion (ex. ratio=4.47), MMP3 (3.97), Osteopontin (1.45), Pten (0.34) and genes of unknown function, were found deregulated in f.

Conclusion: f show two distinct subtypes in a 3D cell culture model. Gene expression profiling of f revealed features highly similar to the (myo)fibroblast phenotype found in f. Our 3D invasion model constitutes a highly useful tool for high-content pharmacological screenings.

PP147
NLRP3-inflammasome pathway activation in fibrotic lung diseases in human bronchoalveolar lavage fluid (BALF)
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NLRP3-inflammasome triggers an immune response via maturation of interleukin-1ß (IL-1ß) in a caspase-1-dependent way. Our aim was to investigate the NLRP3 pathway activation in idiopathic and autoimmune pulmonary fibrosis.

We studied BALF and peripheral blood leukocyte samples from 10 IPF pts, 5 RA-ILD pts and 4 controls. All samples were treated with LPS and pulse ATP TFNα and IL-1ß levels were measured using ELISA. LPS treatment increased TFNα levels in all groups and IL-1ß levels in the control and RA-ILD but not in the IPF (p<0.05). The ATP pulse resulted in elevated blood TFNα and IL-1ß levels in all groups. Inhibition of caspase-1 resulted in decreased TFNα secretion in IPF and RA-ILD blood leukocytes compared to controls (p<0.05). LPS plus leupeptin treatment in BALF resulted in a twofold increase in TFNα and IL-1ß levels in RA-ILD, whereas the IPF group exhibited a decrease in both TFNα and IL-1ß levels. This effect was slightly reversed when NLRP3 activation was blocked via inhibition of caspase-1.

The RA-ILD group showed a tendency to up-regulate the NLRP3 pathway compared to controls and IPF. The IPF group seems to lose the ability to activate this pathway in the presence of infectious stimuli, thus suggesting a compromise of the innate immunity regulation in IPF.

PP148
ILP2 protects against LPS-induced lung injury and mortality
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Lung injury is the initial event in the pathogenesis of idiopathic pulmonary fibrosis and acute lung injury (ALI). In ALI, acute respiratory distress syndrome. But though the inciting events in these pulmonary pathologies may be similar, their differing outcomes suggest that lung injury may activate different pathways. We previously identified lysophosphatidic acid (LPA) signaling specifically through its receptor LPA1 in the pathogenesis of pulmonary fibrosis (PF), finding that LPA1KO mice were protected from bleomycin-induced lung fibrosis. Here we investigated the role of ILP2 in the pathogenesis of both PF and ALI in LP2KO mice.

Methods: To study ALL LP2KO and WT mice were challenged with LPS. BAL was analyzed for cell counts and total protein. Additional mice were challenged with i.p. LPS and survival was monitored. To study PF, LP2KO and WT mice were challenged with i.t. bleomycin. BAL was analyzed for cell counts and total protein. Levels were measured using ELISA. LPS treatment increased ILP2 levels in all groups. Inhibition of caspase-1 resulted in decreased ILP2 secretion in IPF and RA-ILD blood leukocytes compared to controls (p<0.05). LPS plus leupeptin treatment in BALF resulted in a twofold increase in ILP2 and IL-1ß levels in RA-ILD, whereas the IPF group exhibited a decrease in both TFNα and IL-1ß levels. This effect was slightly reversed when NLRP3 activation was blocked via inhibition of caspase-1.

The RA-ILD group showed a tendency to up-regulate the NLRP3 pathway compared to controls and IPF. The IPF group seems to lose the ability to activate this pathway in the presence of infectious stimuli, thus suggesting a compromise of the innate immunity regulation in IPF.
Results: In ALI, LPA2KO mice had higher BAL leukocyte and protein levels, and lung collagen content was not different between ALI and WT mice. LPA2KO mice showed increased survival compared to WT mice (p = 0.02). In contrast, in PF, LPA2KO mice showed lower BAL protein levels and reduced collagen content compared to WT mice (p = 0.04). The survival of LPA2KO mice was not statistically different from WT mice. LPA2KO mice treated with indomethacin showed increased survival compared to WT mice (p = 0.03), indicating the role of LPA signaling in the regulation of survival in ALI and PF.

Conclusion: LPA signaling through LPA2 mediates protective anti-inflammatory effects in the LPS-induced model of ALI, while in the PF model, LPA2 mediates cardioprotective effects. These findings highlight the potential role of LPA signaling in the development of acute lung injury and pulmonary fibrosis.

PP149
Retinoic acid-TGF-β1 crosstalk during alveolar regeneration in hyperoxic mice
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This study aimed to detect whether retinoic acid (RA) has an effect on alveolar regeneration in adult hyperoxic mice and to investigate the relationship between RA and TGF-β1 during alveolar repair. Adult C57BL/6J mice were divided into 4 groups and administered (intraperitoneally, daily, for ten days): peanut oil/dimethylsulfoxide (PoDMSO); RA dissolved in PoDMSO; PoDMSO following T2hr hyperoxia (100% oxygen); RA following hyperoxia. The structure in alveolar areas was investigated by microscopy. TGF-β1, Smads and RAGE expressions were assessed by ELISA, WB and qRT-PCR in the lung. The lung of hyperoxic mice was characterized by damage of alveolar wall, reduced in numbers of alveoli and septa, and increased in alveolar diameter and mitotic index, depending on using of Smad3/TGF-β1 signaling. RA2 protein expression did not alter in all groups. Exogenous RA in hyperoxic mice improved degenerative alterations, induced partially alveolarization and depressed RAGE mRNA. This effect of RA originated from the inhibition of Smad3/TGF-β1 signaling via reduced Smad4 mRNA and increased Smad7 protein levels. Exogenous RA induced alveolarization and restricted Smad3/TGF-β1 signaling by decreasing of Smad4 mRNA in healthy mice. RA improved the alveologenesis and regulated Smad3/TGF-β1 signaling at transcriptional and translational levels via Smad4 and Smad7 in healthy and hyperoxic mice. RA can be used to repair of TGF-β1 induced lung damage in hyperoxic mice, except for type I pneumocytes differentiation.

PP150
Effect of Pirfenidone on pulmonary fibrosis due to Paraquat poisoning in rats
Shanash Sedda, 1 Amithosein Keshavarz1, Shima Aran2, Hamidreza Abbasi1, Seyed Reza Mirzadeh1,2, Shervin Taslimi1, Alireza Ghaffari1.

To evaluate the effectiveness of Pirfenidone (PF), a new anti-fibrotic drug on paraquat-induced pulmonary fibrosis in rats. Inhalation exposure of rats to paraquat (20 mg/kg) was used. Severity of the lung disease was evaluated using a histological score and BAL protein levels. Pirfenidone treatment significantly reduced the histological score and BAL protein levels compared to the control group. The results of this study suggest that PF has a potential to be used as a treatment for paraquat-induced pulmonary fibrosis.

Conclusion: PF can be used as a potential anti-fibrotic drug for the treatment of paraquat-induced pulmonary fibrosis.
Effects of the Hedgehog (Hh) pathway inhibitor GDC-0449 on lung cancer cells and cisplatin resistant lung cancer cells are mediated by lung cancer Effects of the Hedgehog (Hh) pathway inhibitor GDC-0449 on lung cancer cells. This effect is mediated by inhibition of stem cell-like... 

We aimed at investigating if Hh pathway inhibitor GDC-0449 is effective in the lung cancer cell lines HCC (adeno-carcinoma) and H1339 (small cell lung carcinoma) and also the corresponding cisplatin resistant lung cancer cells, and if possible effects of GDC-0449 are mediated via SPs. GDC-0449 inhibited concentration dependently cell growth in both lines, and also cisplatin resistant cells. In HCC and H1339 SPs of 0.57 and 0.46 % could be identified, respectively, while in cisplatin resistant cell lines, those were identified as 2.8% and 3.4%, which were significantly higher than the non-cisplatin-resistant lung cancer cell lines. In both cisplatin resistant and non-resistant cells, SP but not non-SP cells were able to reepithelialise the original tumour population. The Hh receptor smoothened was detectable in SP but not in non-SP cells, showing activation of Hh only in SP. GDC-0449 considerably reduced SP in HCC and H1339 cells, and also in cisplatin resistant HCC and H1339 cells. We demonstrate for the first time that GDC-0449 effectively reduces cell growth in lung cancer cell lines, and remarkable in cisplatin resistant lung cancer cells. This effect is mediated by inhibition of stem cell-like SPs.

PP154
Evaluation of the cellular and molecular mechanisms involved in the anti-inflammatory effects of aerobic exercise in a murine model of asthma Rodolfo de Paula Vieira1, Rodolfo de Paula Vieira1, Marco Izzo2.
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Aims: Investigate the participation of ATP, airway epithelial cells and dendritic cells on the anti-inflammatory effects aerobic exercise in a model of chronic allergic airway inflammation.

Methods and results: C57Bl6 mice (n=10) were divided in Control, Exercise, OVA and OVA+Exercise groups, submitted to a chronic OVA protocol and to exercise for 4 weeks. OVA increased the levels of ATP in BALF, which was abolished by exercise. Exercise also reduced the number of eosinophils in BALF and also in the airway wall, beyond the expression of MUC5AC and the collagen deposition. The effects of exercise in sensitized animals were followed by reduced BALF levels of IL-4, IL-5, IL-6, IL-13 and increased levels of IL-17p70 and IL-10, and also by reduced levels of IL-4, IL-5 and IL-13 in re-stimulated mediastinal lymphocytes. Exercise also reduced the expression of IL-23 and IL-12p35 in lung epithelial cells, DCs stimulated with OVA, obtained from exercised animals presented reduced expression of MHC-II and also decreased production of IL-6, KC, IL-12p70 when compared with DCs obtained from non-exercised mice.

Conclusion: We conclude that aerobic exercise reduced chronic airway inflammation, which could be partially attributed to reduced levels of ATP and epithelial expression of P2x in the airways and also to reduced maturation and function of dendritic cells.

PP155
The interaction of endothelial progenitor cells and pulmonary artery smooth muscle cells in PAH: A further step in understanding vascular remodeling? Susanna Dasale1, Silvia Biander2, Katharina Cima3, Christian M. Köhler1.
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In contrast to suggested beneficial effects of endothelial progenitor cells (EPCs) on vascular remodelling in pulmonary hypertension (PH), EPCs might even be harmful by e.g. stimulating pulmonary artery smooth muscle proliferation (paSMC). We investigated the effects of EPCs on paSMCs. Rat bone marrow EPCs were cultured under different growth conditions (0.5% and 10% FCS). Supernatants were collected after 8h and tested for growth stimulating capacity on paSMCs. Proliferation was measured by colorimetry after 48h of incubation. Supernatants were analyzed for their content of key peptides of PH by ELISA. Cell surface receptor activation in SMCs was detected by intracellular β2-Rx. EPC supernatants stimulate paSMCs proliferation. This effect was significantly higher if supernatants from EPCs cultured in 10% FCS were used. In supernatants detected EPCs included VEGF and endothelin-1. Stimulation of Para-2 loaded paSMCs with EPC supernatants led to an increase in intracellular Ca2+ comparable to the effects of pure ET-1. EPC supernatants significantly stimulate the proliferation of paSMCs. It could be suggested that homing of EPCs to vascular lesions as seen in PH might be potentially deleterious.

PP156
A-kinase anchoring proteins (AKAPs) coordinate IL-8 release by airway smooth muscle cells (ASM cells) via the β2-adrenoceptor (β2AR). CMJ Popppina1, LJ Holtzer2, E Kluusmann3, MC Michel3, AH Halayko4, W Timmes5, M Schmidt6, H Maarsingh7, 1 Mol Pharmacol, Groningen, Netherlands; 2 MDC, Berlin, Germany; 3 Clin Devel, BI Pharma, Netherlands; 4 Physiol, Manitoba, Canada; 5 Pathol, Groningen, Netherlands

β2-agonists alleviate broncho-obstruction in COPD by increasing cAMP-dependent PKA/Epic activation in ASM. PKA and Epic both reduce the cigarette smoke extract (CSE)-induced IL-8 release from ASM. AKAPs function as docking sites for cAMP signaling proteins and create CAMP compartments. Interestingly, AKAPs and -12 are involved in β2AR de- and resensitization, respectively. We studied AKAP expression profiles in CSE-exposed ASM and lung tissue of COPD patients and determined IL-8 release as functional readout. Human ASM express AKAP5, -12 and -9. CSE downregulated expression of AKAP12/13 and AKAP5, but not AKAP16. In lung tissue of COPD patients all these AKAPs were downregulated. In ASM, fenoterol dose dependently decreased IL-8 release, as observed by direct activation of PKA (and only marginally) Epac. IL-8 release was augmented by the p31, an AKAP inhibitor. In the presence of a selective AKAP12 inhibitor the reduction in IL-8, whereas the direct PKA activator was still fully effective. St-H3 induced fully the inhibitory effect of fenoterol on CSE-induced activation of ERK, known to underlie IL-8 release, demonstrating that the p31 or AKAP12-13-induced CAMP signalling leads to ERK degradation. In conclusion, AKAPs are expressed in the airways and coordinate the communication between β2AR, CAMP effectors and ERK in reducing CSE-induced IL-8 release. The alterations in AKAP expression could therefore contribute to CAMP and airway treatment.
PP159
Angiotensin-I-7 attenuates pulmonary neutrophil influx and pulmonary hypertension-induced right ventricular hypertrophy in neonatal hypoxic lung and heart injury in rats
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Cyclic angiotensin peptide 1-7 (cAng1-7), a selective ligand for the MAS onco-gene receptor, may be a novel therapeutic agent for neonatal chronic lung disease (CLD) or bronchopulmonary dysplasia by counterbalancing the adverse effects of the potent vasoconstrictor angiotensin II, including pulmonary inflammation and arterial hypertension (PAH)-induced right ventricular hypertrophy (RVH).

We determined the cardiopulmonary effects of cAng1-7 in neonatal rats with hyperoxia-induced CLD in 2 models: a prophylactic and an injury-recovery model. Parameters investigated include lung and heart histopathology, fibrin deposition, and differential mRNA expression in the lungs of key genes involved in inflammation, coagulation and alveolar development.

Prophylactic treatment with cAng1-7 for 10 days improved cardiopulmonary injury by reducing alveolar septum thickness, medial wall thickness of small arteries and the influx of neutrophils, and preventing RVH. cAng1-7 did not reduce alveolar enlargement, the pulmonary influx of macrophages, fibrin deposition and vascular alveolar leakage. In conclusion, cAng1-7 attenuates cardiopulmonary injury by reducing acute lung injury and reversing PAH-induced RVH, but does not affect alveolar and vascular development in neonatal rats with experimental CLD.

PP160
The cell-penetrating P1pal-12 peptide limits pulmonary fibrosis in the murine bleomycin model
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Idiopathic pulmonary fibrosis is the most devastating fibrotic diffuse parenchymal lung disease which remains refractory to available pharmacological therapies. Therefore, novel treatment options are urgently required. Protease-activated receptor 1 (PAR-1) is a heptahedral G-protein coupled receptor that mediates critical signaling pathways in pathology. Interestingly, bleomycin-induced lung fibrosis was shown to be diminished in PAR-1 deficient mice. We thus hypothesized that pharmacological PAR-1 inhibition may be an interesting therapeutic approach to combat pulmonary fibrosis. Consequently, we explored the effect of P1pal-12 (a cell-penetrating blocking the PAR-1/G-protein interaction) during the development of lung fibrosis induced by intranasal instillation of bleomycin. We show that once daily treatment with 0.5, 2.5 or 10 mg/kg P1pal-12, reduced severity and extent of fibrotic lesions in a dose-dependent manner (2.5 and 10 mg/kg). These findings correlated with significant decreases in collagen and α(SMA) mRNA expression levels in treated mice. Moreover, fibrin deposition in the lungs was reduced by 26% ± 3% (p < 0.05) in 2.5 mg/kg treated mice compared to untreated controls. Finally, P1pal-12 reduced bleomycin-induced IL-6 and MCP-1 levels in lung homogenates by 65 ± 3% (p < 0.01) and 36 ± 3% (p < 0.05) respectively. Overall, our data show that P1pal-12 limits lung fibrosis suggesting that targeting PAR-1 may be a promising therapeutic strategy for pulmonary fibrosis.

PP161
Symbiotics reduce airway inflammation and improve airway function in a mouse model for COPD
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Background: Gut health plays an important role in maintaining immunity in and beyond the gastrointestinal tract. Respiratory disorders can be influenced by disturbed gut microbiota. Chronic obstructive pulmonary disease (COPD) is disease is characterized by a progressive airflow limitation caused by an abnormal inflammatory response. Aim of this study is to investigate the effectiveness of dietary fibers and lactic acid producing bacteria in a mouse model for COPD.

Methods: BALB/c mice were instilled intra nasally (i.n.) with LPS, 3x per week and ventilated mice. Treatment with either GOS/FOS or GOS/FOS combined with Bifidobacterium or Probiotic Bifidobacterium or 3)

Results: Treatment with either GOS/FOS or GOS/FOS combined with Bifidobacterium was able to reduce the influx of macrophages and neutrophils into BAL f. Prebiotics without GOS/FOS were not able to modulate airway inflammation in this model. Only treatment with symbiotics was able to attenuate LPS induced reduction in airway function.

Conclusion: A combination of Bifidobacterium and GOS/FOS might be beneficial in COPD.

This study was performed within the framework of Dutch TI-Pharma.

PP162
Imaging Wnt/β-catenin signalling in an ex vivo tissue culture model of lung repair
Friszanka Uhl, Melanie Königshoff. HMGU, Comprehensive Pneumology Center, Munich, Germany

Emphysema is a pathophysiological hallmark of COPD and characterized by airspace enlargement and impaired alveolar repair processes. Recently, decreased Wnt/β-catenin signalling has been linked to impaired epithelial remodeling in human disease and animal models thereof. Here, we aim to further decipher the underlying mechanisms and image structural changes involved in lung repair processes.

We applied an ex vivo tissue culture model from wildtype (C57Bl/6) and Wnt reporter mice (Bat/TopGal) subjected to elastase treatment or PBS. Tissue slices (300 μm) generated using a vibratome were viable in culture for up to 7 days ex vivo (WST-1: d3 211±68% vs. d7 241±67%). Structural integrity of control (C) and emphysematous (E) lung slices was determined by qPCR and immunofluorescence for lung specific cellular markers as well as live tissue imaging. Functional Stiffness was decreased in E lung slices compared with control and further decreased over time shown by ELISA (d1: 135±19 ng/ml C vs. 82±17 ng/ml E). Wnt signalling activation by LLCi led to an increase in Sftpc expression accompanied by increased β-galactosidase staining in alveolar regions and upregulated target gene expression, such as Axin2, Dkk2 or Lef1.

Emphysematous tissue slices closely reflect COPD-like changes in vivo. Lung slices are viable up to 7 days ex vivo allowing determination of structural changes and cell fate in the diseased lung upon signal pathway modification.

PP163
Altered angiogenic potential of ASM from asthmatic patients
Laura Kellnerich, Emmanouil Kyriakakis, Maria Philippova, Thérèse J. Resink, Michael Tamm, Michael Roth, Pieter Borger. Department Biomedizin, Universitätsspital Basel, Basel, Switzerland

Airway remodelling is a key pathology in asthma which causes changes of the airway wall structure, including thickening of airway smooth muscle (ASM) bundles and increased vascularisation. Increased airway wall cells require oxygen and nutrients which are delivered by blood vessels. Understanding the mechanism of neo-vascularisation therefore may lead to novel therapeutic strategies to counteract remodelling. The capacity of ASM cells (ASMC) of asthmatics and non-asthmatics to induce endothelial cell sprouting was determined. Asthma specific expression of angiogenic factors was determined by protein array (43 proteins), and increased expression was confirmed by ELISA. Conditioned Medium (CM) from ASMC cells was tested by endothelial cell sprouting assay. CM of asthma patient derived ASMC induced more sprouting compared to CM derived from controls. The asthma specific increased CXC-chemokines ENA-78, GRO-alpha and IL-8 were confirmed by ELISA. Our results indicate that the angiogenic potential of ASM of asthma patients is higher compared to that of control ASM. The ELR+ chemokines ENA-78, GRO-alpha and IL-8 were upregulated in asthmatics.
and might therefore contribute to neo-vascularisation. Counteracting this process may lead to novel therapies in asthma. (SNF 320003_1249051.)

PP164
The repair of monocyte-derived hepatocytes from alpha antitrypsin deficient patients
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This study explores the culture of monocyte-derived hepatocytes from PiZ alpha antitrypsin deficient (a1ATD) patients and homologous replacement using small DNA fragments (SDFs) to correct the Z defect. Monocytes from 3 patients were de-differentiated with MCSF and IL3 and then differentiated into hepatocytes with FGF-4. Albumin, urea and a1AT were measured. SDFs were transfected into hepatocytes and cDNA checked for the M or Z message. No albumin was detected from monocytes. Hepatocytes secreted 250±50 mg/dL albumin/24h. Monocytes secreted both urea (5±2 μg/dL) and a1AT (272±42 μg/ml) over 24h. Hepatocytes secreted 103±30 μg/dL urea and 311±34 ng/mL a1AT.

Hepatocytes generated PCR products from Z primers. M SDF treated hepatocytes generated bands using M primers, indicating the generation of a corrected transcript. Control transfected hepatocytes produced a1AT (163±42ng/ml), whereas M SDF transfection significantly increased secretion (173±41ng/ml/24h, p=0.04).

PP165
Compression stimulates TGFβ2 release from asthmatic primary bronchial epithelial cells
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Bronchoconstriction leads to mechanical stress and airway remodelling. Bronchial epithelial cells (BECs) respond to this stress by inducing profibrogenic responses; whether this is similar in asthmatic and non-asthmatic populations is unknown.

Hypothesis: Primary BECs from asthmatic and healthy donors respond similarly to mechanical stress by release of TGFβ2.

Method: Bronchial brushings from healthy (n=9) and asthmatic (n=9) volunteers were obtained at bronchoscopy and grown at an air liquid interface. These cultures were then subjected to sham or compression using 5%CO2 in air for 1 hr, or sham compressed. After 24 hr, total TGFβ2 was measured in the basolateral medium.

Results: TGFβ2 concentrations were similar in medium from healthy (median 203 (144-272) (JQ1RI) pg/ml) or asthmatic (246 (162-277) pg/ml) cells following sham compression (p=0.67). Real compression caused no change in normal cells (median 254 (138-282) pg/ml p=0.68) whilst asthma-derived cells increased their TGFβ2 release to 299 (205-365) pg/ml (p=0.02).

Conclusion: BECs from asthmatic patients respond differently to mechanical stress compared to normal cells, suggesting that asthma may be associated with an altered wound healing response.

PP166
Repair of the very immature lung following brief, injurious mechanical ventilation
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Background: Very preterm infants often require mechanical ventilation (MV). This intervention can cause lung injury that contributes to bronchopulmonary dysplasia. To investigate mechanisms of injury and repair in we have developed a novel method of ventilating the lungs of fetal sheep. Using this model MV-induced injury resolves within 15d, but it is not known when repair starts.

Methods: Pregnant sheep at 110d and 125d gestational age (GA; term=147dGA) underwent aseptic surgery in which the fetal trachea was intubated and fetal lungs ventilated for 2h with an injurious MV protocol. Ewes and fetuses remained healthy until necropsy, performed 1d later. Unventilated fetuses were controls, and

Results: Following MV, severe lung injury was present at 1d. At 1d potential repair genes (metallothionein and urokinase receptor) mRNA levels were increased in MV lungs at both stages of development. There was no difference in the mRNA levels of early response genes (TGF, CYR-61, and EGR-1) and inflammatory genes (IL-1β, IL-6, IL-8 and TNFα).

Conclusions: Following MV injury, repair processes, commencing with normalisation of early response and inflammatory gene expression and the activation of repair genes, occurs within 24h.

Figure 1. RA synthesizing enzyme retinaldehyde dehydrogenase (RALDH) 1,2 and 3 expression in primary human ATII and Vascular endothelial cells.

Figure 1. RA synthesizing enzyme retinaldehyde dehydrogenase (RALDH) 1,2 and 3 expression in primary human ATII and Vascular endothelial cells.

906s

Abstracts of the Tenth ERS Lung Science Conference, Estoril, Portugal – March 30–April 1, 2012
PP169
TGF-β1 modulates integrin α5β1 expression through regulation of zyxin in alveolar epithelial cells.
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Enhanced TGF-β1 signalling contributes to epithelial to mesenchymal transition (EMT), the reversible phenotypic switching of epithelial to fibroblast like cells. EMT is process implicated in the development of fibrosis and cancer. TGF-β1 is an important regulator of these processes. We have performed a Smad3 chromatin immunoprecipitation screen in the alveolar epithelial A549 cells and identified the zyxin gene as a novel target of TGFβ1/Smad3 dependent signalling. Zyxin protein mostly concentrates at focal adhesions, cell junctions and along the actin cytoskeleton.
Induction of EMT by TGF-β1 in A549 cells was assessed by reduction of the epithelial cell markers and marked induction of the mesenchymal markers. This effect was accompanied by a phospho Smad3 dependent expression of zyxin. Knockdown of zyxin revealed dissregulated A549 cell junction stability and alterations in focal adhesion formation, as analyzed by confocal laser scanning microscopy. Further, TGF-β1 treatment of zyxin depleted cells displayed significantly increased integrin α5β1 expression levels accompanied by enhanced adhesion to the extracellular matrix and increased cell motility.
The zyxin was identified as a novel target of TGF-β1/Smad3 gene expression. TGF-β1 induced zyxin expression is important for balancing integrin α5β1 expression, cell adhesion and motility in A549 cells.

PP170
BMDMSCs effectively reduced lung inflammation in TDI-induced murine asthma model
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Purpose: The transfer of bone marrow-derived mesenchymal stem cells (BMDMScs) to the injured lungs is a possible treatment for severe asthma. This study investigated the therapeutic effects of BMDMScs in asthma remodeling and inflammation in an experimental TDI-induced asthma animal model.
Methods: BMDMScs were transferred into rats after TDI treatment. BAL cell profiles, histological changes including an inflammatory index and goblet cell hyperplasia, and the airway response to methacholine using plethysmography were analyzed. Smooth muscle actin (SMA) and PCNA protein expression were observed in lung tissue using immunohistochemical staining. The collagen content was measured in lung tissue sections and lung extracts.
Results: The numbers of inflammatory cells in BAL fluid, histological inflammatory index, airway response to methacholine, number of goblet cells, and amount of collagen were increased in TDI-treated rats compared with sham rats. BMDMScs transfer significantly reduced the TDI-induced increase in the inflammatory index and numbers of eosinophils and neutrophils in BAL fluid to levels seen in sham-treated rats (P<0.05). BMDMScs transfer significantly reduced the number of goblet cells, collagen deposition, and immune staining for SMA and PCNA with concomitant normalization of the airway hyperresponsiveness.
Conclusions: The systemic transfer of BMDMScs effectively reduced TDI-induced airway responsiveness, airway inflammation and remodeling.

PP171
Elucidating the regulatory network controlling cell fate determination of airway ciliated cells
Julie Watson, Emma Rawlins. Gurdian Institute, University of Cambridge, Cambridge, United Kingdom
The stem cells of the postnatal mouse airway epithelium have recently been identified, but the molecular mechanisms underlying their fate decisions are unknown. In the conducting airways, secretory cells self-renew and generate ciliated cells (Rawlins, E.L. et al. Cell Stem Cell 2009; 4:528-34) and in the trachea, basal cell self-renew and generate both secretory and ciliated cells (Rock, J.R. et al. PNAS 2009; 106:12771-5) (Fig. 1). We aim to elucidate the regulatory network controlling cell fate decisions in airway stem cells. Our specific objective in this project is to identify the transcription factors that mediate the decision of stem cells to generate terminally differentiated ciliated cells.
Stem cell activity is hard to study in adult lungs, due to slow turnover of the epithelium. We are therefore using the developing mouse airway as a model system. Microarray analysis identified >30 transcription factors (TFs) that are enriched in terminal differentiated ciliated cells, compared to stem cells. Ciliated cell-specific expression of these genes was confirmed by in situ hybridization. We are studying the function of the TFs by overexpressing them in a unique embryonic tracheal organ culture model and observing the effect on cell fate (Fig. 2). Of the 13 TFs screened so far, 7 activated ciliated cell fate, 3 inhibited it and 3 had no effect on it.
We plan to finish the screen, and generate a gene regulatory network model describing the molecular circuitry controlling ciliated cell fate determination.

PP172
Beta-catenin determines upper airway progenitor cell fate and pre-invasive squamous lung cancer progression by modulating epithelial-to-mesenchymal transition
Adam Gugnreco, Liwen Lu, Victor Teixeira, Elizabeth Sage, Karen Groth, Charles Vickers, Jeremy George, Sam Janes. Centre for Respiratory Research, University College London, London, United Kingdom
Human lung squamous cell carcinomas (SCCs) are a leading cause of death, and whilst evidence suggests that basal stem cells drive SCC initiation and progression, the mechanisms regulating these processes remain unknown. In this study we show that beta-catenin signalling regulates basal progenitor cell fate and subsequent SCC progression. In a cohort of preinvasive SCCs we established that elevated basal cell/beta-catenin signalling is positively associated with increased disease severity, epithelial proliferation, and reduced intercellular adhesiveness. We demonstrate that transgene-mediated beta-catenin inhibition within keratin 14-expressing basal cells delayed airway repair while basal cell-specific beta-catenin activation increased cell proliferation, directed differentiation, and promoted elements of early epithelial-to-mesenchymal transition (EMT) including increased Snail transcription and reduced E-cadherin expression. These observations are recapitulated in normal human bronchial epithelial cells in vitro following both pharmacological beta-catenin activation and E-cadherin inhibition, and mirrored our findings in preinvasive SCCs. Overall the data show that airway basal cell/beta-catenin determines cell and its mis-expression is associated with the development of human lung cancer.

PP173
Protease-activated receptor-2 activation triggers alveolar epithelial to mesenchymal cell transition
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Idiopathic pulmonary fibrosis (IPF) is the most devastating form of fibrotic lung disorders. Fibroblast foci, the hallmark of IPF, have been shown to partially originate from lung epithelial cells via epithelial-mesenchymal transition (EMT). Aβ-antagonist reactivation of pulmonary developmental signaling pathways triggers EMT in IPF, but the extracellular signals and cellular receptors involved remain elusive. We recently showed that protease-activated receptor 2 (PAR-2), a pleiotropic cellular receptor, is instrumental in IPF. Here, we explore the role of PAR-2-induced EMT. In lung biopsies of IPF patients, double immunostaining revealed a colocalization of PAR-2 with epithelial cells expressing both epithelial (cytokeratin5) and mesenchymal (vimentin) markers. In vitro, in human lung carcinoma-derived alveolar epithelial cell line (A549), PAR-2 activation with trypsin or its synthetic agonist peptide (AP) leads to the acquisition of fibroblast-like morphology. Western blots analyses of PAR-2 stimulated A549 cells showed an upregulation of the myofibroblast markers alpha-actin (αSMA) and vimentin, collagen secretion and...
beta-catenin upregulation. Immunofluorescence confirmed beta-catenin translocation to the nucleus subsequently to PAR2 activation. Beta-catenin inhibition prevented PAR2-induced expression of αSMA. In conclusion, PAR2 directly triggers EMT in vitro in epithelial cells via beta-catenin upregulation. These results may be clinically relevant in IPF.

PP174 Pluripotent stem cells express HGF in fibrotic lungs
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Idiopathic pulmonary fibrosis (IPF) & fibrotic nonspecific interstitial pneumonia (NSIP) are progressive diseases. Hepatocyte growth factor (HGF) is a multipotent growth factor & plays important role in epithelial repair. We studied the expression of HGF in fibrotic lungs & characterized HGF producing cells. Immunohistochemistry was performed using HGF & cMet receptor antibodies, & a panel of antibodies to characterize HGF positive cells on paraffin embedded lung tissue from patients. More HGF positive cells were detected in NSIP compared to UIP located mainly in the interstitial space close to the fibrotic area. A close correlation between NSIP & UIP was observed. NSIP lungs expressed more cMet positive alveolar epithelium. The clinical significance of the presence of HGF expressing, pluripotent stem cells in UIP & NSIP needs further evaluation.

PP175 Pathways to transdifferentiation of primary human alveolar epithelial cells
Vijay D’Souza1,2, Amiq Gazdhar1,3, Pluripotent stem cells express HGF in fibrotic lungs

PP176 Role of tumor necrosis factor alpha polymorphisms and systemic inflammation in chronic obstructive pulmonary disease: A population based study from north India
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Background & aim: Chronic obstructive Pulmonary Disease (COPD) has a genetic component, explaining susceptibility. The study aimed to investigate the genetic effects of TNF Alpha gene on the pathogenesis of COPD. Methods: The study included 160 patients of smoking-related COPD, 80 smokers with normal lung function and a control group of 140 healthy controls. We compared allele and genotype frequencies of 4 tag single nucleotide polymorphisms by PCR-RFLP technique in the TNF α gene region at +489G/A, –863C/A, and –857C/T, +376G/A in all subjects. Results: COPD patients had a significantly lower A allele frequency (97 vs. 15.1%, OR=0.6, p<0.048) and a significantly lower A carriern phenotype frequency (93 vs. 30.2%, OR=0.52, p=0.042) than healthy smokers. The –863C/A genotype was associated with a better FEV1/FVC ratio (79 vs. 71.5%, p=0.034), and higher BMI (24.9 vs. 23.6 kg/m2, p=0.048). The –863 C/A polymorphism is likely to be a factor that influences COPD phenotype and its progression.

Conclusion: TNF-α –863 A allele polymorphism is likely to be a factor that influences COPD phenotype and its progression.

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Activation and migration of neutrophils into the lung is a central factor in both the onset and progression of acute lung injury (ALI). The assessment of neutrophil biology and trafficking in the lung is fraught with methodological pitfalls. Human ex vivo ALI models could provide a tractable platform with which to investigate neutrophil trafficking in the lung.

Human lungs from brain dead donors (N=3) were cold preserved and transferred to our institution. Lungs were placed on an ex vivo lung perfusion circuit and following rewarming, E Coli lipopolysaccharide (LPS, 5mg) was injected intra-bronchially into the RML. The LLL was used as the control. CT images, tissue biopsies and BALF for cytosin preparations were taken at T=0 and 4 hours after LPS injury.

CT Images showed ground glass infiltrate in the RML at 4 hours with otherwise normal lung by CT criteria (Figure 1). Compared to control lung (Fig. 2A), at 4 hours, LPS injured lung (Fig. 2B) demonstrated a neutrophilic alveolitis while BAL cytopsin of LPS injured lung showed a predominance of neutrophils (Fig. 2C).

Figure 1. CT image of LPS injured lung at 4 hours.

Figure 2

Further characterisation of this novel model allied with established methodology in pulmonary neutrophil trafficking will provide a powerful tool to investigate neutrophil biology in human ALI.

PP178 Modulation of in vitro epithelial wound closure by mesenchymal stem cells
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Introduction: Destruction of alveolar walls characterizes emphysema. Tissue repair is a potential therapeutic property of Mesenchymal Stem Cells (MSCs), thought to be mediated at least partly by paracrine mechanisms. We hypothesized that MSC-conditioned medium (MSC-CM) enhances epithelial wound closure in vitro.

Methods: We generated circular 3 mm wounds in confluent cultures of bronchial epithelial NCi-H292 cells. Next, cultures were incubated with MSC-conditioned medium, diluted 1:5 with serum free (SF) RPMI or control media. Conditioned media were generated by culture of MSCs in SF LG-DMEM medium with or without cytoxim (20ng/ml IL-1f and TNF-α). Percentage closure of wounds at time t=24, 48, 72 hours was compared to wound size at t=0. Experiments were done in duplicate, and repeated 3 times.

Results: SF MSC-CM from MSCs stimulated with cytomix significantly enhanced wound closure at t=24 and 48 hours, compared to negative control and SF LG-DMEM with cytoxin (mean difference in wound closure at t=48 was 36%; 95% CI of the difference [-16.9-55.4%] and 17.6% [-1.7-36.8%], respectively) (Fig. 1).

SF MSC-CM from control-treated MSCs did not increase wound closure.

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Conclusion: Wound closure in mechanically wounded NCI-H292 was significantly enhanced by conditioned media from MSCs exposed to pro-inflammatory cytokines.
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