Hot Topics from the Assemblies

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Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

Authors: Stokholm J, Chawes B, Vissing N *et al.*
Lancet Respir Med 2016; 4: 19–26.
Summary: Acute, asthma-like episodes in young children are extremely common and are responsible for a high proportion of hospital admissions. It has previously been shown that bacteria and viruses may be aetiological agents for these episodes, but currently antibiotic therapy is not routinely advised.

In this double-blind study the investigators assessed the effect of giving azithromycin in these acute asthma-like episodes. Children aged 1–3 years were recruited from the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort. 158 asthma-like episodes in 72 children were randomly assigned to receive either azithromycin (79 episodes) or placebo (79 episodes) for an episode of asthma-like symptoms lasting at least 3 days.

The primary outcome of the study was duration of the acute respiratory episode after treatment, which was 63% shorter for those children receiving azithromycin compared with placebo (95% CI 56.0–69.3%, $p<0.0001$). If treatment started earlier, the effect size was further increased with an 83% shortening of duration when treatment was started prior to the sixth day of symptoms, compared with a 36% reduction if started on or after the sixth day ($p<0.001$). There was no significant difference in the treatment effect between episodes where a bacterial pathogen was detected and episodes where no bacteria were detected, suggesting that the potential benefit may be related to anti-inflammatory rather than anti-bacterial effects.

This study shows that there may be a role for treating acute respiratory episodes in young children with macrolide antibiotics, but the exact underlying mechanisms are unclear. Further investigation is required concerning the potential consequences of long-term use of macrolides in children. Particular areas for investigation should be the possible increase in serious cardiac events, as previously associated with macrolide use, as well as the contribution to development of resistant pathogens.
Reviewed by: Naina McCann (UK, Assembly 10)

The effect of macrolide resistance on the presentation and outcome of patients hospitalized for *Streptococcus pneumoniae* pneumonia

Authors: Cilloniz C, Albert RK, Liapikou A, *et al.*
Am J Respir Crit Care Med 2015; 191: 1265–1272.
Summary: *S. pneumoniae* (pneumococcus) remains the most frequent pathogen in community-acquired pneumonia (CAP). Current international guidelines recommend that empiric antibiotic treatment should always cover this pathogen.

It is known that pneumococcal resistance to β-lactams is high (40%) and macrolide resistance rates vary between 18 and 35%. There is concern about the efficacy of antibiotic treatment against pneumococcus with a high level of resistance to macrolides. There are also conflicting data describing the effect of macrolide resistance on the presentation and outcomes of patients with pneumococcal pneumonia. The clinical relevance of macrolide resistance of pneumocccus in CAP is therefore unclear.

This retrospective, observational study aimed to determine the effect of macrolide resistance on the presentation and outcomes of 643 patients with pneumococcal pneumonia seen over a 14-year period in a Hospital Clinic in Barcelona, Spain. 22% of patients had macrolide resistant pneumococcus. Patients with macrolide resistance did not present with more severe illness than those without resistance and also had similar rates of intensive care unit admission and requirement for mechanical ventilation (MV), but lower rates of noninvasive MV and shock. Although patients with macrolide-resistant pneumococcus had fewer pulmonary complications, they had similar 30-day mortality rates to patients with macrolide sensitive disease. In addition, this study found no evidence to suggest that hospitalised patients with macrolide resistant pneumococci had worse clinical outcomes if they were treated with guideline-compliant *versus* noncompliant regimens.
Reviewed by: Catia Cilloniz (Spain, Assembly 10)

Association between tuberculosis and Parkinson disease: a nationwide, population-based cohort study

Authors: Shen CH, Chou CH, Liu FC, *et al.*
Medicine 2016; 95: e2883.
Summary: Infectious diseases may contribute to the development of Parkinson's disease (PD). Tuberculosis (TB) is of particular interest, as a

latent infection with *Mycobacterium tuberculosis* may persist for years before disease develops, which itself may depend on the development of other immune-compromising conditions. The declining TB mortality rate also suggests more people surviving the disease might live longer and go on to develop PD. If the two are independently associated, a longitudinal study controlling for comorbidities that connect the two diseases would best capture this connection.

Shen *et al.* conducted a population-based, retrospective cohort study of 121951 TB patients and 487800 frequency-matched (1:4 matched based on age, sex and entry year) individuals without TB using the National Health Insurance Research Database, which comprises claims data for Taiwanese residents between 1996 and 2011. Patients entered the TB cohort on the date of TB diagnosis and were followed until either a diagnosis of PD was made or the end of 2011. Poisson regression was used to estimate the incidence rate ratio of PD and multivariable Cox proportional hazard models estimated the risk of PD adjusting for other comorbidities.

The authors concluded *via* log-rank test that the cumulative incidence of PD was significantly higher in the TB cohort than in the non-TB cohort. After adjustment for age, sex and all comorbidities, patients with TB had a 1.38-fold increased risk of PD compared with the people without TB, although this risk decreased with follow-up period.

The authors proposed pathways of neuroinflammation and immune modulation as reasons for the association. Future work assessing the relevance of genes in the dopaminergic pathway on human TB risk is needed to refine the associations between PD and TB risk.

Reviewed by: Kyle Fluegge (USA, Assembly 10)

Nivolumab *versus* docetaxel in advanced squamous-cell non-small-cell lung cancer

Authors: Brahmer J, Reckamp KL, Baas P, *et al.*
N Engl J Med 2015; 373: 123–135.

Summary: Nivolumab is a humanised anti-PD1 immune-checkpoint-inhibitor antibody. This randomised phase III trial compared docetaxel (a taxane drug validated for second-line treatment in advanced nonsmall cell lung cancer; 75mg·m^{-2}, every 3 weeks, *i.v.*) with nivolumab (3mg·kg^{-1}, every 2 weeks, *i.v.*) in patients with advanced squamous-cell lung carcinoma with progression after a first-line chemotherapy. The primary end-point was overall survival (OS), and secondary end-points were response rate, progression-free survival (PFS), biological efficacy as measured by PD-L1 expression in immunohistochemistry and safety. 272 patients were randomised (135 to nivolumab and 137 to docetaxel). The median OS was 9.2 months with nivolumab *versus* 6.0 months with docetaxel (hazard ratio 0.59, 95% CI 0.44–0.79; p<0.001). Response rate was 20% with nivolumab *versus* 9% with docetaxel (p=0.008). The median PFS was 3.5 months with nivolumab *versus* 2.8 months with docetaxel (hazard ratio 0.62, 95% CI 0.47–0.81; p<0.001). After a minimal follow-up of 11 months, the median duration of response was not reached in nivolumab arm, *versus* 8.4 months in docetaxel arm. No differential effect of PD-L1 expression on OS and PFS was observed. Grade 3–4 toxicities occurred in 7% of patients with nivolumab *versus* 55% with docetaxel.

Based on these results, nivolumab received European Medicines Agency approval for the treatment of advanced squamous-cell nonsmall cell lung carcinoma as second-line treatment in 2015.

Reviewed by: Etienne Giroux Leprieur (France, Assembly 11)

Effect of opioids *vs* NSAIDs and larger *vs* smaller chest tube size on pain control and pleurodesis efficacy among patients with malignant pleural effusion: the TIME1 randomized clinical trial

Authors: Rahman NM, Pepperell J, Rehal S, *et al.*
JAMA 2015; 314: 2641–2653.

Summary: TIME1 is a large multicentre, randomised phase III trial of 320 patients with malignant pleural effusion (MPE) investigating the effect of NSAIDs *versus* opiates and the use of small (12F) *versus* large bore chest tubes (24F) with regards to pain control and pleurodesis efficacy. The study included 16 centres in three countries and participants were individuals with MPE managed with talc pleurodesis *via* either poudrage or slurry.

The results showed the administration of NSAIDs is not superior to opiates in pain management, as scores in the visual analogue scale (VAS) were not significantly different between groups. A statistically significant difference was detected between the pain scores of the smaller *versus* the larger bore chest tubes. Although smaller chest tubes were related to less pain compared with larger tubes, the overall difference of 6 mm on the VAS scale was small and thus not considered clinically important.

Further analysis revealed the anti-inflammatory effect of NSAIDs did not appear to affect the efficacy of pleurodesis, suggesting that these drugs can be safely prescribed in patients with MPE. Nevertheless, small bore chest tubes failed to meet the non-inferiority criteria for pleurodesis efficacy compared with larger chest tubes.

Overall the results suggest that NSAIDs should not be avoided for post-pleurodesis pain relief and could be an alternative medication for MPE patients at risk of opiate toxicity. Despite the widespread use of 12F chest tubes and their recommendation in national guidelines, there is now an argument for the use of larger bore chest tubes on the basis of these results. The outcomes of TIME1 study raise the necessity of further investigating and updating current clinical guidelines for MPE management.

Reviewed by: Nikolaos I. Kanellakis and Ioannis Psallidas (UK, Assembly 11)

Hot topics are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by Junior ERS members. To become a hot topic author, please contact Aran Singanayagam: e-mail: aransinga@gmail.com