Hot topics from the Assemblies

Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit

Authors: Palmer LB, Smaldone GC.

Am J Respir Crit Care Med 2014; 189: 1225–1233.

Summary: It has been postulated that inhaled antibiotics have an advantage over systemic antibiotics in respiratory infections by delivering higher concentrations to the airways and limiting systemic toxicity. Within an intubated population, delivery of aerosolised antibiotics is simple and effective as they are already connected to a closed-circuit ventilator system, maximising dose delivery. Critically unwell patients are at high risk of colonisation by multidrug-resistant (MDR) organisms; this is due to multiple factors such as prolonged hospitalisation and longer term exposure to systemic antibiotics. Inhaled antibiotics may, therefore, be an excellent yet previously unconsidered option in intubated and mechanically ventilated patients in the intensive care unit (ICU) setting.

Palmer and Smaldone conducted a double-blind, randomised, placebo-controlled trial of critically ill, intubated ICU patients in order to explore this theory. Patients with evidence of respiratory infection were randomised to receive either aerosolised antibiotics (vancomycin in patients with Gram-positive organisms and gentamicin or amikacin in patients with Gram-negative organisms) or placebo. This was in addition to appropriate systemic antibiotics.

In patients who received aerosolised antibiotics, 26 out of 27 pathogens were eradicated. Remarkably this included 14 out of 16 multidrug-resistant pathogens. This compared with 2 out of 23 eradicated in the placebo group (1 out of 11 MDR pathogens). An additional positive finding was that no resistance to the aerosolised antibiotics was seen; this may be especially important given that resistance to systemic antibiotics was found to be much higher in the placebo group. The outcomes were primarily microbiological; however, there were small beneficial effects on clinical outcomes seen in the group receiving aerosolised antibiotics, including reduced tracheal secretions and lower white cell counts.

It is apparent from this study that aerosolised antibiotics should be considered as a potentially useful option in patients with respiratory infections, particularly when caused by MDR pathogens; however, larger multicentre studies are now required to confirm these beneficial effects on harder patient outcomes.

Reviewed by: Katy McAllister (UK, Assembly 2)

Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis

Authors: Gillespie SH, Crook AM, McHugh TD, *et al.*

N Engl J Med 2014; 371: 1577–1587.

Summary: A 6-month treatment for drug-sensitive tuberculosis (TB) has been the standard regime since the early introduction of antituberculous chemotherapy. Shortening duration of treatment would have major advantages in terms of compliance and healthcare utilisation, particularly in developing countries where TB is a major burden. Early phase studies have demonstrated that moxifloxacin-based regimes caused a more rapid decline in TB bacterial load and early culture conversion compared with standard treatment, suggesting that introducing moxifloxacin into standard treatment could result in earlier efficacy and, therefore, a shorter regime.

Gillespie *et al.* performed a phase III trial (REMoxTB) testing two moxifloxacin-containing 4-month regimes against the standard 6-month regime in patients with previous untreated TB infection. The primary outcome was the proportion of patients with bacteriologically or clinically defined failure or relapse, 18 months after randomisation. The study randomised 1931 patients across Africa, Asia and Central America.

Non-inferiority of the shorter regimes was not demonstrated. Despite quicker time to culture negativity in the moxifloxacin groups, the control (6 months) group had a lower risk of relapse (8%) compared with 15% in the group in which moxifloxacin was used instead of ethambutol, and 20% in the group in which moxifloxacin replaced isoniazid.

Unfortunately, this study failed to show that anti-TB chemotherapy could be shortened to 4 months with moxifloxacin, and raises important issues for future design of studies, given that earlier microbiological efficacy did not translate into safe shortening of treatment.

Reviewed by: Sara Lobnitz (Canada, Assembly 10)

Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study

Authors: Tkacova R, McNicholas WT, Javorsky M, *et al.*

Eur Respir J 2014; 44: 931–941.

Summary: The effects of sleep apnoea on the cardiovascular system are increasingly recognised but the pathophysiology remains poorly understood. Particularly, it is not clear to what extent hypertension and cardiovascular risk represent a complication, rather than a comorbidity due to shared risk factors, in patients with obstructive sleep apnoea.

In this study, 24 sleep centres, across Europe, established a European sleep apnoea database to study the cardiovascular complications of sleep apnoea. The database included key covariates associated with cardiovascular risk and hypertension incidence including age, sex, smoking, hyperlipidaemia and diabetes.

In 11 911 patients, 41% had systemic hypertension. Both the apnoea–hypopnoea index and 4% oxygen desaturation index were associated with hypertension, but after adjustment for other confounders associated with cardiovascular risk, oxygen desaturation was the independent risk factor for hypertension.

This study suggested that episodes of desaturation overnight are associated with hypertension and argue that this is a direct consequence of intermittent hypoxia. This supports recent randomised controlled trial data, such as Gottlieb *et al.* in the *New England Journal of*

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

Medicine 2014, which showed that continuous positive airways pressure significantly reduced blood pressure compared with oxygen alone.
Reviewed by: John McBride (UK, Assembly 4)

Lipoxin generation is related to soluble epoxide hydrolase activity in severe asthma
Authors: Ono E, Dutile S, Kazani S, *et al.*
Am J Respir Crit Care Med 2014; 190: 886–897.
Summary: In bronchial asthma, pro-resolving mediators such as lipoxin (LX) can suppress leukocyte recruitment into the airways, inhibit degranulation of leukocytes, attenuate the generation of oxidative stress mediators and suppress bronchoconstriction. LX generation is known to be defective in severe asthma.
The authors aimed to reveal the pathomechanism behind decreased LX production in severe asthma and study if LX generation might modulate cardinal features of asthmatic airway inflammation. 24 patients with nonsevere asthma (NSA) and 19 patients with severe asthma (SA) participated in the study.
Airway oxidative stress was higher in SA than in NSA as shown by the increased concentration of 8-isoprostane (8-IP) in sputum supernatant. The sputum levels of 8-IP and LXA_4 were inversely correlated in SA. The activity of soluble epoxide hydrolase, which influences airway LX generation, showed negative correlation with LXA_4 levels both in NSA and SA sputa. Furthermore, the pharmacological inhibition of soluble epoxide hydrolase resulted in increased production of LXA_4 in whole blood samples and bronchoalveolar lavage cells of patients with SA. Interactions between circulating leukocytes and platelets promote leukocyte recruitment into the airways in SA. The authors found that more platelet–leukocyte aggregates were formed in SA than in NSA and LXA_4, and 15-epi-LXA_4 inhibited platelet–leukocyte interactions in SA. Finally, the direct action of LXs on lung structural cells were examined using human lung sections. 15-epi-LXA_4 reduced bronchial contraction induced by tumour necrosis factor-α.
In summary, LX generation in the airways is compromised by the heightened oxidative stress in SA. Treatment with soluble epoxide hydrolyse inhibitors or LX analogues are promising candidates to attenuate airway inflammation and inhibit bronchoconstriction in SA.
Reviewed by: Zsofia Lazar (Hungary, Assembly 5)

Asthma increases pulmonary thromboembolism risk: a nationwide population cohort study
Authors: Chung W-S, Lin C-L, Ho F-M, *et al.*
Eur Respir J 2014; 43: 801–807.
Summary: Chronic inflammatory disorders have been associated with activation of the coagulation cascade and increased risk of venous thromboembolism. This has been proven for inflammatory bowel disease, rheumatoid arthritis, diabetes mellitus and chronic obstructive pulmonary disease. Now, bronchial asthma can be added to this list.
Chung *et al.*, in their nationwide population-based cohort longitudinal study on the risk of development of pulmonary embolism (PE) in people with bronchial asthma, showed that the risk of developing PE is significantly increased in asthmatics.
The authors followed 31 356 newly diagnosed asthma patients for a total of 186 182 person-years and compared them with 125 157 randomly selected non-asthmatic individuals with 743 374 person-years of follow-up and found a 3.24-fold increased risk of PE in the asthmatic cohort compared with the non-asthmatic cohort (hazard ratio 3.24, 95% CI 1.74–6.01). The overall incidence rate of PE showed a 3.38-fold increase in asthmatic patients compared with the non-asthmatic cohort (10.2 *versus* 3.09 per 100 000 person-years). The hazard ratio increases with the increase in number of emergency room visits and admissions compared with the non-asthmatic cohort. Inclusion of PE as a comorbidity in asthma may significantly alter the diagnostic and treatment strategies for bronchial asthma and may give a new dimension to the management of difficult-to-treat asthma as well as severe exacerbations.
Reviewed by: Sheetal Chaurasia (India, Assembly 6)

The utility of nodule volume in the context of malignancy prediction for small pulmonary nodules
Authors: Mehta HJ, Ravenel JG, Shaftman SR, *et al.*
Chest 2014; 145: 464–472.
Summary: Indeterminate pulmonary nodules pose a critical clinical question: benign or malignant? The answer directs their further management (observation or surgery). To answer this question, the American College of Chest Physicians recommends the estimation of the pretest probability of malignancy either qualitatively, by using clinical judgment, and/or quantitatively, by using a validated model. Swensen's 1997 prediction model, based on clinical and chest radiological data (diameter, location, edge and other characteristics) of the nodule, has been external validated and is commonly used in clinical practice.
This study investigated if the predictive value of the Swensen model increases when adding any of three novel functions of nodule volume: nodule volume (model 1), volume-to-diameter ratio (model 2) or sphericity index (the measured nodule volume divided by the volume of a sphere with a diameter equal to that of the nodule) (model 3).
A total of 233 computed tomography (CT) scan-detected nodules $<$15 mm in diameter from 221 consecutive subjects were examined for probability of malignancy, applying first the Swensen and then the three above described models. A definitive diagnosis of malignancy was established either by surgical resection, biopsy or stability for at least 2 years demonstrated by serial follow-up CT scans.
The authors described that, using a 0.5 probability of malignancy as a cut-off, the Swensen model correctly classified 67% of the nodules (malignant or benign), while the three models correctly classified a significant higher percentage of the nodules (model 1: 83%; model 2: 88%; and model 3: 88%).
This work demonstrates that the addition of nodule volume as a variable to an existing malignancy prediction model enhances its prediction ability for pulmonary nodules $<$15 mm in diameter. It also suggests that the prediction ability of the existing models can be increased by incorporating novel parameters of the nodules.
Reviewed by: Eleftheria Chaini (Greece, Assembly 11)