Hot topics from the Assemblies

Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomized double-blind placebo-controlled trial

Authors: Uzun S, Djamin RS, Kluytmans JAJW, *et al.*
Lancet Respir Med 2014; 2: 361–368
Summary: This study represents a significant development in the use of long-term azithromycin maintenance treatment in a subgroup of patients with chronic obstructive pulmonary disease (COPD). Patients with >3 exacerbations in the preceding year were randomised to receive thrice-weekly placebo or azithromycin treatment. 92 patients were randomised to receive azithromycin (n=47) or placebo (n=45) and reviewed every 3 months for 1 year. The primary outcome was rate of exacerbations. The statistically significant reduction in exacerbations in patients treated with azithromycin was sustained after adjustment for covariates. The rate ratio of exacerbations with azithromycin to placebo was 0.58 (95% CI 0.42–0.79; p=0.001). Median time to first exacerbation was 59 days with placebo (95% CI 31–87) and 130 days with azithromycin (CI 28-232; p=0.001). The odds ratio for hospital admission did not differ between groups (OR 1.34, 95% CI 0.67–2.70; p=0.41). In terms of quality-of-life measures (St Georges Respiratory Questionnaire and SF-12) there was a difference in favour of azithromycin at 3 months which was not maintained at 12-month follow up. The most commonly reported side effect of diarrhoea was more prevalent in the azithromycin group (p=0.015). Fewer patients in the azithromycin group had colonisation with new respiratory pathogens.
This study has significant implications for clinical practice. The authors recommend long-term azithromycin treatment in patients with COPD, refractory to standard care, although they caution in favour of monitoring for macrolide resistance. Risks of macrolide resistance and exposure to side effects can be minimised through targeted therapy to this subgroup of patients.
Reviewed by: Serena Strickland (UK, Assembly 1)

Effects of a functional variant c.353T>C in snai1 on risk of two contextual diseases. Chronic obstructive pulmonary disease and lung cancer

Authors: Yang L1, Yang X, Ji W, *et al.*
Am J Respir Crit Care Med 2014; 189: 139–148.
Summary: There is a well-described link between chronic obstructive pulmonary disease (COPD) and lung cancer, a portion of which may relate to common exposure to tobacco smoke; however, for any level of tobacco exposure, patients with COPD have a six-fold greater risk factor for lung cancer than smokers without COPD. Airway epithelial mesenchymal transition (EMT) expression is induced by smoking, and it is particularly strong in COPD. Thus could be link between smoking, COPD and lung cancer. Furthermore, lung cancer uses EMT to become invasive and therefore fatal in over 85% of cases. There are five major EMT regulatory genes (Snai1, Slug, Zeb1, Zeb2, and Twist1) in humans acting as molecular switches of EMT processes. In this large cohort study, the authors hypothesised that germline variants in these five major genes encoding EMT regulators may influence the development of both COPD and lung cancer. Functional assays were also performed to further assess the biological effects of these genetic variants. The authors reported that the exon variant c.353T>C of Snai1 was significantly associated with risks of both diseases, and the genetic variant affected lung cancer development through a mediation effect of COPD. In contrast, the c.353C genotype of Snai1 decreases individuals' susceptibility to COPD and thus lung cancer. Furthermore, the c.353C genotype decreased prevalence of lung cancer metastasis at diagnosis among smokers.
This study confirms the importance of EMT and key drivers of EMT in COPD and lung cancer and the link between the two. It is quite reassuring that leading respiratory journals are now recognising the potential central importance of EMT in the pathogenesis of both COPD and its relation to lung cancer.
Reviewed by: Sukhwinder Singh Sohal (Australia, Assembly 3)

The cost of lost productivity due to premature cancer-related mortality: an economic measure of the cancer burden

Authors: Hanly PA and Sharp L.
BMC Cancer 2014 14: 224.
Summary: This interesting article by Hanly and Sharp views cancer through its economic impact lens measuring monetary losses as well as productivity loss due to premature cancer-related mortality. The study was based on publically available data on cancer deaths in Ireland in 2005–2009 and the final costings were in euro currency value of 2009. Hanly and Sharp estimated years of potential productive life lost (YPPLL) & World age-standardised mortality rates (WASRs), causes of cancer-related death, household productivity and caring costs for each gender and cancer. There were a total of 4276 male and 3791 female cancer-related deaths in Ireland during this period. Lung cancer was the most common cause of cancer-related death in males and had the highest premature mortality cost (€84.0 million; 16.5% of total costs), followed by cancers of the colo-rectum (€49.6 million; 9.7%) and breast. In 2009, all cancer sites generated a total of €509.5 million in premature mortality costs. In both sexes, lung cancer accounted for 16.5% (€84.0 million) of overall costs while it was reported as the most expensive male cancer costing €62.9 million (19% of total male cancer costs). Lung cancer was once again the most costly site in terms of lost household production (€13.5 m) and caring activities (€7.8 m) in males
This study provides the first actual estimates of lost productivity costs for multiple cancer sites including lung

Hot topic articles are short (approx. 200 word) 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 James Chalmers, email: j.chalmers@dundee.ac.uk

cancer for a western European country using population data.

The findings of this study provide valuable information for lung cancer and set the foundations for readdressing the commissioning and structure of lung cancer services with the aim to promote early detection and healthcare interventions to address current population needs.

Reviewed by: Joe Benson (UK, Assembly 11)

Lung niches for the generation and maintenance of tissue-resident memory T cells

Turner DL, Bickham KL, Thome JJ, *et al.*
Mucosal Immunology 2014; 7: 501–510

Summary: Recent studies indicated that a subset of memory T cells is retained at the site of pathogen entry as a tissue-resident memory T cells (TRM). The lung, which is constantly exposed to airborne antigens, contains numerous TRM cells that are important for the protection of reinfection by pathogens. The mechanisms of TRM generation and maintenance in the lungs are still not very well described. In this study, Turner *et al.* used an intravenous antibody-labelling approach to distinguish $CD69^+$ TRM from circulatory T cells in the lung following influenza infection. They found that a small $CD4^+$ and $CD8^+$ TRM fraction (<10% of total $CD4^+$ or $CD8^+$ T cells in the lungs of naïve animals) increased dramatically at the peak of response and remained elevated up to 120 days post infection. Using immunofluorescent microscopy, the authors showed that $CD4^+$ TRM clustered between airways and pulmonary vessels in broncho-vascular bundles, while circulating $CD4^+$ T cells were distributed throughout the lungs parenchyma and alveolar walls. Moreover, TRM cells in this specific lung niche persisted independently from circulating and lymphoid populations. The authors also analysed human tissues for the presence of $CD8^+$ T cells specific for influenza or cytomegalovirus (a non-respiratory virus) using dextramer reagents, which detect antigen-specific T cells. They found that majority of influenza-specific $CD8^+CD69^+$ TRM cells were located in the lung, whereas influenza-specific $CD8^+$ T cells in the spleen were $CD69^-$, indicating that they are circulating memory T cells. Cytomegalovirus-specific $CD8^+CD69^+$ TRM cells were, however, present at comparable numbers in spleen and lungs, suggesting that distinct viruses differentially promote the generation of TRM in specific sites.

Overall, these results suggest that respiratory pathogens determine the anatomic location and distribution of TRM cells and might have important implications for vaccine design.

Reviewed by: Berislav Bosnjak (Austria, Assembly 5)

The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients

Authors: Lee S–D, Huang M–S, Kang J, *et al.*
Respir Med 2014; 108: 600–608.

Summary: An observational 6-month study investigated whether the chronic obstructive pulmonary disease (COPD) assessment test (CAT) score could predict the risk and time to next exacerbation of 495 non-asthmatic COPD patients. Patients were invited in to the study with COPD defined by a forced vital capacity/forced expiratory volume in 1 s ratio <0.7, a smoking history ⩾10 pack-years and at least one treated exacerbation within the previous 12 months. Patients performed spirometry to define GOLD stage and completed the CAT questionnaire at eight-week intervals. CAT scores were categorised into four groups (0–9, 10–19, 20–29 and 30–40). Patients in the higher scoring group showed a longer history of COPD with more frequent exacerbations and poorer lung function. They had a higher exacerbation risk and shorter time to next exacerbation compared with those in the lower categories. When used as a continuous variable, the CAT score still proved valuable for predicting these outcomes. Adjusting the CAT score for age, sex, body mass index, COPD history, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage severity, smoking status, comorbidities and influenza vaccination made little difference to the predicted outcomes when compared with non-adjusted scoring, proving significantly useful when minimal clinical history is known. The CAT score also showed reliability when assessing a subgroup of COPD patients with cardiovascular comorbidities. Interestingly, GOLD stage showed no significant relationship to exacerbation imminence or severity of next exacerbation.

Results from this study suggest the simple CAT score could improve clinical management of COPD patients and associated therapies, while also providing a helpful resource in clinical research when looking at COPD exacerbations as a predicted outcome.

Reviewed by: Megan Crichton (UK, Assembly 5)

Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial

Authors: Mandal P, Chalmers JD, Graham C, *et al.*
Lancet Respir Med 2014; 2: 455–463.

Summary: Antibiotic use and chest physiotherapy remain the main therapeutic approaches in managing bronchiectasis. Studies that lead us towards a decrease in the frequency and duration of antibiotic therapy are needed. In this paper, the recognised anti-inflammatory properties of statins are shown to improve cough in bronchiectasis using the Leicester Cough Questionnaire (LCQ). This is therefore one of the first studies to find non-antibiotic anti-inflammatory treatment can improve clinical outcomes in bronchiectasis. This study concluded that 6-month use of atorvastatin significantly improved cough using the LCQ. The same authors previously validated the use of this scoring system in bronchiectasis. The LCQ has also been shown to be a valid, reliable and responsive instrument to measure health status in COPD patients. In this proof-of-concept randomised controlled trial, 30 individuals were assigned active treatment with high-dose (80mg) atorvastatin and 30 were allocated a placebo. The placebo was not precisely matched in appearance, a limitation recognised by the authors. All assessments were done at baseline and 6 months. Blood measurements, adherence to treatment and LCQ score where also checked at 3 months. Despite the small sample size, at 6 months the study found an improvement in cough (mean difference 1.5 units) between the active treatment and placebo group. There was no improvement in quality of life using the St George Respiratory Questionnaire, no reduction in exacerbations or markers of airway inflammation, with the exception of an increase in apoptotic neutrophils in the sputum of treated patients. One-third of patients given atorvastatin had adverse events compared with 10% of the placebo group.

This study therefore suggests a limited benefit of statins on cough that requires further investigation.

Reviewed by: Hani Abo-Leyah (UK, Assembly 10).