Hot topics from the Assemblies

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Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial
Authors: Bilton D, Tino G, Barker AF, *et al.*
Thorax 2014; 69 :1073–1079
Summary: Mannitol improves mucus clearance in non-cystic fibrosis (CF) bronchiectasis and improves mucus clearance and pulmonary function test results in patients with CF. It is not clear to what extent inhaled mannitol has an impact on exacerbation rates and quality of life in patients with non-CF bronchiectasis.
In this study, 84 sites across the world conducted a 52-week, double-blind, randomised controlled trial of inhaled mannitol 400 mg twice daily *versus* a control of inhaled mannitol, 50 mg twice daily.
461 patients received blinded study treatment. The primary endpoint was the annual rate of exacerbation in the mannitol and the control arms. The rate was 1.69 (95% CI 1.48–1.94) and 1.84 (95 % CI 1.61–2.10), respectively, and was statistically non-significant (p=0.31). The secondary endpoints of this study were time to first exacerbation, it was increased on high-dose mannitol (165 *versus* 124 days and HR 0.78; p=0.022) and the change in Saint George's Respiratory Questionnaire score which improved on high-dose mannitol (–2.4 units; p=0.046). Condition aggravated, nasopharyngitis and bacteria sputum identified were the three most frequent adverse events. In the mannitol group, serious adverse effects were less frequent (18.5 *versus* 22.4%).
The study did not show difference in annual exacerbation rate between high- and low-dose mannitol. Despite this, mannitol therapy was safe and there was improvement in time to first exacerbation and quality of life. Mannitol is considered as a potentially useful option for treating patients with non-CF bronchiectasis.
Reviewed by: Samir Challita and Pietro Kheir (Lebanon, Assembly 5)

Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial
Authors: Blum CA, Nigro N, Briel M, *et al*.
Lancet 2015; 385: 1511–1518
Summary: Adjunct treatment of community acquired pneumonia (CAP) with systemic corticosteroids has been discussed for the past 60 years through a number of randomised controlled trials (RCTs), systematic reviews and meta-analyses; all yielding conflicting results. Therefore, Blum *et al*. studied the use of adjunct prednisone therapy for patients with CAP in a multicentre, double-blind, randomised placebo-controlled trial. Patients (aged ≥18 years, recruited within 24 h of presentation) were selected from seven tertiary care hospitals in Switzerland and randomised to either therapeutic prednisone (50 mg daily, 7-day course), or placebo. The primary endpoint was days to clinical stability, defined as stable vital signs for at least 24 h. The prednisone group (n=392) had a shorter median time to clinical stability (3.0 days, IQR 2.5–3.4) *versus* placebo (n=393; 4.4 days, IQR 4.0–5.0) (hazard ratio 1.33, 95% CI 1.15–1.50; p<0.0001). At day 30, there was no difference in pneumonia-associated complications, the secondary endpoint (11 (3%) in the prednisone group and 22 (6%) in the placebo group, odds ratio 0.49 (95% CI 0.23–1.02); p=0.056). Both groups similarly showed adverse events compatible with corticosteroid use to be rare. The exception to this was the incidence of in-hospital hyperglycaemia needing insulin treatment, which was higher in the prednisone group (76 (19%) *versus* 43 (11%); OR 1.96, 95% CI 1.31–2.93; p=0.001). This study reinforces the data of various clinical trials, systematic reviews and meta-analyses. Consequently, it significantly but not conclusively, tips the balance of evidence in favour of corticosteroid use in CAP.
In summary, 7 days in-hospital corticosteroid treatment for admitted CAP patients shortens time to clinical stability without increasing complications. These findings are clinically relevant and may reduce hospital costs and increase efficiency.
Reviewed by: Fiona Claxton and Rebecca Huang (UK, Assembly 7)

Change in serum marker of oxidative stress in the progression of idiopathic pulmonary fibrosis
Authors: Matsuzawa Y, Kawashima T, Kuwabara R, *et al.*
Pulm Pharmacol Ther 2015; 32: 1–6
Summary: Idiopathic pulmonary fibrosis (IPF) is characterised by irreversible alveolar injury due to formation of fibroblastic foci leading to deposition of extracellular matrix ultimately leading to fibrosis. Previous studies suggest a role of oxidative stress in disease development due to the presence of elevated level of oxidants in bronchoalveolar lavage samples of IPF patients. However the relationship between progression of IPF and changes in serum oxidative stress is still not established. This study aimed at investigating the changes in serum oxidative stress values associated with progressive IPF.
Serum oxidative stress was assessed using a d-Roms (determination of reactive oxygen metabolites) test that measures total hydroperoxide content in blood, and pulmonary function tests were performed in 43 untreated IPF patients recruited from a hospital department and 30 healthy controls. Oxidative stress was higher in IPF patients compared with controls. Changes in different parameters such as pulmonary function, oxidative stress and serum markers assessed over 6 months in 27 untreated patients suggested an elevation in the oxidative stress values which was associated with poor pulmonary function. 13 patients who had an acute exacerbation with IPF showed significantly higher oxidative stress values compared to patients with stabilised IPF. Selection bias could have occurred since the study was retrospectively conducted. Although serum was not the appropriate specimen to study oxidative stress in lung, using

bronchoalveolar lavage samples repeatedly might be too invasive. However, analysing breath condensate samples could be an effective way of studying the extent of oxidative stress damage in IPF patients.
In conclusion, this study suggests that progression in IPF patients was associated with increased in serum oxidative stress and decrease in lung function.
Reviewed by: Rishab Kapoor (UK, Assembly 8)

A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation
Authors: Corris PA, Ryan VA, Small T, *et al.*
Thorax 2015; 70: 442–450
Summary: Lung transplantation has proved to be successful in carefully selected individuals suffering from end stage lung diseases. However, post-lung transplant long-term graft survival is hindered by the development of bronchiolitis obliterans syndrome (BOS). This is characterised by airway obstruction due to progressive fibroblast proliferation and extracellular matrix deposition in the smaller airways ultimately leading to loss of lung function that is associated with decline in forced expiratory volume in 1 s (FEV1).
Corris *et al*. conducted a single-centre randomised placebo-control trial to study the effect of azithromycin (over 12 weeks) in 46 lung transplant recipients with BOS. Lung function assessment was carried out at regular intervals for all patients recruited in nearly 4 years of study. The primary outcome was the change in FEV1. Azithromycin treatment lead to ≥10% gain in FEV1 from baseline in nine out 23 intention-to-treat patients. No significant gain in FEV1 was observed in the placebo group. However, out of 64 target patients, only 48 were randomised. Overall, three and four adverse incidents were observed, in the azithromycin and placebo group, respectively, that were independent of the study medication.
This study suggested the therapeutic role of azithromycin in treatment of BOS and is the only randomised trial. Further study needs to be conducted to stratify patients with respect to risk of developing BOS and to determine the optimum treatment duration.
Reviewed by: Shameem S. Ladak (UK, Assembly 8)

External validation of blood eosinophils, *F*eNO and serum periostin as surrogates for sputum eosinophils in asthma
Authors: Wagener AH, de Nijs SB, Lutter R, *et al.*
Thorax 2015; 70: 115–120
Summary: Asthma is a disease that consists of many sub-phenotypes. There is still a persistent need for accessible and reliable markers which can preferably reflect the response to the treatment and predict asthma exacerbations. Sputum eosinophilia is a key asthma indicator but inducing sputum is cumbersome and frequently unsuccessful. Blood eosinophils, exhaled nitric oxide fraction (*F*eNO) and serum periostin have all been entertained as surrogate markers but their relationship with asthma phenotypes have not been validated. The present study ventures to explore these relationships in two different cohorts of asthmatics.
Asthma was described in two cross-sectional studies: 1) an external validation cohort of mild and moderate asthmatics (n=110); and 2) a replication cohort with more severe asthmatics (n=37). Measurements of lung function, atopy, sputum eosinophils as well as peripheral blood eosinophils, *F*eNO and serum periostin were obtained for all participants. Receiver operating characteristic (ROC) curve analysis was performed on the last three of those parameters, separately or together, to look for the most exact marker that reflected sputum eosinophil count of ≥3%. In the external validation cohort, both blood eosinophils and *F*eNO correlated moderately with sputum eosinophils ≥3% (r=0.59 and r=0.52, respectively; p<0.001) but no correlation was found with serum periostin. Diagnostic accuracy of blood eosinophils (described as area under the ROC curve (AUC)) was 89% and cut-off value of $\geq 0.27 \times 10^9$ per L achieved 78% sensitivity and 91% specificity. *F*eNO was also discriminative between eosinophilic and non-eosinophilic inflammation with an AUC of 78%. Optimal sensitivity and specificity, respectively, of 63% and 92%, was achieved at an *F*eNO ≥42ppb. Serum periostin did not exhibit satisfactory accuracy. In the replication cohort blood eosinophils could detect eosinophilic inflammation in 85%, while periostin did not achieve such accuracy (AUC of 54%).
In conclusion, blood eosinophils could be used as an accurate surrogate marker for sputum eosinophilia in asthma with different severity which can be beneficial to the disease management. *F*eNO and periostin can be used to complement asthma phenotyping.
Reviewed by: Roxana Mincheva (Sweden, Assembly 5)

Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary diseases
Authors: Paulin LM, Diette GB, Blanc PD, *et al.*
Am J Respir Crit Care Med 2015; 191: 557–565
Summary: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality globally. Although smoking is considered as the principal contributing factor of COPD, recent evidence suggests that 15% of COPD can be attributed to particulate matter and gases from occupational sources and this scenario persists even in a population where smoking is non-concomitant. The present study aimed to investigate the association of occupational exposure with COPD disease severity among a cohort of former and current smokers in the USA.
Paulin *et al.* of the SPIROMICS research group took a cohort of 1075 current/former smokers among which 721 had established COPD. The likelihood of occupational exposure was estimated using a job–exposure matrix classified as not exposed, intermediately exposed and highly exposed. Disease severity was assessed through 6-minute-walk distance (6MWD), modified Medical Research Council (mMRC) dyspnoea score, COPD assessment test (CAT), St. George's Respiratory Questionnaire (SGRQ), 12-component Short-Form Physical Component (SF-12) and exacerbation-associated healthcare utilisation.
The investigators found that occupational exposure was highly associated with COPD (OR 1.44, 95% CI 1.04–1.97) after adjusting other confounding factors. Among the COPD patients, job exposure was associated with reduced 6MWD (–26.0 m), worse mMRC (β 0.23; p<0.01), CAT (β 1.8; p<0.01), SGRQ (β 4.5; p<0.01) and SF-12 scores (β –3.3; p<0.001). They also observed that COPD patients with a job exposure had higher odds of exacerbation-associated health care utilisation (OR 1.53, 95% CI 1.04–2.25).
These results indicate that job history is an important component in COPD morbidity globally and it is associated with disease severity and worse quality of life of COPD patients and strongly suggests that clinicians should inquire about job or work-related exposure while managing patients.
Reviewed by: Subhabrata Moitra (India, Assembly 6)

Hot topic articles are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by Junior ERS members (aged 35 years and under). To become a hot topic author please contact Neil Saad: e-mail: neil.saad11@imperial.ac.uk