

APSR Respiratory Research Review

Making Education Easy

Issue 12 - 2007

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Welcome. With this edition, APSR Respiratory Research Review has reached its first birthday!

We would like to thank you our readers, and of course our sponsors for all the support, encouragement and positive comments we've received over the past 12 months. We are looking forward to bringing you plenty more of the latest in clinical research during the next year.

A reminder that the APSR will hold its 12th Annual Congress (2nd Joint Congress of the APSR and ACCP) at the Gold Coast Convention and Exhibition Centre near Surfers Paradise, Queensland, Australia from 30 November to 4 December 2007. The programme will feature the latest developments in respiratory medicine, focusing on relevance to the Asia Pacific region. Put it in your diaries and register now!

We hope you enjoy the latest edition and welcome your feedback.

Prophylactic cranial irradiation in extensive small-cell lung cancer

Authors: Slotman B et al

Summary: This study assessed the effects of prophylactic cranial irradiation on prevention of brain metastases in patients with extensive small-cell lung cancer and a response to initial chemotherapy. 286 patients aged 18 to 75 years were randomised to either radiation or control. Follow-up CT or MRI scans were conducted following symptoms suggestive of brain metastases. The risk of symptomatic brain metastases was significantly reduced in the treatment group (HR 0.27; 95% CI 0.16 to 0.44; $p < 0.001$). At one year, the cumulative incidence of metastases was 14.6 and 40.4% in the irradiation and control groups respectively. Median disease-free survival was increased from 12 to 14.7 weeks with irradiation, and overall survival increased from 5.4 to 6.7 months. One year survival was 27.1 and 13.3% in the irradiation and control groups respectively. Although there were side effects associated with radiation treatment, there were no clinically significant effects on global health status.

Comment: The recommendations from this study are clear – prophylactic cranial irradiation should be part of standard care for all patients with small-cell lung cancer who had a response to initial chemotherapy and that it should be part of the standard treatment in future studies involving these patients.

<http://content.nejm.org/cgi/content/abstract/357/7/664>

Reference: *N Engl J Med* 2007; 357:664-72

Coming Educational Seminar of the APSR – ESAP

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Mobile radiographic screening for TB amongst drug users and homeless persons

Authors: de Vries G et al

Summary: The authors present data on trends and demographic and disease-related characteristics of cases of TB in Rotterdam between 1993 and 2005, and consider the impacts of a mobile radiographic screening unit introduced in 2002. A total of 206 cases of TB were identified amongst the study population, representing 11.4% of the total for the Rotterdam area. There was a decline in the annual number of cases identified, from 24 at the beginning of the programme, to 11 in 2005. Between 1997 and 2002, the strains of *Mycobacterium tuberculosis* identified in 80% of the infected study population were consistent with the strains already prevalent in these groups – suggesting recent transmission. (Recent transmission of TB was considered to have occurred if mycobacterial DNA fingerprints were identical to others occurring in the same risk group within the previous 2 years.) By 2005, the number of cases suggesting recent transmission had declined to 45%. The authors concluded that mobile screening programmes may be beneficial in these communities and that DNA fingerprinting may be a useful method of evaluating their success.

Comment: A novel approach to the difficult problem of identifying TB among illicit drug users and homeless persons. This approach could be adapted for use in similarly disadvantaged communities in other countries.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/2/201>

Reference: *Am J Respir Crit Care Med* 2007; 176:201-7

A nasal cannula can be used to treat obstructive sleep apnoea

Authors: McGinley BM et al

Summary: The use of nasal insufflation in subjects with obstructive sleep apnoea (OSA) was assessed in this open-label, non-comparative study. 11 subjects (mean age 47.9 years) with mild to severe OSA were given warm, humidified air at 20 L/minute through an open nasal cannula. The intervention significantly reduced the mean apnea-hypopnea index from 28 to 10 events per hour ($p < 0.01$). 8 of 11 subjects experienced less than 10 events per hour. Nasal insufflation was also associated with a significant decrease in the respiratory arousal index from 18 to 8 events per hour ($p < 0.01$). 4 of 11 subjects experienced less than 5 events per hour. Measurements of pharyngeal pressure and ventilation taken in a subset of subjects suggested the mechanism of action for these effects was related to an increase in end-expiratory pharyngeal pressure, which alleviated upper airway obstruction and improved ventilation.

Comment: A proof of concept study suggesting that a nasal cannula administering warm and humidified air at 20 L/minute is effective in the treatment of OSA. Importantly it was also well tolerated which may improve compliance compared with CPAP therapy. Further research is now urgently required to determine whether this approach may be a viable treatment alternative for OSA.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/2/194>

Reference: *Am J Respir Crit Care Med* 2007; 176:194-200

C-reactive protein, OSA and cognitive dysfunction in school-aged children

Authors: Gozal D et al

Summary: This study examined the systemic inflammatory response in children with obstructive sleep apnoea (OSA). 278 children aged 5 to 7 years underwent overnight polysomnography and neurocognitive testing and blood drawn the next morning to measure serum levels of high-sensitivity C-reactive protein (hsCRP). Mean hsCRP was significantly higher in children with OSA (0.36 ± 0.11 mg/dl) compared to snoring children without OSA (0.19 ± 0.07 mg/dl; $p < 0.01$). Significantly increased levels of hsCRP were also observed in children with OSA and cognitive deficits (0.48 ± 0.12 mg/dl) compared to those with OSA and normal cognitive scores (0.21 ± 0.08 mg/dl; $p < 0.002$). These results suggest that the systemic inflammatory response is increased in children with OSA, and that the level of the response is related to the risk of cognitive deficit.

Comment: An interesting study suggesting that the magnitude of the systemic inflammatory responses elicited by OSA is a major determinant of increased risk of neurocognitive dysfunction in children.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/2/188>

Reference: *Am J Respir Crit Care Med* 2007; 176:188-93



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Worldwide trends in the prevalence of asthma symptoms: International Study of Asthma and Allergies in Childhood (ISAAC) Phase III

Authors: Pearce N et al

Summary: This study reports the worldwide trends in the prevalence of asthma symptoms from Phase III of the ISAAC programme. The Phase I survey was repeated after an interval of 5 to 10 years in 106 centres in 56 countries in 13 to 14 year old children and in 66 centres in 37 countries in 6 to 7 year old children. The time trends in asthma symptom prevalence showed different regional patterns. There was a marked reduction in asthma symptom prevalence in English language countries; in contrast, an increase in asthma symptom prevalence occurred in other regions such as Latin America, Eastern Europe and Africa.

Comment: The key asthma paper from Phase III of the ISAAC programme showing that the prevalence of asthma has finally peaked and is now decreasing in many English-speaking countries and in Western Europe. While this trend is good news for Australia and New Zealand, the study also shows that the prevalence of asthma is now increasing in some parts of Asia. As a result, the burden of asthma in the Asia Pacific region is continuing to rise, although the regional differences are lessening.

<http://thorax.bmj.com/cgi/content/abstract/62/9/757>

Reference: *Thorax* 2007; 62:758-66

Traditional Chinese herbal remedies for asthma and food allergy

Authors: Li X-M

Summary: This review presents an update on the potential benefits of a number of Chinese herbal remedies for asthma and food allergies. The author comments that despite an increasing prevalence of these diseases, no curative therapies are yet available, and that in addition there are some concerns over the safety of commonly used treatments such as corticosteroids, particularly in children. An increasing interest from consumers with regard to alternative medicines (including traditional Chinese herbal remedies) has now extended into the healthcare sector. Scientific research into many of these therapies is being undertaken, and may lead to new therapies and improved outcomes for patients.

Comment: This review presents an important update on the most promising Chinese herbal remedies for asthma and food allergy. It is worth reading not only to have a better understanding of the evidence of their efficacy and safety to date, but also the issues relating to their use as alternatives or complementary medicines.

<http://www.sciencedirect.com>

Reference: *J Allergy Clin Immunol* 2007; 120:25-31

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Pneumothorax recurrence rates with video-assisted thoracoscopic surgery or open surgery

Authors: Barker A et al

Summary: The authors conducted a systematic review and meta-analysis to compare recurrence rates for pneumothorax in patients undergoing video-assisted thoracoscopic surgery compared with those having open surgery. 29 studies (4 randomised, 25 non-randomised) were included. Relative risk for recurrence with video-assisted surgery vs open surgery using the same pleurodesis method was 4.88 (95% CI 2.67 to 8.92) in non-randomised trials, 3.95 (95% CI 0.85 to 18.19) for randomised trials, and 4.73 (95% CI 2.69 to 8.29; $p < 0.01$) for both combined. Similar results were obtained using a random effects model (RR 4.73, 95% CI 2.69 to 8.29; $p < 0.01$), including only comparative studies (RR 3.99, 95% CI 2.58 to 6.16; $p < 0.01$), including only high quality studies (RR 4.01, 95% CI 1.84 to 8.73, $p < 0.01$), and on a simulation biased in favour of video-assisted surgery when there were no events in either group (RR 3.55, 95% CI 2.16 to 5.85; $p < 0.01$). The risk of recurrent pneumothorax is consistently around 4-times greater with video-assisted compared to open surgery.

Comment: This study needs to be read with the journal editorial [pp294-5] to put the findings in perspective, in particular consideration of the absolute risk, together with the relative risk of recurrence.

<http://lib.bioinfo.pl/pmid:17662881>

Reference: *Lancet* 2007; 370:329-35

Independent commentary by Professor Richard Beasley

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Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

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<http://www.apsresp.org/pdf/review-sponsorship.pdf>

Effect of 1-year treatment with roflumilast in severe COPD

Authors: Calverley PMA et al

Summary: This randomised, placebo-controlled, double-blind clinical trial assessed the effects of roflumilast on lung function and frequency of exacerbation over 1 year in patients with stable COPD. 1,513 patients (mean post-bronchodilator FEV₁ 41% predicted) were randomised to treatment with roflumilast (500 µg) or placebo once daily. Post-bronchodilator FEV₁ was significantly improved with roflumilast (39 ml; p = 0.001). There were no significant between-group differences in exacerbation rates (0.86 vs 0.92 for roflumilast and placebo respectively) or in the St. George's Respiratory Questionnaire total score. A retrospective analysis found a 36% decrease in exacerbation rate with roflumilast in patients with GOLD stage IV disease (1.01 vs. 1.59 with placebo; p = 0.024). Diarrhoea, nausea and headache were the most common adverse events associated with roflumilast treatment, and generally resolved over time. More subjects from the roflumilast group withdrew from the study during the first 3 to 4 weeks.

Comment: The clinical significance of these findings is difficult to determine. One interpretation is that this study suggests that if PDE4 inhibitors are to have a role in COPD, it would be limited to those patients with severe disease and frequent exacerbations.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/2/154>

Reference: *Am J Respir Crit Care Med* 2007; 176:154-61

Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine

Authors: Leroux-Roels I et al

Summary: This randomised controlled trial examined the safety and immunogenicity of a recombinant H5N1 split-virion vaccine formulated with a proprietary adjuvant system. Eight groups of 50 volunteers aged 18–60 years were administered 2 doses of an inactivated split A/Vietnam/1194/2004 NIBRG-14 (recombinant H5N1 engineered by reverse genetics) vaccine, 21 days apart. Each of 4 antigen doses (3.8, 7.5, 15 and 30 µg haemagglutinin) were tested with and without adjuvant. More adverse events were recorded with the adjuvanted vaccines, but most were mild-to-moderate and transient. No serious adverse events occurred. Significantly greater immunogenicity was observed with the adjuvanted vaccines at all dose levels, and immune responses exceeded FDA and EU licensure requirements even at the lowest dose of adjuvanted vaccine. 77% of those who received 3.8 µg of the adjuvanted vaccine seroconverted for neutralising antibodies against a strain derived by reverse genetics from a drifted H5N1 isolate (A/Indonesia/5/2005, clade 2).

Comment: Worthwhile reading to get an update on prototype influenza vaccines and to understand the concept of adjuvantation to increase the immune response and allow for an increase in the production capacity of the influenza vaccine during a pandemic. The cross-clade neutralising antibody responses recorded imply that such a vaccine could be deployed before a pandemic outbreak which is an important mitigation strategy.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673607612975/abstract>

Reference: *Lancet* 2007; 370:580-9

Nebulized denufosal tetrasodium in cystic fibrosis

Authors: Deterding RR et al

Summary: This randomised, placebo-controlled, double-blind phase II trial assessed the safety and efficacy of 28 days of inhaled denufosal tetrasodium (20, 40 or 60 mg once daily) in 89 patients with mild cystic fibrosis. (This novel agent is a selective P2Y₂ agonist. It enhances mucosal hydration and mucus clearance by activating Cl⁻ secretion and inhibiting epithelial Na⁺ transport through a non-cystic fibrosis trans-membrane conductance regulator mechanism in the lung.) A pooled analysis of all three doses found patients receiving denufosal had significantly greater changes in respiratory parameters including FEV₁ (p = 0.006), FEF_{25%-75%} (p = 0.008), FVC (p = 0.022), and FEV₁/FVC (p = 0.047). Denufosal tetrasodium was generally well tolerated, and there was no evidence of any dose-response relationships with regard to adverse events. The most common adverse event (cough) was observed in 47 and 52% of denufosal and placebo patients respectively. Discontinuation rates for denufosal were similar to those with placebo.

Comment: A novel therapeutic approach for the treatment of cystic fibrosis. The use of P2Y₂ agonists to improve mechanisms of mucus clearance in CF holds promise as it targets the primary "root cause" of the disease, with the ultimate goal of initiating therapy very early in life to prevent or slow the initial pathobiology of CF airways disease.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/4/362>

Reference: *Am J Respir Crit Care Med* 2007; 176:362-9

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