The Australasian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children

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ABSTRACT

- A family history of allergy and asthma identifies children at high risk of allergic disease.
- Dietary restrictions in pregnancy are not recommended.
- Avoiding inhalant allergens during pregnancy has not been shown to reduce allergic disease, and is not recommended.
- Breastfeeding should be recommended because of other beneficial effects, but if breast feeding is not possible, a hydrolysed formula is recommended (rather than conventional cow's milk formulas) in high-risk infants only.
- Maternal dietary restrictions during breastfeeding are not recommended.
- Soy formulas and other formulas (eg, goat's milk) are not recommended for reducing food allergy risk.
- Complementary foods (including normal cow's milk formulas) should be delayed until a child is aged at least 4–6 months, but a preventive effect from this measure has only been demonstrated in high-risk infants.
- There is no evidence that an elimination diet after age 4–6 months has a protective effect, although this needs additional investigation.
- Further research is needed to determine the relationship between house dust mite exposure at an early age and the development of sensitisation and disease; no recommendation can yet be made about avoidance measures for preventing allergic disease.
- No recommendations can be made about exposure to pets in early life and the development of allergic disease. If a family already has pets it is not necessary to remove them, unless the child develops evidence of pet allergy (as assessed by an allergy specialist).
- Women should be advised not to smoke while pregnant, and parents should be advised not to smoke.
- No recommendations can be made on the use of probiotic supplements (or other microbial agents) for preventing allergic disease at this time.
- Immunotherapy may be considered as a treatment option for children with allergic rhinitis, and may prevent the subsequent development of asthma.

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In the second half of the 20th century, asthma and other allergic diseases became dramatically more common in Western countries, and Australia has one of the highest allergy prevalence rates in the world. Up to 40% of Australian children have evidence of allergic sensitisation, and many will go on to develop allergic diseases such as food allergies, eczema, asthma and allergic rhinitis. These conditions frequently persist into adulthood, placing a significant burden on individuals and the health care system. It is self-evident that environmental changes must be responsible for the increasing propensity for allergic disease. There is an ongoing search for causal associations that will help to identify strategies to reverse this trend. Strategies that reduce the risk or the severity of disease expression could have enormous impact. At this stage, most allergy prevention strategies are relatively crude, with small or unconfirmed effects, and newer strategies are still in experimental stages.

The complete Australasian Society of Clinical Immunology and Allergy (ASCIA) position paper on allergy prevention in children summarises the existing evidence with the aim of informing and refining current guidelines for allergy prevention. It is available at <http://www.allergy.org.au/pospapers/Allergy_prevention.htm>. Here, we present a concise summary of that position statement, outlining details most relevant for clinicians and areas that require further research. The "strength of recommendations" are based on the World Health Organization (WHO) "Categories of Evidence" wherever possible (see Box). In many areas the evidence is non-existent or is not particularly robust.

Identifying infants at risk of allergic disease

Children born into atopic families are more likely to develop allergic diseases (50%–80% risk) compared with those with no family history of atopy (20% risk). The risk appears to be higher if both parents are allergic (60%–80%), and the risk is also higher if the mother (rather than the father) has allergic disease.[1] Functional genetic polymorphisms may determine differences in vulnerability to environmental change, underscoring the complexity of gene–environmental interactions. This area is still poorly understood.

The role of allergens

The guiding principle behind allergen avoidance strategies is the hypothesis that reducing allergen levels may reduce the risk of allergen sensitisation, and hence the risk of allergic disease. However, despite a clear association between sensitisation and the development of allergic disease, the processes leading to sensitisation appear to be independent to those leading to disease. Moreover, in many cases, allergen avoidance strategies have been ineffective in reducing allergic sensitisation or associated with unexpected paradoxical effects. For example, although successful house dust mite (HDM) reduction in pregnancy has been associated with better lung function in preschool children, the same study showed an increased risk of sensitisation to HDM.[2]

Allergen exposure during pregnancy

Randomised double-blind controlled trials have not shown that avoiding multiple potential food allergens during pregnancy reduces

the risk of allergic disease in children.[3] The current consensus is that this practice should be discouraged because of potential nutritional compromise to the mother and fetus.

Recommendations

- Avoiding foods in pregnancy is not recommended for preventing allergic disease (strength of recommendation — A).
- It is difficult to justify HDM reduction strategies in pregnancy based on current evidence and the possibility of an increased risk of sensitisation[2] (strength of recommendation — B).

Breastfeeding versus formula feeding

There are inherent limitations in studies addressing this question (confounding factors, recruitment and reporting biases, perceptions modifying feeding practices, inability to randomise and blind). Importantly, many studies do not make the distinction between "exclusive breastfeeding" and "any" breastfeeding. Many studies have shown a weak protective effect on early symptoms of allergic disease (reviewed in Foucard[4]), including atopic eczema,[5] and early wheezing.[6] A systematic review of 12 prospective studies (8183 infants) found that exclusive breastfeeding in the first months of life was also associated with reduced rates of subsequent asthma (odds ratio [OR], 0.70; 95% CI, 0.60–0.81), and that the protective effect was greater in high-risk children (OR, 0.52; 95% CI, 0.35–0.79).[7]

Recommendations

- Breastfeeding should be recommended because of many beneficial effects (except where contraindicated, such as with maternal HIV infection).
- The current consensus is to recommend exclusive breastfeeding for at least the first 4–6 months in children at high risk of allergic disease (strength of recommendation — B).
- The reported protection that breastfeeding confers against allergic disease in the early years of life is relatively small, and some studies suggest there may instead be an increased risk of such disease in later life.

Maternal allergen avoidance during lactation

There is no convincing evidence that allergen avoidance during lactation has a protective effect. Although several studies indicate that maternal avoidance of potential food allergens (milk, egg, and fish) while breastfeeding may reduce the risk of atopic eczema in the first years of life, other studies do not confirm this (details of these studies are available at <http://www.allergy.org.au/pospapers/Allergy_prevention.htm>). While a systematic Cochrane review suggested some benefits on early atopic eczema, methodological limitations make the findings difficult to interpret.[8]

Recommendation

- Maternal dietary restrictions during breastfeeding are not recommended for disease prevention (strength of recommendation — A).

Infant formulas

The most recent Cochrane reviews of allergy and infant feeding concluded that hydrolysed formulas reduce the risk of infant allergy (compared with cow's milk formulas),[9] but that these hydrolysed formulas should not be offered in favour of breast milk for allergy prevention.[9,10] Significant effects have been observed with both partially and extensively hydrolysed formulas,[11] but because of great variations in study design and diagnostic criteria, the relative efficacy of the different formulas tested in different studies cannot be compared directly.

Prospective studies have shown that soy formulas are as allergenic as normal cow's milk formulas,[11] but some controversy remains. Soy formulas and other milks (such as goat's milk formula) are not recommended for the prevention of allergic disease.

Recommendations

- If exclusive breastfeeding is not possible in high-risk infants, a hydrolysed formula (rather than a conventional cow's milk-based formula) is recommended (strength of recommendation — A).
- Both extensively hydrolysed and partially hydrolysed formulas have been shown to have protective effects in high-risk infants with atopic heredity (strength of recommendation — A). Partially hydrolysed formula is available in Australia without prescription. Extensively hydrolysed formula is available with prescription, but is only subsidised for the treatment of infants with combined cow's milk and soy milk allergy.
- Soy formulas and other formulas (such as goat's milk) are not recommended for reducing the risk of food allergy (strength of recommendation — B).

Infant diet

Studies suggest that delaying the introduction of solid foods may reduce the incidence, or delay the onset, of infantile allergic diseases in the first year of life, including atopic dermatitis, food[12,13] and other allergies, and wheezing.[10] However, these effects are modest, and long-term benefits are not certain. In children with existing sensitisations or overt allergic disease (or those deemed to be at high risk for other reasons), it has been common clinical practice to recommend avoidance of potentially allergenic foods such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2–4 years of age. This practice is based on a theoretical benefit to protect

World Health Organization categories of evidence and strength of recommendations

Categories of evidence:

- Ia Evidence from meta-analysis of randomised controlled trials
- Ib Evidence from at least one randomised controlled trial
- IIa Evidence from at least one controlled study without randomisation
- IIb Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
- IV Expert opinion

Strength of recommendations:

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

an "immature immune system". Nevertheless, although the "benefit" is not known, the "costs" of doing nothing are perceived as high, and the "cost" of this intervention is relatively low. There is no evidence that avoiding peanuts, nuts and shellfish during early life is harmful for high-risk children.

Recommendations

- Complementary foods (including normal cow's milk formulas) should be delayed for at least 4–6 months (strength of recommendation — B; the meta-analysis in question[10] did not look at this intervention in isolation). This preventive effect has only been demonstrated in high risk infants with atopic heredity, and preterm infants (strength of recommendation — B).
- There is no evidence that dietary elimination after the age of 4–6 months has a preventive effect, though this needs additional investigation (strength of recommendation — B).
- Avoidance of peanut, nut and shellfish for the first 2–4 years of life may be recommended in high risk children as this is unlikely to cause harm, however it must be emphasised that there is no evidence to support this (strength of recommendation — D).

Exposure to house dust mite

There is a dose relationship between house dust mite (HDM) population levels in the home and sensitisation to HDM.[14] Stringent environmental control measures can dramatically reduce HDM numbers,[15] and even less stringent measures (mite covers for bedding and washing instructions) significantly reduce HDM numbers.[16]

Although some studies have suggested benefits of reducing early HDM exposure, long-term data are still not available. Conflicting evidence[15] and recent reports of increased sensitisation risk have raised concern.[2] Further follow-up of ongoing cohorts is required before any recommendations can be made within the public health context.[15]

Recommendations

- HDM avoidance has been shown to benefit some patients with established disease and sensitivity, but whether reduced exposure will protect against the development of new disease remains uncertain.
- No recommendation can be made at this time regarding the implementation of HDM avoidance measures for preventing allergic disease. HDM avoidance measures in pregnancy and early infancy may delay the onset of allergic disease, but no long-term data are available and the effects on sensitisation are inconsistent (strength of recommendation — B).

Exposure to pet allergens

In some (but not all) studies, pet exposure in the first year of life has been associated with a lower prevalence of asthma and airway reactivity in later childhood and with less sensitisation to not only pet allergens, but also less sensitisation to other allergens at 6 years of age (see position paper on ASCIA website: <http://www.allergy.org.au/pospapers/Allergy_prevention.htm>). The potential mechanisms are not yet understood, but may relate to higher environmental levels of bacterial endotoxin in the presence of cats, dogs and cockroaches in the home. A systematic review concluded that exposure to pets increases the risk of asthma and wheezing in older children (over 6 years) but not in children aged less than 6 years.[17]

Recommendations

- In patients with established allergic disease and sensitisation to pet allergens, removing pets may be of benefit.
- There is no consistent evidence that either exposure to, or avoidance of, pet allergens has a protective effect against development of allergic disease. No recommendations can be made about exposure to pets and prevention of allergic disease (strength of recommendation — B).
- If a family already has pets, it is not necessary to remove them for the purposes of allergy prevention; however, it is also not recommended to acquire new pets for the purposes of allergy prevention (strength of recommendation — B).

The role of pollutants and irritants

Maternal smoking in pregnancy has adverse effects on infant lung development.[18] Parental smoking has also been associated with wheezing illness in early childhood.[19] The relationship between cigarette smoke exposure and atopy is less clear.

The role of other indoor pollutants is poorly understood. In some populations, the use of home gas appliances has been associated with an increased risk of HDM sensitisation and subsequent respiratory symptoms,[20] but this needs to be confirmed.

Recommendations

- Pregnant women should be advised not to smoke.
- Parents should be advised not to smoke (strength of recommendation — B).
- Children should not be exposed to cigarette smoke in confined spaces (strength of recommendation — B).
- Parents should also minimise exposure to indoor air pollutants (strength of recommendation — C).

The role of early infection and other microbial exposure

The potential for bacterial products to inhibit allergic inflammation have made these logical agents for allergy prevention. It was recently demonstrated that giving probiotic bacteria (in the final weeks of pregnancy and the first 6 months of life) protected against the development of atopic eczema at 1 year and 4 years of age.[21] Other studies are under way to further evaluate the benefits of probiotics in preventing allergic disease.

Recommendations and comments

- No conclusions can be made at this time about microbial infection and prevention of allergic disease (strength of recommendation — C).
- Although probiotics appear to be safe, follow-up studies are needed to confirm long-term effects. No recommendations can be made at this time because of limited evidence.
- The use of other bacterial products for allergy prevention is still experimental.

The role of immunomodulatory dietary nutrients

There is growing interest in the role of dietary components with recognised immunomodulatory effects on the development of allergic disease, such as antioxidants and polyunsaturated fatty acids (PUFA). Preliminary studies of the role of omega-3 (n-3) PUFA supplementation in infancy have reported reduced prevalence of wheeze at 18 months and allergic cough at 3 years, but no effect on wheeze at 3 years.[22,23] Furthermore, there was no effect on sensitisation to foods, or atopic dermatitis.

Recommendation

- No recommendations can be made at this time because of limited evidence.

Secondary prevention in children with early sensitisation or disease

Existing strategies to prevent allergies are relatively ineffective and a significant proportion of "high risk" children will still develop sensitisation or disease. If these children can be identified when they have early disease, future strategies may provide avenues for:

- reducing the risk of progression to new sensitisations, and other persistent forms of disease (in the "atopic march"); and/or
- reducing the severity of the disease.

Preliminary evidence suggests that early interventions in allergic children may modify the progression of sensitisation patterns and the development of new allergic diseases. Children treated with specific (pollen) immunotherapy for allergic rhinitis are significantly less likely to develop asthma than those who do not receive active treatment.[24] Immunotherapy can also reduce the development of new sensitisations in patients monosensitised to aeroallergens (house dust mite).[25] Other interventions, such as the use of antihistamines (cetirizine) in children with early disease are also being investigated because of preliminary evidence that this may modify disease progression.

Recommendation

- Immunotherapy in children with allergic rhinitis may prevent the subsequent development of asthma (level of evidence — 1b).

The future: primary allergy vaccination?

The use of allergen vaccines or preventive immunotherapy has long been proposed as one method of primary prevention.[26] The enteric mucosal immune system plays an extremely efficient and pivotal role in the development of tolerance. Studies using "high dose" mucosal delivery of aeroallergen combinations in infants at high risk of allergic disease (or those with early evidence of sensitisation such as food allergy) are about to commence. Future methods of safely promoting tolerance in humans may include novel "allergen vaccine" strategies.

Concluding comments

There is a growing need to reduce the mounting personal, social and economic costs of allergic disease. While there has been some success in managing established disease, strategies to prevent the development of these processes will be of greater value in the long term.

Currently, our capacity to prevent allergic disease is constrained by limited understanding of disease pathogenesis and aetiological factors, particularly of the early exposures responsible for the recent increase in allergic disease. There is also an inability to accurately identify atopic individuals before sensitisation occurs. All of these areas need to be investigated more fully to determine how tolerance mechanisms can be promoted without adverse effects.

Further information

For the full ASCIA position paper on allergy prevention in children, including references and further information on allergy, asthma or immune diseases, visit http://www.allergy.org.au, the website of the Australasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA is the peak professional body of Clinical Allergists and Immunologists in Australia and New Zealand.

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Competing interests

None identified.

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