

# APSR Respiratory Research Review

Making Education Easy

Issue 5 - 2007

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**Welcome** to the latest edition of APSR's Respiratory Research Review. I would like to convey my thanks to everyone who has responded to me personally about the Review and to the APSR committee for their support of this initiative. We are always delighted to receive feedback so let me know if you have a suggestion and please share the Review with colleagues.

This edition features some interesting work on improving adherence to tuberculosis treatment in a resource-poor setting, a familiar circumstance for many working in the region. Also included is a study on the effect of prophylaxis for TB in children with HIV – a potentially effective public health intervention for areas with high HIV and TB infection rates.

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

Kind regards,

**Richard Beasley**

Chair, Education Committee, APSR

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## Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma

**Authors:** The American Lung Association Asthma Clinical Research Centers

**Summary:** This double-blind study randomised 489 patients with poorly controlled asthma to receive either placebo, theophylline (300 mg/d), or montelukast (10 mg/d) in addition to existing medications for 24 weeks, during which episodes of poor asthma control (EPACs) were recorded. These included decreased peak flow, increased  $\beta$ -agonist use, increased oral corticosteroid use, or unplanned consultations/admissions. Whilst both active therapies caused small improvements in FEV1 prior to bronchodilator use, neither theophylline or montelukast had any effect on EPAC rates compared to placebo (95% CI) nor did patient symptoms improve in response to the additional treatment in either group. Only patients not treated with inhaled corticosteroids benefited from added low-dose theophylline ( $p < 0.002$ ) in their management. The authors concluded that theophylline is worth considering as a reasonable alternative for patients not receiving inhaled corticosteroids.

**Comment:** A case is made for the use of low-dose theophylline in patients who cannot or will not use ICS – montelukast does not appear to be a cost-effective option. Perhaps the most intriguing finding of this study is the low compliance rate – 40% of subjects in the montelukast and theophylline groups had no detectable blood levels of their drug by the end of the study. Measures to improve compliance remain a neglected issue in long-term asthma management – innovative strategies urgently need to be developed.

<http://ajrccm.atsjournals.org/cgi/content/abstract/175/3/235>

**Reference:** *Am J Respir Crit Care Med* 2007; 175: 235-242



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## Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study

**Authors:** Gauderman WJ et al

**Summary:** Does how close a child lives to local traffic affect his or her lung development? A question addressed in a prospective study of 3677 southern Californian children, followed up for 8 years with a mean initial age of 10. Lung function was measured annually and regression analysis used to determine if the growth in lung function over this 8 year period was linked to the child's exposure to traffic from large roads and if these effects were associated with the level of local air pollution. Results showed children living within 500m of a motorway had both significantly poorer development of lung-function over these 8 years with forced expiratory volume in 1 s (FEV<sub>1</sub>, -81 ml, p=0.01) and maximum mid-expiratory flow rate (MMEF, -127 ml/s, p=0.03) and attained lung function at 18 years (mean percent-predicted 97.0% for FEV<sub>1</sub>; p=0.013 and 93.4% for MMEF; p=0.006), compared with children who lived at least 1500m away (95% confidence levels). Inferior air quality also had a negative impact on lung growth independent of that caused by traffic exposure.

**Comment:** The public health relevance of their findings is that the current emphasis on regional air quality might need to be modified to consider local variations in air pollution. In many urban areas population growth is forcing the construction of housing and schools close to busy roads – as a result, many children live and attend school in close proximity to a major source of air pollution.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673607600373/abstract?isEOP=true>

**Reference: Lancet 2007; 369: 571-577**

## A five-gene signature and clinical outcome in non-small-cell lung cancer

**Authors:** Chen H-Y et al

**Summary:** The authors randomly assigned 185 specimens for one or both of microarray analysis and real-time reverse-transcriptase polymerase chain reaction (RT-PCR) analysis. The association between level of gene expression and survival was evaluated in 125 randomly selected patients who had experienced surgical resection of non-small cell lung cancer. The authors develop a gene-expression model to predict results of this surgical intervention. Another 60 patient samples were randomly assigned to validate results. 16 genes were identified which were associated with survival and the authors selected 5 genes (DUSP6, MMD, STAT1, ERBB3, and LCK) for further analysis. This combination of five genes was confirmed as a predictor of relapse-free and overall survival.

**Comment:** A landmark study on the use of genetic profiling to predict clinical outcome in NSCLC. It is likely that genetic status may soon become established in clinical practice, not just to stratify patients with lung cancer according to risk, but also to identify preferred therapeutic approaches.

<http://content.nejm.org/cgi/content/abstract/356/1/11>

**Reference: N Engl J Med 2007; 356: 11-20**

## Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting

**Authors:** Thiam S et al

**Summary:** A strategy aimed at improving patient compliance in the treatment of tuberculosis (TB) in third-world countries was implemented in a study carried out between June 2003 and January 2005 in Senegal. 1522 newly diagnosed TB patients, over the age of 15 were randomised to receive either the existing program (control group) or the new strategy which included better communication with medical staff, local treatment, choice of a directly observed therapy (DOT) supporter by the patient and closer following of patients (intervention group). Effectiveness was measured by the proportion of patients who completed the 8 months of therapy and the proportion who failed to comply. More patients participating in the intervention group were successful in their treatment (88% compared with 76% of the control group) and fewer failed to stay the course of therapy (5.5% compared with 16.8%), supporting the use of the intervention strategy over the established regimen. The authors suggest these methods could be applied to other treatment areas in similar countries.

**Comment:** A model to be considered in similar resource-poor populations in the Asia-Pacific region. While the success of this strategy undoubtedly related to the multi-targeted approach, the observation that the choice of a DOT supporter from among the patient's family members was a key component, is worthy of note.

<http://jama.ama-assn.org/cgi/content/abstract/297/4/380>

**Reference: JAMA 2007; 297: 380-386**

*Independent commentary by Professor Richard Beasley*

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## A prospective long-term study of 220 patients with a retrievable vena cava filter for secondary prevention of venous thromboembolism

**Authors:** Mismetti P et al

**Summary:** This prospective, single-centre study enrolled 220 consecutive patients, 98.6% of whom were successfully implanted with ALN filters (ALN Implants Chirurgicaux; Ghisonaccia, France) between April 1999 and June 2005 and 67.3% of patients completed the 18-month follow up course. Filters remained in situ for a median of 166 days, with retrieval being required in a quarter of all of patients between 6 and 352 days (median 51) post insertion. This was successful in nearly all cases at the first attempt (92.7%). Adverse clinical events involved complications in 11.8% of cases immediately following surgery and 37 out of 217 patients (17%) experiencing one or more episodes of venous thromboembolism. Given their ease of use, safety and success in preventing embolic events, it is suggested that there is merit in assessing these filters more fully.

**Comment:** An informative case-series of the ALN retrievable IVC filter. The challenge is to determine how long to keep the filter in – long enough to prevent PE during high-risk periods but removed before the benefit is counter-balanced by the increased risk of recurrent DVT. See Decousus H et al, NEJM 1998; 338: 409-415. <http://www.chestjournal.org/cgi/content/abstract/131/1/223>

**Reference:** *Chest* 2007; 131: 223-229

## Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial

**Authors:** Taylor AL et al

**Summary:** This study was designed to investigate if the use of early probiotic supplements can prevent development of allergic disease in infants identified as high-risk. 231 newborns, with mothers with allergy, received lactobacillus acidophilus (LAVRI-A1) or placebo each day for six months. They were then examined for atopic dermatitis (AD) and other allergy symptoms at 6 and 12 months and received skin prick tests (SPT) after 12 months. After 6 months, rates of AD were similar in both groups (probiotic, 25.8%; placebo, 22.7%;  $p=0.629$ ), at 12 month there was no difference. Interestingly, rates of sensitisation at 12 months was significantly higher in the probiotic group ( $P=.030$ ). There appeared to be no associated risk of AD development or sensitization relative to presence of culturable Lactobacilli or Bifidobacterium in stools in the first month. There was an increased risk of cow's milk sensitization ( $P=.012$ ) at 6 months with Lactobacillus present. The authors concluded there was no risk reduction of allergen sensitization associated with early probiotic supplementation.

**Comment:** An important negative study of probiotic supplementation in infancy to reduce the risk of atopic disease. While the jury is still out on this issue, their findings of an increased risk of sensitisation with probiotics would suggest that a trial of probiotics cannot be recommended for "allergy prevention" in high-risk infants at this stage.

<http://www.jacionline.org/article/PIIS0091674906017982/abstract>

**Reference:** *J Allergy Clin Immunol* 2007; 119: 184-191

## Spacer inhalation technique and deposition of extrafine aerosol in asthmatic children

**Authors:** Roller CM et al

**Summary:** This study was developed to identify differences in deposition of inhaled corticosteroid in the airways associated with different breathing techniques. 24 children (5-17 yrs) with mild asthma took ICS via a metered-dose inhaler from a spacer. The children were divided into two groups – one taking five tidal breathes following each actuation, the other using slow maximal inhalation with a 5-10 second breath hold. Researchers noted results of anterior and posterior planar  $\gamma$ -scintigraphic scans (120-s acquisition). Results grouped patients according to age (5-7;  $n=4$ , 8-10;  $n=4$  and 11-17;  $n=4$ ). Lung deposition in each group was higher for the breath hold technique and more marked in younger age groups. ( $58.1 \pm 6.7$  vs  $35.4 \pm 18.3$ ;  $56.6 \pm 5.2$  vs  $47.5 \pm 13.0$ ;  $58.4 \pm 9.2$  vs  $54.9 \pm 11.2$ ). Both techniques also showed oropharyngeal and gastrointestinal deposition reduction when compared to a previous study in children using the same ICS inhaled via a breath-activated device.

**Comment:** Spacer inhalation technique in children – tidal breathing is OK, but the slow single maximum inhalation with a 5-10 second breath held results in greater drug delivery. The practical recommendation from the authors is that for children with asthma >5 years should be trained in the maximum deep breath technique, and children between 2 and 5 years the tidal breathing pattern.

<http://erj.ersjournals.com/cgi/content/abstract/29/2/299>

**Reference:** *Eur Respir J* 2007; 29: 299-306



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## Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids

**Authors:** Williams LK et al

**Summary:** This study investigated adherence to ICS therapy based on different racial groupings and calculated ICS adherence according to filled-prescription and dosage data. Predictive variables were recorded and included some environmental issues previously associated with asthma mortality – age, sex, ethnicity, socioeconomic status (SES), average ICS copay, comorbidities, and locality crime rate. Of the 176 patients investigated ICS adherence was lower in the African American subjects than in white patients (n = 75 vs 94; 40% vs 58%, respectively; P =0.002). White women were less adherent than white men. For African American patients, younger patients were more adherent and those in areas with higher crime rates were less adherent. Even after making adjustments for a variety of SES factors, areas with higher crime rates continued to be a predictor of adherence in African Americans. The authors concluded that a better appreciation and understanding of a patient's environmental stresses may help improve adherence.

**Comment:** Interesting study which is likely to be relevant to disadvantaged ethnic minorities within the Asia-Pacific region. Adding to the known predictors of poor compliance, such as socioeconomic and psychosocial factors, ethnicity and co-morbidity, it is now evident that stresses in the form of exposure to crime plays an important role. These findings reinforce the importance of strong social and community support for disadvantaged communities.

<http://www.jacionline.org/article/PIIS0091674906020045/abstract>

**Reference:** *J Clin Allergy Immunol* 2007; 119: 168-175

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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.

## Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial

**Authors:** Sorkness CA et al

**Summary:** This study drew a comparison of three different regimens for achieving asthma control in children (6-14yrs) with mild to moderate persistent asthma. The regimens were: fluticasone 100 µg twice daily (FP monotherapy); fluticasone 100 µg/salmeterol 50 µg in the morning and salmeterol 50 µg in the evening (combination); and montelukast 5 mg in the evening. Investigators recorded FEV1/FVC, bronchodilator response, exhaled nitric oxide, PC20 and asthma control days. FP monotherapy provided more asthma control days than montelukast (64.2% vs 52.5%; P =0.004) and showed superior improvements in all other measures. Combination also provided more asthma control days than montelukast. FP monotherapy improved other dimensions of asthma control when compared with Combination. The authors concluded FP monotherapy was the preferred paediatric treatment for mild-moderate persistent asthma with FEV1 ≥ 80% predicted, a result consistent with current international guidelines.

**Comment:** Convincing evidence of the superior efficacy of ICS compared with LTRA therapy in the treatment of childhood asthma. It is difficult to interpret the comparison of the ICS versus ICS/LABA combination regime, due to the different baseline ICS doses administered. Regardless, this study reinforces the important role of ICS in the long-term treatment of childhood asthma.

<http://www.jacionline.org/article/PIIS0091674906021221/abstract>

**Reference:** *J Clin Allergy Immunol* 2006; 119: 64-72

## Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial

**Authors:** Zar HJ et al

**Summary:** This study measured the impact of isoniazid prophylaxis on deaths and the incidence of tuberculosis in children with HIV. 263 young children (median 24.7 mths) provided data that led to the safety monitoring board's recommendation to stop the placebo arm of the study. Mortality was less in the isoniazid arm (n=132) than the placebo arm (11 (8%) vs 21 (16%), HR 0.46, 95% confidence interval 0.22 to 0.95, P=0.015). This benefit was seen in all clinical categories and ages and was similar regardless of dosing (3 x a week or daily). Tuberculosis incidence was also reduced in the isoniazid group (5 cases vs 13 cases for placebo; HR 0.28, 0.10 to 0.78, P=0.005) and all cases confirmed by culture were in children from the placebo group. The authors concluded prophylaxis with isoniazid could be an effective public health intervention as it provided survival benefits and reduced tuberculosis incidence in children with HIV.

**Comment:** Although this study was undertaken in South Africa, the results are likely to be applicable to populations in the Asia-Pacific region, in which there is a high prevalence of both TB and HIV.

<http://www.bmj.com/cgi/content/abstract/334/7585/136>

**Reference:** *BMJ* 2007; 334: 136

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