



# APSR Respiratory Research Review

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Issue 15 - 2007

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## Welcome to the final APSR Research Review for 2007.

This month's review raises a number of important and often difficult ethical and conceptual issues – the ethics of organ donation for lung transplantation, the role of lung transplantation in cystic fibrosis in children, mechanical ventilation in patients with neuromuscular disorders, regulatory control of air pollution and the requirement to undertake RCTs of pharmacological agents in different ethnic groups. It is hoped that consideration of these issues is useful to members of the APSR in their clinical, teaching, research and advocacy roles in the region.

This is the last review in which Professor Beasley provides expert comment. After 12 months in the role he is handing over this responsibility to Dr Lutz Beckert, Respiratory Physician at Christchurch Hospital in New Zealand.

To all our readers and sponsors, we thank you for your support in 2007. Have a wonderful Christmas and we'll see you again in the New Year.

## Long-term effects of caffeine therapy for apnea of prematurity

**Authors:** Schmidt B et al

**Summary:** This study examined the long-term effects of methylxanthine therapy on neurodevelopment and growth in infants treated for apnea of prematurity. 2,006 infants with very low birth weight (500 to 1,250g) were randomised to receive methylxanthine therapy (caffeine) or placebo for as long as treatment for apnea of prematurity was necessary. The primary outcome (death or neurodevelopmental disability at a corrected age of 18 to 21 months) occurred in 40.2% of caffeine vs 46.2% of placebo recipients (odds ratio 0.77, 95% CI 0.64–0.93; p = 0.008). Caffeine reduced the incidence of cerebral palsy and cognitive delay at follow-up compared with placebo, but not rates of death, deafness or blindness. In conclusion, use of caffeine for apnea of prematurity improves the likelihood of survival without neurodevelopmental disability at 18 to 21 months.

**Comment:** A significant neuroprotective effect of caffeine for the treatment of apnea of prematurity in very low birth weight infants. As proposed in the accompanying editorial, we can now conclude that the gains of caffeine therapy outweigh the possible risks (N Engl J Med 2007; 357: 1967-8).

<http://content.nejm.org/cgi/content/short/357/19/1893>

**Reference:** N Engl J Med 2007; 357:1893-1902

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## Factors associated with lung function decline in patients with non-CF bronchiectasis

**Authors:** Martinez-Garcia MA et al

**Summary:** This study identified factors associated with lung function decline in adults with stable, non-CF bronchiectasis. 76 adult men and women with bronchiectasis diagnosed by CT scan were included in the study and followed for 24 months. Mean FEV<sub>1</sub> decreased by 52.7 mL/year during follow-up. Chronic *pseudomonas aeruginosa* infection, more frequent severe exacerbations and systemic inflammation were all significant independent factors associated with accelerated decline of lung function. None of the long-term treatment strategies had a significant effect on the decline in FEV<sub>1</sub>. The investigators concluded that chronic *P. aeruginosa* colonisation, severe exacerbations and systemic inflammation are independently associated with disease progression in patients with non-CF bronchiectasis.

**Comment:** This study highlights the importance of colonisation with *P. aeruginosa* as a risk factor for progressive loss of lung function in non-CF bronchiectasis. Novel therapeutic regimes are required if this serious complication of bronchiectasis is to be adequately treated.

<http://dx.doi.org/10.1378/chest.07-0490>

**Reference:** *Chest* 2007; 132:1565-72

## Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension

**Authors:** Reichenberger F et al

**Summary:** This open-label study investigated the effects of sildenafil (50mg three times daily) in 104 patients with inoperable chronic thromboembolic pulmonary hypertension (WHO functional class II-IV). Treatment with sildenafil reduced pulmonary vascular resistance from 863 dyn·s·cm<sup>-5</sup> at baseline to 759 dyn·s·cm<sup>-5</sup> after 3 months, and improved 6-minute walking distance from 310m at baseline to 361m after 3 months and 366m after 12 months. The acute haemodynamic effects of a single dose of sildenafil 50mg during initial right heart catheterisation in a subset of 67 patients did not predict long-term outcome. In conclusion, open-label treatment with sildenafil caused significant functional improvement in patients with inoperable chronic thromboembolic pulmonary hypertension.

**Comment:** Promising data on the use of sildenafil in inoperable CTEPH. The clinical point to note is that the acute effect measured at right heart catheterisation is not a good guide to the long-term response to therapy. A therapeutic trial is preferred in patients who are eligible for this treatment. Note the high dose used of 50mg 3 times daily.

<http://dx.doi.org/10.1183/09031936.00039007>

**Reference:** *Eur Respir J* 2007; 30:922-7

## Long-term associations of outdoor air pollution and mortality in Great Britain

**Authors:** Elliott P et al

**Summary:** This study investigated the link between air pollution and mortality in Great Britain. Annual black smoke (BS) and sulphur dioxide (SO<sub>2</sub>) concentrations since 1966 were compared with all-cause and cause-specific mortality after adjustment for social deprivation and urban/rural classification. BS and SO<sub>2</sub> concentrations were significantly associated with mortality, particularly due to respiratory illness. The adjusted excess relative risk of respiratory mortality was 3.6% per 10 µg/m<sup>3</sup> BS and 13.2% per 10 ppb SO<sub>2</sub> in the period 1982-1998 compared with 19.3% per 10 µg/m<sup>3</sup> BS and 21.7% per 10 ppb SO<sub>2</sub> in the period 1994-1998. The investigators concluded that air pollution has long-term effects on mortality.

**Comment:** Yet another study showing that exposure to air pollution has long term effects increasing the risk of respiratory related mortality, even at what may be considered as relatively low levels. These findings underlie the importance of public health protection through regulation and control of air pollution.

<http://dx.doi.org/10.1136/thx.2006.076851>

**Reference:** *Thorax* 2007; 62:1088-94

Independent commentary by Professor Richard Beasley



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## Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate (GOAL study)

**Authors:** Pedersen SE et al

**Summary:** The Gaining Optimal Asthma control (GOAL) study randomised 3,416 patients with uncontrolled asthma to receive salmeterol/fluticasone propionate or fluticasone propionate for 1 year. This analysis examined factors affecting treatment response and assessed the clinical benefits of both treatments in patients with not well-controlled (NWC) asthma. Factors that significantly increased the likelihood of having NWC asthma in the GOAL study included smoking, male sex, history of ICS use and treatment with fluticasone propionate alone. Between 86% and 96% of patients with NWC asthma had improvements in at least 1 clinical outcome. In conclusion, long-term treatment with salmeterol/fluticasone propionate or fluticasone propionate alone is associated with clinical improvement in most patients. Smoking cessation is essential.

**Comment:** The most important finding from this study is that smoking has the greatest negative influence on patients achieving well-controlled asthma despite "optimal" therapy. Smoking asthmatics represent a high priority group for smoking cessation measures and if nicotine replacement therapy is unsuccessful a trial of bupropion, varenicline or nortriptyline is warranted

<http://dx.doi.org/10.1016/j.jaci.2007.07.016>

**Reference:** *J Allergy Clin Immunol* 2007; 120:1036-42

## Comparison of salmeterol/fluticasone propionate in Japanese and Caucasian asthmatics

**Authors:** Kawai M et al

**Summary:** This randomised, double-blind study compared the effects of ethnicity on response to salmeterol/fluticasone propionate in Japanese and Caucasian patients with asthma. 18 Japanese and 17 Caucasian patients (FEV<sub>1</sub> > 50% predicted; > 35% reversibility) received salmeterol 50 mcg twice daily and fluticasone propionate 250 mcg twice daily, either as a single inhaler combination (SFC) or concurrently (S+FP) for 2 weeks each in a crossover manner. Both regimens caused marked bronchodilation for 0 to 12 hours post-dose. There were no differences between the ethnic groups with regard to improvements in sGaw and FEV<sub>1</sub> with either SFC or S+FP over the 2-week treatment period. The investigators concluded that the therapeutic response to salmeterol and fluticasone propionate (either in combination or administered concurrently) was independent of ethnicity in Japanese and Caucasian patients with asthma.

**Comment:** Further studies of this kind are required due to the different pharmacological responses that have been identified to a range of pharmacological therapies in different ethnic groups.

<http://dx.doi.org/10.1016/j.rmed.2007.07.001>

**Reference:** *Respir Med* 2007; 101:2488-94

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## The Japanese Respiratory Society guidelines for the management of respiratory infections

**Comment:** These revised JRS guidelines for the management of CAP in adults have been published as a supplement in *Respirology*. It is informative to compare and contrast the Japanese guidelines with the British (*Thorax* 2001; 56 (Suppl IV) and American (*Clin Infect Dis* 2007; 44: S27-72) guidelines.

**Reference:** *Respirol* 2006; 11(Suppl 3):S79-S133

## Discrimination of exudative pleural effusions using biological markers

**Authors:** Daniil ZD et al

**Summary:** This study investigated the use of 7 biological markers (adenosine deaminase [ADA], interferon- $\gamma$ , C-reactive protein [CRP], carcinoembryonic antigen, interleukin-6, tumour necrosis factor- $\alpha$  and vascular endothelial growth factor) to discriminate between different pleural effusions. Concentrations of these markers were measured in pleural fluid from patients with malignant (n = 45), parapneumonic (n = 15) and tuberculous (n = 12) pleural effusions. The investigators found that it was possible to discriminate between the 3 groups of patients using the markers, particularly ADA and CRP. A patient with an ADA concentration > 45  $\mu\text{L}^{-1}$  and a CRP concentration < 4 mg/dL<sup>-1</sup> was more likely to have tuberculous pleural effusion, whereas an ADA concentration < 40  $\mu\text{L}^{-1}$  and a CRP concentration > 6 mg/dL<sup>-1</sup> was indicative of parapneumonic pleural effusion, and a CRP concentration < 4 mg/dL<sup>-1</sup> was indicative of malignant pleural effusion. It was concluded that ADA and CRP levels might be sufficient for discriminating between the 3 different types of exudative pleural effusion.

**Comment:** An informative study of the use of a number of biological markers to help determine the major cause of exudative pleural effusions. Although ADA and CRP have the greatest discriminative ability, the data do not exclude the usefulness of one or more of the other markers in certain circumstances.

<http://dx.doi.org/10.1183/09031936.00126306>

**Reference:** *Eur Respir J* 2007; 30:957-64

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## When should home mechanical ventilation be started in patients with different neuromuscular disorders?

**Authors:** Dreher M et al

**Summary:** This study investigated the use of home mechanical ventilation (HMV) in patients with a variety of neuromuscular disorders. 66 patients who started on HMV for symptomatic chronic hypercapnic respiratory failure over a 9-year period were included in the study. Thirty-one patients had rapidly progressive disease (19 had amyotrophic lateral sclerosis [ALS] and 12 had Duchenne muscular dystrophy [DMD]) and 35 patients had slowly progressive disease. At the start of HMV, forced vital capacity was > 50% predicted in 8 patients, and 40.3% predicted overall. Patients with ALS were more hypercapnic ( $p = 0.03$ ) and more hypoxaemic ( $p < 0.001$ ) than DMD patients at the start of HMV, but had better lung function ( $p = 0.005$ ). Maximal inspiratory mouth occlusion pressure was lower than international consensus guidelines (3.0 vs 5.88 kPa). Median survival was significantly longer in DMD patients (132 months) than in patients with slowly progressive diseases (82 months) or ALS (16 months). The investigators concluded that specific selection criteria are needed for the use of HMV in patients with neuromuscular disorders because the underlying neuromuscular disease has a major impact on outcome.

**Comment:** This study highlights the difficulty in deciding at what stage patients should receive NPPV for different neuromuscular disorders. Although the main neuromuscular disorders have different physiological parameters, require different ventilation settings and long term survival rates, the authors have been able to provide useful clinical guidelines.

<http://dx.doi.org/10.1111/j.1440-1843.2007.01116.x>

**Reference:** *Respirol* 2007; 12:749-53

## Lungs don't grow on trees: the ethics of increasing organ donation rates for transplantation and their relevance to the Asia-Pacific region

**Authors:** Westall GP & Snell GI

**Comment:** A timely editorial on the ethics of organ donation for transplantation. The issues discussed are thought-provoking and relevant to those involved in lung transplantation in the Asia-Pacific region.

**Reference:** *Respirol* 2007; 12:631-3

## Lung transplantation and survival in children with CF

**Authors:** Liou TG et al

**Summary:** This study examined data from the US Cystic Fibrosis Foundation Patient Registry and the Organ Procurement and Transplantation Network to identify factors affecting survival in children with cystic fibrosis undergoing lung transplantation. 248 of the 514 children with cystic fibrosis who were on the waiting list for lung transplantation in the period 1992 through 2002 received a lung transplant. Proportional-hazards survival modeling found that Burkholderia cepacia or Staphylococcus aureus infection decreased post-transplantation survival, as did older age. Diabetes decreased survival while on the waiting list but did not decrease post-transplantation survival. Only 5 children had a significant estimated benefit from lung transplantation whereas 315 had a significant risk of harm, 76 had an insignificant benefit and 118 had an insignificant risk of harm. In conclusion, prolongation of life should not be expected in children with cystic fibrosis undergoing lung transplantation.

**Comment:** These findings seriously question the benefits of lung transplantation for children with CF. The clinical and ethical implications are discussed in the editorial, which is worth reading (N Engl J Med 2007; 357: 2186-8).

<http://content.nejm.org/cgi/content/short/357/21/2143>

**Reference:** *N Engl J Med* 2007; 357:2143-52

## Clinical use of ibuprofen is associated with slower FEV1 decline in children with CF

**Authors:** Konstan MW et al

**Summary:** This observational study used data from the Cystic Fibrosis Foundation Patient Registry to examine the effects of ibuprofen on FEV1 decline in children and adolescents (aged 6 to 17 years) with cystic fibrosis. The rate of decline in lung function in 1,365 patients with FEV<sub>1</sub> > 60% predicted who received ibuprofen was compared with 8,960 untreated patients of similar age and disease severity. Ibuprofen recipients had a slower decline in lung function than untreated patients over a 2- to 7-year period ( $p < 0.0001$ ), but were more likely to require hospitalisation for gastrointestinal bleeding (annual incidence 0.37 vs 0.14%;  $p < 0.001$ ). The investigators considered that the apparent benefits of ibuprofen on lung function in patients with cystic fibrosis outweighed the small risk of gastrointestinal bleeding.

**Comment:** Evidence that the real world use of ibuprofen may be associated with a slower rate of lung function decline in children with mild to moderate CF lung disease. It is likely that these results will lead to an increase in the use of ibuprofen among patients with CF. However, note the increased risk of GI bleeding.

<http://dx.doi.org/10.1164/rccm.200702-181OC>

**Reference:** *Am J Respir Crit Care Med* 2007; 176:1084-9

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