

Do allergens play a role in early childhood asthma?

Andrew S Kemp

THE RELATIONSHIP between allergen sensitisation and childhood asthma is complex and controversial. Opinions range from the belief that allergen exposure is the principal cause of asthma (a view prominent in the United States and favoured by many allergists) to the belief that allergen sensitisation is an epiphenomenon that reflects the atopic diathesis, but has little to do with induction of the disease or exacerbation of symptoms (a view common among physicians in the United Kingdom and Australasia and favoured by many respiratory physicians).

However, even the proponents of the view that allergen sensitisation is a principal cause of asthma have doubts. Perhaps no one has done more to investigate house-dust mite (HDM) sensitisation as a cause of asthma than Platts-Mills, who recently concluded: "Theories about the causes of the increase in asthma have focused on two scenarios: (a) that changes in houses, combined with increased time spent indoors, have increased exposure to relevant allergens; or (b) that changes in diet, antibiotic use, immunizations, and the pattern of infections in childhood have led to a change in immune responsiveness, such that a larger section of the population makes T_H2 rather than T_H1 responses, including IgE antibodies to inhaled allergens. What is clear is that current theories do not provide either an adequate explanation of the increase or a practical approach to reversing the current trend."¹

I define "early childhood asthma" as asthma occurring in the first five years of life. There are two important questions to consider when reviewing a possible role for allergens in early childhood asthma: (a) Do allergens play a significant role in induction of the disease; and (b) Do allergens play a significant role in triggering symptoms in established disease?

What is the evidence for these propositions?

The prevalence of asthma is related to the degree of allergic sensitisation

In a New Zealand study, 41% of children sensitised to one allergen had asthma symptoms, compared with 96% of children sensitised to six allergens.² However, such a finding does not necessarily establish that allergens are responsible for either the induction or triggering of asthma symptoms. An alternative and equally plausible interpretation is that the propensity to develop allergic sensitisation (ie, the degree of

ABSTRACT

What we know

- Sensitisation to indoor allergens (house-dust mite, cat) is related to the level of exposure to these allergens in early childhood.
- The prevalence of asthma in childhood is independent of allergen exposure in early life.
- Asthma occurs in a substantial number of young children in the absence of allergen sensitisation.
- Asthma and allergic sensitisation have increased in recent decades, but there is no conclusive evidence that this is due to changes in environmental allergens.

What we need to know

- Have changes in environmental allergens contributed to the increasing incidence of asthma in recent decades?
- Is early childhood asthma (or certain subtypes of asthma) an allergen-induced disease?
- Is it possible to modify asthma by environmental allergen manipulation in early childhood?
- Is it possible to modulate the immune response to allergens in a favourable direction in early childhood?

MJA 2002; 177: S52-S54

atopy) is a reflection of the underlying inflammatory imbalances that also lead to airway inflammation resulting in asthma.

Sensitisation to indoor allergens (HDM, cat) is related to the level of exposure in early childhood

The risk of sensitisation to indoor allergens by three years of age is lower in homes with low (\leq 25th percentile) allergen concentrations (risk: 1.6% [HDM], 2.0% [cat]) than in homes with high (\geq 75th percentile) allergen concentrations (risk: 6.5% [HDM], 6.3% [cat]).³

Asthma prevalence in childhood is independent of allergen exposure in early life

Lau et al followed up 939 children from birth to seven years. Although sensitisation to indoor allergens was associated with the environmental allergen concentration, there was no temporal or dose relation between asthma development and allergen exposure. They concluded that "Our data do not support the hypothesis that exposure to environmental allergens causes asthma in childhood, but rather that the induction of specific IgE responses and the development of childhood asthma are determined by independent factors".⁴

Department of Immunology, Royal Children's Hospital, Parkville, VIC.

Andrew S Kemp, PhD, FRACP, Head.

Correspondence: Professor Andrew S Kemp, Department of Immunology, Royal Children's Hospital, Flemington Road, Parkville, VIC 3052.
kempa@cryptic.rch.unimelb.edu.au

Asthma occurs in a substantial number of young children in the absence of allergen sensitisation

A considerable proportion of early childhood asthma is not associated with allergen sensitisation. In a prospective US study, 49% of children with persistent wheezing at age six did not react to any common allergens on skin-prick testing.⁵ If allergens do play a role in such cases, it must be by mechanisms other than IgE sensitisation.

Attempts to reduce the level of indoor allergens do not appear to alter the development or symptoms of childhood asthma

A study on the effect of allergen avoidance (principally HDM) in early life, with follow-up to four years of age, showed no difference in the prevalence of asthma at age two or four years⁶ between the low-allergen group and controls. In another study, stringent efforts to maintain a low-allergen environment from birth did not significantly affect the incidence of wheeze by one year of age in high-risk infants.⁷ These studies suggest that allergen reduction does not affect the primary development and symptoms of early childhood asthma.

To consider the effect of allergens as triggers in established asthma in early life, it is necessary to extrapolate from findings in older children. However, it has also been difficult to establish whether environmental allergens are a major trigger of asthma in older children. A meta-analysis of 23 studies concluded that attempts at reducing exposure to HDM allergens appeared to be ineffective in reducing asthma symptoms.⁸ Although the specifics of the individual trials may be disputed, the fact remains that it is extraordinarily difficult to demonstrate that allergen reduction alters the symptoms or natural history of childhood asthma. This may be because allergen levels in a specific environment (eg, HDM in bedding) are reduced but not eliminated and the reduction may not be sufficient to alter any allergen-induced symptoms. Alternatively, allergens may not be a trigger in most asthma attacks in childhood.

Modulation of the immune response to allergens in older children has inconsistent results

Immunotherapy has not been shown to be of benefit in early childhood asthma. In a double-blind, placebo-controlled trial of multiple-allergen immunotherapy in allergic children (mean age, nine years) with moderate to severe perennial asthma,⁹ 77% of children received immunotherapy containing HDM allergens for over two years. There was no discernible reduction in perennial asthma. Nevertheless, attempts to modulate the immune response to allergens should not yet be discarded. In a recent meta-analysis of 24 studies, immunotherapy was judged to be effective in 17 (71%) of the studies.¹⁰ The benefit of immunotherapy relates principally to grass-pollen-induced asthma. However, this is unlikely to be relevant to early childhood asthma, as grass pollen sensitisation develops later in childhood.

Asthma and allergic sensitisation have increased in recent decades, but there is no evidence that this is due to changes in environmental allergens

Between 1992 and 1997, the relative prevalence of asthma in Australian children aged 8–11 years increased by 26% and skin-prick sensitivity to HDM increased by 63%.¹¹ Peat¹² has estimated that halving the levels of HDM exposure would prevent asthma in only 6% of the childhood population. If increased HDM exposure were largely responsible for the increased prevalence of asthma, it might be inferred that there must have been a marked increase in HDM allergens in the environment. Yet there is no evidence of such an increase in the past two decades.

The relationship between infections in early life and asthma and allergic sensitisation is unclear

The protective effect of larger family size on the development of atopy has been observed in many studies. It has been postulated that this is due to an increased incidence of common respiratory virus infections, resulting in an increased T_H1 stimulus in early life.

Two studies have prospectively examined the effect of respiratory tract viral infection in early childhood. An Australian study showed that having an upper respiratory tract infection in the first six weeks of life was associated with increased risk of asthma at age seven.¹³ In contrast, a German study demonstrated that having more than one respiratory virus infection in the first year of life conferred a protective effect on the development of asthma up to the age of seven years.¹⁴ A concern of the German study may have been an under-reporting of respiratory tract infections. Forty-four per cent of children in the study were reported to have had four or fewer episodes of viral infection in the first three years of life, whereas prospective studies have shown that normal infants experience an average of 7–8 upper respiratory tract infections in the first year.¹⁵

Further analysis of the Australian data¹³ showed that having an upper respiratory tract infection by one month after birth was associated with a fivefold increased risk of sensitisation to rye allergen for children born in the pollen season (unpublished data). Thus, respiratory infections in early life may promote allergen sensitisation, depending on the timing of the infection relative to allergen exposure.

Conclusions

If allergens played a significant role in triggering early childhood asthma, we might expect that environmental manipulation (decreasing allergen load) or modulation of the immune response by immunotherapy would be worthwhile. At the present time, there is no proof that the use of such measures for treating asthma in early childhood is beneficial. Furthermore, the available evidence suggests that allergen avoidance does not significantly reduce the development of asthma, but the results of further prospective studies of allergen avoidance in early life may shed more light on the subject.

References

1. Platts-Mills TA, Carter MC, Heymann PW. Specific and nonspecific obstructive lung disease in childhood: causes of changes in the prevalence of asthma. *Environ Health Perspect* 2000; 108(Suppl 4): 725-731.
2. Sears MR, Herbison GP, Holdaway MD, et al. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989; 19: 419-424.
3. Wahn U, Lau S, Bergmann R, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99: 763-769.
4. Lau S, Illi S, Sommerfeld C, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; 356: 1392-1397.
5. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133-138.
6. Hide DW, Matthews S, Tariq S, Arshad SH. Allergy allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996; 51: 89-93.
7. Custovic A, Simpson BM, Simpson A, et al. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001; 358: 188-193.
8. Gotzsche PC, Hammarquist C, Burr M. House dust mite control measures in the management of asthma: meta-analysis. *BMJ* 1998; 317: 1105-1110.
9. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997; 336: 324-331.
10. Caffarelli C, Sensi LG, Ross RN, et al. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther* 2000; 22: 329-341.
11. Downs SH, Marks GB, Sporik R, et al. Continued increase in the prevalence of asthma and atopy. *Arch Dis Child* 2001; 84: 20-23.
12. Peat JK. Can asthma be prevented? Evidence from epidemiological studies of children in Australia and New Zealand in the last decade. *Clin Exp Allergy* 1998; 28: 261-265.
13. Ponsonby AL, Couper D, Dwyer T, et al. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. *Thorax* 1999; 54: 664-669.
14. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001; 322: 390-395.
15. Bosken CH, Hunt WC, Lambert WE, Samet JM. A parental history of asthma is a risk factor for wheezing and non-wheezing respiratory illnesses in infants younger than 18 months of age. *Am J Respir Crit Care Med* 2000; 161: 1810-1815. □