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REVIEW

Asthma year in review 2006–7

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Summary This review focuses on papers published between September 2006 and September 2007 that either answer important clinical questions, or signpost important areas for future research.

FETAL LUNG HEALTH

Concern that children with lower lung function are at increased risk of developing chronic obstructive pulmonary disease in adulthood[1] has focused attention on the long-term effects of low lung function in infancy. The study by Håland *et al.*,[2] from the Oslo Research Group for Asthma and Allergy in Childhood, provides tantalising evidence that very early changes in lung function are clinically important. The researchers measured the fraction of expiratory time to peak tidal expiratory flow to total expiratory time (t_{PTEF}/T_E) in 802 infants during the first weeks of life. The advantage of t_{PTEF}/T_E is that it can be obtained from spontaneously breathing, awake infants. Its drawback is that airway size, lung and chest wall mechanics, and respiratory control may all affect this variable. Study infants were followed-up prospectively for 10 years, at which time the development of asthma was assessed in just over three-quarters of the original group. Looking back, the researchers found that a reduced value for t_{PTEF}/T_E at birth was a significant risk factor for current asthma, suggesting that small decrements in lung development *in utero* are clinically significant. If lower levels of t_{PTEF}/T_E are due to reversible intra-uterine environmental factors, it may therefore be possible to optimise fetal lung health by therapeutic interventions in pregnant women.

VITAMIN D AND PRESCHOOL WHEEZE

The role of vitamin D in respiratory disease has been a source of interest for some time. For example, the association between the winter dip in vitamin D and peaks for epidemic influenza has led to the hypothesis that vitamin D protects against viral respiratory infections.[3] In an epidemiological study, Camargo *et al.*[4] tested the hypothesis that high maternal vitamin D intake protects children against wheeze in the preschool period. This prospective study looked at 1194 mother–child pairs, and assessed vitamin D intake in mothers in the first and second trimester, and in infants at 6 and 12 months, using a validated food frequency questionnaire. The primary outcome was a diagnosis of recurrent wheeze at 3 years of age. A significant reduction in this outcome (odds ratio 0.45) was found in children of mothers who had high vitamin D intakes (cutoff 400 IU/day), compared with mothers and infants with low intakes. However, high intake of vitamin D in infants (cutoff 200 IU/day) perse was not associated with decreased risk of recurrent wheeze. This study therefore suggests that the beneficial effect of vitamin D is acting on the fetus. However, the study does not prove a causal association. In The Netherlands, Dijkstra *et al.*[5] found that 63% of pregnant women who were dark skinned or who wore veiled clothing were vitamin D deficient. Furthermore, 16% of low-risk pregnant women had low levels of vitamin D. If translated to the UK population, this would represent over 100 000 infants/year exposed to low vitamin D levels *in*

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utero (http://www.statistics.gov.uk/cci/nugget.asp?id=369). With this high prevalence of low maternal vitamin D, it may be feasible to test the causal link between vitamin D and preschool wheeze in a randomised controlled trial (RCT) where maternal vitamin D is optimised in the treatment arm, and control mothers receive oral placebo and usual care.

INHALED STEROIDS AND PRESCHOOL WHEEZE

The evidence base to guide treatment of preschool wheeze remains weak. Indeed, the 2007 US Asthma Guideline Expert Committee commented that 'treatment for young children who have asthma has not been studied adequately. Most recommendations for treatment are based on limited data and extrapolations from studies in older children and adults' (http://www.nhlbi.nih.gov/guidelines/asthma/08_sec4_lt_0-11.pdf). It is encouraging, therefore, that two high-quality RCTs were published last year that address the hypothesis that inhaled steroids, started in young children before they would normally be justified by clinical symptoms alone, prevent the development of troublesome asthma. First, Guilbert *et al.*[6] tested whether daily inhaled fluticasone (FP 88 μg), given for 2 years to preschool wheezers (mean 3 years) at high risk for the development of atopic asthma at school age, reduces wheezing in the 12 months after cessation of treatment (i.e. the third study year). Second, in a group of younger children (mean 10 months), Bisgaard *et al.*[7] assessed the effect of inhaled budesonide (400 μg/day), started each time children developed an attack of wheeze. During the 3-year trial period, budesonide or placebo was started 3 days into each attack of wheeze, and continued for 2 weeks. The primary outcome of the study by Guilbert *et al.*[6] was the number of episode-free days in the follow-up year, whereas Bisgaard *et al.*[7] assessed the development of persistent wheeze. Both trials were convincingly negative. FP had no effect on the severity of wheeze in the follow-up year, and short-burst budesonide had no effect on the proportion of children developing recurrent wheeze. These trials also provide information on the short-term efficacy of inhaled steroids. Intermittent budesonide had no effect on any short-term measure of wheeze severity. In contrast, FP treatment was associated with less bronchodilator use during the 2-year active treatment period (14 vs 10 days/year; FP vs placebo), and less use of oral montelukast (mean 11 vs 24 days/year). These secondary outcome data of the FP trial should be interpreted with caution. First, the clinical relevance of short-term outcomes was not defined *a priori*. Second, there was no difference between FP and placebo for unscheduled physician visits or hospitalisations. Thus, the beneficial short-term effects of FP may be modest, possibly trivial. A meta-analysis of the studies of short-term effects of FP in children with preschool wheeze with careful consideration of phenotype (see below) may now be possible.

INTERMITTENT TREATMENT FOR INTERMITTENT WHEEZE

Future asthma therapies are likely to be guided by consideration of both disease severity and symptom pattern (asthma phenotype). A classic example where consideration of phenotype may be helpful in targeting therapy is preschool wheeze. In contrast to most school-age asthmatics, the majority of wheezy preschool children do not have classical atopic asthma, with its propensity to interval symptoms and chronic eosinophilic airway inflammation. Rather, they have discrete viral-triggered attacks with no evidence of chronic airway inflammation between episodes. The standard approach to a preschool child with frequent severe viral-triggered attacks (e.g. requiring repeated hospital admissions), but no interval symptoms, is to step up regular asthma therapy. In contrast, a phenotypic approach suggests that intermittent treatment may be more effective. Intermittent treatment was tested by Robertson *et al.*,[8] who assessed the efficacy of a short course of montelukast in children with intermittent asthma. Children with intermittent asthma ($n = 220$) aged 2–14 years were randomised to receive a short course of oral montelukast or placebo, started at the first sign of every cold, and continued until the wheeze resolved (for a minimum of 7 days). The study found that intermittent montelukast resulted in fewer unscheduled health resource utilisations (primary outcome) over the 12-month trial period compared with placebo (Table 1). However, for the individual child, the beneficial effects of montelukast do not appear particularly impressive (the authors describe them as 'modest'). More information on the efficacy of intermittent therapy in a well-defined group of preschool wheezers will be provided by an ongoing RCT, where

Table 1 Absolute number of health resource utilisations for asthma during all treated episodes in the study of Robertson *et al.*[8]

	Montelukast $n = 97$	Placebo $n = 105$	Odds ratio (95% CI)
Total episodes treated, *n*	345	336	
GP visits	114	139	0.70 (0.50–0.95)
Specialist visits	14	21	0.63 (0.32–1.27)
Emergency department	25	46	0.48 (0.29–0.82)
Hospital admission	10	13	0.74 (0.32–1.71)

CI, confidence interval.
Treatment was either intermittent oral montelukast started at the first sign of a cold, or placebo. A beneficial effect of intermittent montelukast is most pronounced for general practitioner (GP) and emergency department attendances.