307. Hot topics in respiratory infections

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Multidimensional approach to non-cystic fibrosis bronchiectasis. The FACED score

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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]): FEV_1 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,*number of lobes affected; cut-off point at 2 lobes; OR:1.9 [1.1-3.5]; 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.

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Clostridium difficile infection (CDI): Are junior doctors aware of risk factors and markers of severity?

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Introduction: There are approximately 20 000 cases of CDI in England per annum.1 Lower Respiratory Tract Infections are the main indication for antibiotic prescription in hospitals.2 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:
[1] http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_132045.pdf
[2] Chalmers, J et al. Proposed changes to the management of lower respiratory tract infections in response to the Clostidium difficile epidemic. J Antimicrob Chemother. 2010. 65: 608-18.

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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 spu-

tum samples were obtained from 30 COPD patients at four time points: stable state, exacerbation onset, 2 and 6 weeks post exacerbation. 454 high-throughput pyrosequencing was performed on samples from each of these visits to examine changes to the global microbiome.
Results: Firmicutes and Proteobacteria were the major phylum groups in most of the samples. Streptococcus, Haemophilus and Moraxella were the most frequently occurring operational taxonomic units at genus level. Cluster analysis revealed 3 groups that could be defined by the Proteobacteria:Firmicutes(P:F) ratio; 1)high firmicutes, 2)mixed proteo-firmicutes and 3)high proteobacteria.
Comparing clinical characteristics of these patients, there were no significant differences between groups with regards to GOLD stage, gender, smoking history, BMI, number of exacerbations in the previous 12 months and post bronchodilator FEV1. In the high proteobacteria group the sputum neutrophil count was increased and there was a non-significant trend towards better quality of life as measured by the SGRQ and CRQ.
Dynamic changes in the microbiome were observed between stable, exacerbation and recovery visits, although these changes did not reach statistical significance.
Conclusions: The COPD microbiome can be defined using molecular techniques, but more research is required to further determine its clinical importance in COPD exacerbations.

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Admission serum glucose levels are a risk factor predicting short- and long-term mortality in community acquired pneumonia
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Objective: To examine whether or not acute dysglycemia predicts an adverse outcome in subjects with community acquired pneumonia (CAP).
Participants: 6,891 CAP patients with community acquired pneumonia included in the prospective German CAP Competence Network (CAPNETZ) study between 2003 and 2009.
Main outcome measures: Uni- and multivariable hazard ratios (HR) adjusted for gender, age, body mass index (BMI), current smoking status, CRB-65 and various co-morbidities for 28-, 90-, and 180-day mortality of CAP were calculated according to serum glucose levels on admission.
Results: In patients without known diabetes, an elevated glucose level at admission was an independent predictor of 28-, 90- and 180-day mortality in CAP. As compared to individuals with normal glucose levels on admission, subjects with mild acute hyperglycemia (glucose on admission 6–<11 mmol/L) had a significantly increased HR for death at 90 days (1.55; 95%CI: 1.18 to 2.04; P<0.001), which increased to 6.04 (95%CI: 4.18–8.74; P<0.001) if admission glucose levels were ≥14 mmol/L. In sensitivity analyses the predictive value of admission glucose levels was confirmed for short- (28 days) and long-term mortality (180 days). Patients with previously diagnosed diabetes had an increased overall mortality as compared to patients without diabetes (crude HR 2.47 95%CI 2.05 to 2.98; P<0.001). This outcome was not significantly affected by admission glucose levels (P=0.18).
Conclusions: Admission glucose levels predict an adverse outcome in CAP in patients without known diabetes. Hence, acute hyperglycemia may identify patients in particular need of intensified care to reduce mortality in CAP.

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Long-term use of inhaled corticoids on the development of pleural effusion in community-acquired pneumonia
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Introduction: Long-term use of inhaled corticosteroids (ICS) in patients with Chronic Obstructive Pulmonary Disease (COPD) has been associated with increase risk of CAP. Most recently, ICS have been associated with less severity of CAP and decreased risk of pneumonia-related mortality. Pleural infection is a frequent complication of CAP that may increase mortality. The aim of this study was to assess the influence of long-term use of ICS on the incidence and severity of parapneumonic effusion and empyiema in patients with different baseline respiratory diseases.
Methods: We conducted a single centre cohort study of 3602 patients consecutively collected with CAP. We assessed clinical, radiographic and pleural fluid 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 (COPD: 56%). Long-term use of ICS was significant 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% CI, 0.28-0.64, p<0.001). Prior treatment with ICS was significantly associated with lower incidence of empyiema compared to those without ICS treatment (3% vs 16%, p=0.05).
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: CibeRes-ISCiii-CB06/06/0028 and IDIBAPS.

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Pulmonary immunostimulation with macrophage-activating lipopeptide-2 in influenza-A-virus infected mice increased survival of subsequent pneumococcal pneumonia
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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-A/H1N1/PR/8/34-virus* infected female C57BL/6 mice received the TLR-2 ligand macrophage-activating lipopeptide-2 (MALP-2) intratracheally 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.

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Safety and pharmacokinetics of two dose strengths of ciprofloxacin dry powder for inhalation (DPI) in patients with moderate to severe COPD
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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*

	Plasma		Induced sputum	
	32.5mg (n=12)	48.75mg (n=12)	32.5mg (n=11)	48.75mg (n=11)
AUC, mg·h/l	0.600/16.0[#]	0.901/16.2[#]	552/119.3[§]	505/132.5[§]
C_{max}, mg/l	0.114/26.8	0.183/26.3	409/89.9	454/141.3
$t_{1/2}$, h	6.00/23.2	4.99/17.9	–	–
t_{max}[¤], h	0.875	1.00	0.550	0.583

*Geometric means/%CV; [#]AUC(0–∞); [§]AUC(0–t_{last}); [¤]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.

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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%, Coronavirus 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 1.1 (0.8-1.4) $p<0.0001$. The TCD8 response has a predominance of Tc17 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) $p<0.0001$.

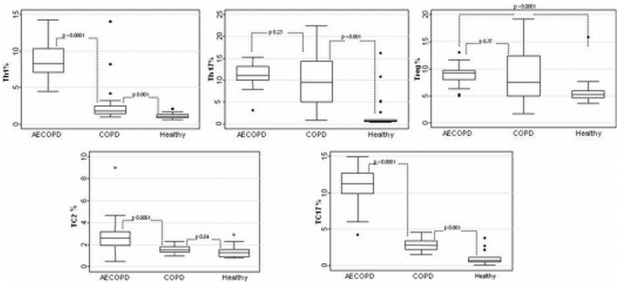

Figure 1. Distribution of T-cell subpopulation CD4 (Th1, Th17 and Treg) and CD8 (Tc2 and Tc17). Analysis post-hoc U-Mann-Whitney $p<0.016$.)

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.