Hot topics from the Assemblies

INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD
Authors: Rossi A, van der Molen T, Ricardo del Olmo, *et al*.
Eur Respir J 2014; 44: 6, 1548–1556
Summary: Inhaled corticosteroids (ICS) remain a highly controversial treatment for stable chronic obstructive pulmonary disease (COPD). Data linking high-dose ICS with complications, such as pneumonia and fractures, has necessitated a re-evaluation of their role in COPD management. Guidelines currently suggest ICS for patients with a forced expiratory volume in 1 s (FEV1) <50% predicted (or <60% in some regions) and a history of exacerbations. Nevertheless, it is well known that ICS and combination ICS/long-acting β-agonist (LABA) treatments are commonly used outside these groups. In view of the increasingly recognised dangers of ICS treatment, data demonstrating the safety of discontinuing ICS treatment is welcome.
INSTEAD was a 26-week double-blind double-dummy study of patients with moderate COPD (FEV1 50–80% predicted) who had been receiving ICS/LABA for ≥3 months. Patients were randomised to either the LABA indacaterol 150 µg once daily or salmeterol/fluticasone 50/500 µg twice daily with a primary outcome of trough FEV1 at 12 weeks.
This study demonstrated that treatment with LABA alone was non-inferior to treatment with ICS/LABA in this patient group, with no significant differences in FEV1, St George's Respiratory Questionnaire, dyspnoea or other secondary end-points.
This study provides reassurance that ICS/LABA can be substituted with a bronchodilator-only regime in patients with moderate COPD, which could be very beneficial in avoiding the long term adverse effects of inhaled corticosteroids.
Reviewed by: Marcus Höfl (Germany, Assembly 5)

Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised double-blind placebo controlled SNAP trial
Authors: Cooper S, Taggar J, Lewis S, *et al*.
Lancet Respiratory Medicine 2014; 2: 728–737
Summary: Smoking in pregnancy is harmful to both mother and fetus, but methods of smoking cessation in pregnant mothers is complicated by a lack of data regarding the safety of smoking cessation aids such as nicotine replacement therapy (NRT).
This study aimed to assess the impact of NRT on infant outcomes up to 2 years after birth in the context of a randomised controlled trial. The original randomised trial did not show a benefit of NRT over placebo in terms of the number of mothers abstaining from cigarettes at delivery, but did show an initial benefit, doubling the rate of smoking cessation at 4 weeks after starting the trial.
In this follow-up study, the authors evaluated infant outcomes at 2 years. They defined a positive outcome as the absence of disability or problems with behaviour or development as assessed by questionnaire.
Randomisation to nicotine replacement therapy compared with placebo was associated with a 1.40 higher odds of no impairment. This was despite no evidence that nicotine replacement therapy was effective at promoting abstinence (only 24 mothers out of 888 surveyed had successfully given up smoking during pregnancy). This fascinating study suggests that even the brief 4 week abstinence induced by NRT resulted in improved outcomes for children. Even brief smoking cessation during pregnancy may have significant benefits for mother and child.
Reviewed by: Mary Porter (UK, Assembly 6)

β-Lactam monotherapy versus β-lactam–macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial.
Authors: Garin N, Genné D, Carballo S, *et al*.
JAMA Intern Med 2014; 174: 1894–1901
Summary: Combination antibiotics, consisting of β-lactams and macrolide have been consistently associated with improved outcomes in community-acquired pneumonia in retrospective and observational studies. Randomised controlled trials, have, however been lacking to date. Macrolides have important side effects and can induce antimicrobial resistance and therefore their use must be robustly justified. This study aimed to demonstrate non-inferiority of monotherapy with a β-lactam alone compared with combination therapy. The authors recruited 580 patients with moderate–severe pneumonia not requiring intensive care unit admission. The trial was open label and the primary outcome was the proportion of patients reaching clinical stability (a US Food and Drug Administration approved end-point for clinical trials in pneumonia) at day 7.
Overall, there was a high proportion of patients reaching clinical stability in the macrolide group compared with the monotherapy group, which did not reach statistical significance (41.2% versus 33.6%; p=0.07). Monotherapy did not achieve non-inferiority to combination therapy.
There was, however, ammunition for both macrolide enthusiasts and for those sceptical of the role of macrolides. A subgroup analysis demonstrated the benefit of combination therapy for 31 patients who isolated atypical pathogens (OR 0.33, 95% CI 0.13–0.85; p=0.02) with no benefit of macrolide treatment in the remaining 549 patients (OR 0.99, 95% CI 0.80–1.22; p=0.9). This therefore suggests that all patients with moderate–severe pneumonia need to be treated with empirical macrolides in order to avoid treatment failure in the small group of patients isolating atypical pathogens.
This study supports guideline recommendations for empirical macrolide treatment, but the risk/benefit ratio of macrolides remains to be clarified. This study may also suggest a possible role for rapid point-of-care tests, such as PCR and urinary antigen tests that can exclude atypical pathogens as it appears that macrolides confer no benefit once these are excluded.
Reviewed by: James Griffin (UK, Assembly 10)

The effect of intravenous interferon-β-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open label study

Authors: Bellingan G, Maksimow M, Howel DC, *et al*.

Lancet Respir Med 2014; 2: 98-107

Summary: Vascular leak plays an important role in the development of conditions like acute respiratory distress syndrome (ARDS) and septic shock. Dysfunction of the endothelial barrier contributes to the severe tissue damage and organ dysfunction which, in the lungs, results in alveolar flooding and impaired gas exchange.

CD73 is a central regulator of pulmonary capillary permeability. CD73 is expressed on pulmonary endothelial cells, and protects the endothelial barrier by enhancing adenosine production. Interferon-β enhances the protective effects, by increasing CD73 expression.

In the current study, important efforts were made to translate these preclinical data into clinical practice. Using human recombinant interferon-β-1a (FP-1201) they demonstrated that ex vivo incubation of human lung tissue with FP-1201 indeed enhanced CD73 expression in the endothelium of pulmonary vessels. In a subsequent open label study in adult ARDS patients, they first determined an optimal tolerated dose in a dose-escalation phase (15 patients). All subsequently enrolled ARDS patients (22 patients) were treated with this dose (10 μg per day during 6 days), and compared with a control cohort (59 patients). Treatment with FP-1201 resulted in reduction in pro-inflammatory cytokines, improvement of oxygenation and a significant reduction in mortality (OR 0.19, 95% CI 0.03-0.72, compared with control cohort).

Although these data need confirmation in a randomised, placebo-controlled trial, this study indicates that protecting the pulmonary endothelial barrier may be a very effective way to treat ARDS. As vascular leak plays a role in other conditions as well, the application of FP-1201 may extend beyond ARDS alone.

Reviewed by: Jurjan Aman (The Netherlands, Assemblies 2 and 3)

Oronasal mask versus helmet in acute hypercapnic respiratory failure

Authors: Pisani L, Mega C, Vaschetto R, *et al*.

Eur Respir J 2014; 45: 691–699

Summary: The helmet is a relatively novel interface for noninvasive mechanical ventilation (NIV), which improves tolerance and allows longer continuous NIV application. However, in hypercapnic patients, the helmet has been shown to be less efficacious than an oronasal mask. In this study, a new helmet, specifically designed for use in hypercapnic patients was compared with an oronasal mask. This was a pilot randomised trial of 80 patients with COPD and acute hypercapnic respiratory failure who required NIV. The authors compared the interfaces primarily with respect to arterial blood gases (ABGs), discomfort and tolerance (number of interface switches); in addition, they assessed dyspnoea, vital signs, NIV discontinuation and NIV failures leading to intubation. Both interfaces equally improved ABGs after 1 and 6 hours without differences in tolerance, vital signs or rates of failure. However, there was evidence that discomfort increased for patients with a helmet and, although decreased, the dyspnoea rate was significantly higher at 6 hours among helmet patients compared with patients using a mask.

These results indicate that the helmet could be valid alternative to a mask in hypercapnic patients to improve ventilation without affecting the patient's discomfort. The use of the helmet for first-line treatment and as part of a rotating strategy, which prevents the occurrence of side-effects related to a single interface, should be assessed in larger randomised controlled trial.

Reviewed by: Federico Longhini (Italy, Assembly 2)

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