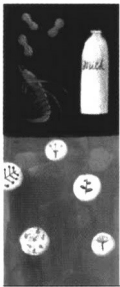


THEME ALLERGY



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Allergy prevention

Current recommendations and new insights

Background

The prevalence of allergic disease has increased considerably in recent decades and Australia has one of the highest rates of allergic disease in the world. As there is currently no cure for allergic diseases, prevention offers a logical approach to addressing the rising burden of disease. The factors responsible for this escalation in prevalence remain unclear, and strategies for allergy prevention remain limited.

Objective

This article discusses current recommendations for allergy prevention and highlights new insights into allergic disease.

Discussion

History of allergic disease in a first degree relative is currently the only useful indicator for increased risk of developing allergic disease in a child. Prevention strategies should be directed to these high risk individuals. Currently, maternal dietary restriction during pregnancy or lactation and aeroallergen avoidance are not recommended. Breastfeeding is recommended, and where not possible or insufficient, a partially hydrolysed formula should be used in high risk infants. Introduction of solids should be delayed to 4–6 months of age. There is no evidence that delaying solids beyond this age is of benefit. There is currently insufficient evidence to recommend the addition of probiotics for allergy prevention.

■ **The worldwide prevalence of atopic diseases such as asthma, allergic rhinitis, atopic dermatitis and food allergy has increased considerably in recent decades. Australia has one of the highest rates of allergic disease in the world.¹ Asthma prevalence appears to have plateaued,² and the increase in eczema and allergic rhinitis is slowing. However, food allergy and anaphylaxis rates are rising exponentially.³ In the 12 years from 1993 to 2005 the rate of hospitalisations for anaphylaxis in the 0–4 years age group in Australia rose from 4.1 to 19.7 per 100 000, with most of the increase attributable to an increase in anaphylaxis to food.⁴**

Although significant advances in our understanding of atopic disease have been made, the reasons for these escalating prevalence rates remain poorly understood. Epidemiological evidence suggests that early life influences are important for determining one's risk for the development of atopic disease.⁵ It is likely that a myriad of genetic and environmental influences are at play. Much attention is now being focused on exploring and developing allergy prevention strategies. Here we explore the current recommendations for primary allergy prevention during pregnancy and early childhood.

When to implement strategies for allergy prevention

Allergy prevention strategies are recommended for babies at 'high risk' of developing allergic disease. A child is considered to be at 'high risk' of developing allergic disease if there is a positive family history of allergic disease (asthma, allergic rhinitis, atopic dermatitis and food allergy) in one or more first degree relatives (parents or siblings). Children born to atopic families (parents or siblings) are more likely to develop allergic disease (50–80%) compared to those with no family history of atopy (20%).⁵ To date, no genetic markers have been identified that accurately predict the development of allergic disease in an individual, therefore family history of allergy is the only useful marker to identify those children at risk of developing allergic disease.



Maternal diet during pregnancy

There is no evidence that avoidance of allergenic foods during pregnancy reduces the development of allergic disease in children.⁷ Furthermore, maternal elimination diets during pregnancy may adversely affect maternal and/or fetal nutrition.

Maternal elimination diets during pregnancy are not recommended for allergy prevention

Environmental allergen avoidance during pregnancy

Reduction in house dust mite levels can be achieved.⁸ However while some studies have suggested benefit with reducing house dust mite exposure during pregnancy and/or early infancy, others have reported an increased risk of sensitisation.⁹ Marks et al¹⁰ recently reported no difference in prevalence of asthma, wheeze or atopy at 5 years of age with house dust mite avoidance during infancy. Longer term data on the effect of house dust mite avoidance is currently not available. The relationship between pet exposure and the development of allergic disease is also unclear at this stage. Given this conflicting evidence, house dust mite avoidance measures are not recommended for prevention of allergic disease. No recommendation can be made regarding pet exposure for the purpose of primary allergy prevention. However, if there is established allergic disease – asthma, allergic rhinitis – and pet allergy, avoidance is recommended.

Aeroallergen avoidance in pregnancy or early childhood is not recommended. There is insufficient evidence to recommend either exposure to, or removal of, pets for the purpose of allergy prevention

Breastfeeding

Many studies addressing the association between breastfeeding and the development of atopic diseases have been retrospective, with inherent difficulties in reporting biases and likely confounding factors. It is also difficult to dissect the effects of breastfeeding from delayed introduction of complementary feeds as both interventions are often combined. There is evidence that exclusive breastfeeding and avoidance of complementary feeds in the first 3–4 months of life is associated with a reduced risk for developing allergic disease in early childhood, particularly atopic dermatitis during infancy and childhood asthma.^{11–14} There is no evidence that exclusive breastfeeding for longer periods (6+ months) has a protective effect against allergic disease and some studies have found an increased risk for asthma, eczema or atopy at 5 years of age.^{15,16} The long term effects of breastfeeding on the development of allergic disease in later childhood and adulthood is also uncertain, with longitudinal studies reporting a small increased risk for allergic disease and sensitisation with exclusive breastfeeding for 3–6 months or prolonged for 6 months

or more.^{17–20} A large Tasmanian cohort study found that exclusive breastfeeding for the first 3 months of life was protective against infant eczema and early asthma at 7 years (in children with a maternal history of asthma or allergic rhinitis), and food allergy (in all children), but was associated with a slightly increased risk for asthma (in children with maternal history of allergic disease), food allergy and rhinitis (in all children) at 14, 32, and 44 years of age.²⁰ Similarly, the Tuscon Children's Respiratory Study found a protective effect against early recurrent wheeze in the first 6 years, but increased risk of asthma and wheezing at 6–13 years of age.¹⁸

One might therefore speculate that exclusive breastfeeding may be protective against allergic disease in early life but not in later life, and that exclusion of complementary feeds is only beneficial if limited to the first 3–4 months of life. Indeed, there is emerging evidence that introduction of complementary feeds while breastfeeding may promote the development of tolerance.²¹ Current evidence demonstrates a protective effect of exclusive breastfeeding for the first 3–6 months of life against early allergic disease, particularly eczema and asthma. Long term effects remain uncertain.

Breastfeeding should be encouraged (except where contraindicated) because of its many beneficial effects and protective effects against early allergic disease. However, long term benefits remain uncertain

Maternal allergen avoidance during lactation

Currently, there is no convincing evidence that allergen avoidance during lactation has a protective effect against allergic disease.²²

Maternal allergy avoidance during lactation is not recommended for allergy prevention

Infant formulas

Both extensively hydrolysed and partially hydrolysed formulas have been shown to have a small protective effect on the development of atopic disease in high risk infants compared to cow's milk formulas.²³ There are limited studies comparing partially hydrolysed and extensively hydrolysed formulas and current evidence suggests they provide similar beneficial effects against allergic disease, although further long term studies are required to confirm this.²³ When breastfeeding is not possible or insufficient, it is recommended that a partially or extensively hydrolysed formula be used in high risk infants. Hydrolysed formulas should not be offered in preference to breast milk for allergy prevention. In Australia, extensively hydrolysed formulas are only available for the treatment of established cow's milk and soy allergy and are not available for the purpose of allergic disease prevention (Table 1).



Soy based formulas have been shown to be equally allergenic when compared to cow's milk formulas.^{24,25} A recent Cochrane review concluded that soy based formula feeding should not be recommended for the prevention of allergy.²⁶

Partially hydrolysed formulas are recommended in high risk babies when breastfeeding is not possible or is insufficient

The use of soy milk based formulas is not recommended for the prevention of allergic disease

Table 1. Brand names of different types of formulae

	Brand name
Partially hydrolysed formulae	NAN HA
	Novalac HA Infant Formula
Extensively hydrolysed formulae	Alfare
	Pepti-Junior

Introduction of solid foods

The current Australian recommendation is for exclusive breastfeeding in the first 4–6 months of life (see *Resource*). This recommendation to delay the introduction of solids was made in part on the basis of studies showing that early introduction of solids (<3–4 months) was associated with an increased risk of atopic dermatitis.²⁷ There is no evidence that delayed introduction of solids beyond 4–6 months of age is of benefit for the prevention of allergic disease.²⁸ A recent systematic review concluded that there is currently insufficient evidence to support the association between early introduction of solid foods and the development of atopic disease.²⁹ There has also been increasing concern that the commonly recommended practice of delaying introduction of solid foods for longer periods than 4–6 months and up to 2–4 years may actually increase, rather than decrease, the risk of allergic disease. The development of tolerance to food allergens is an antigen driven process and emerging evidence suggests that early and repeated exposure to food proteins during a proposed 'window' between 4–6 months of age may be optimal for the induction of tolerance. Delayed introduction of foods after 6 months of age may lead to increased development of food allergy and other allergic disease.^{30,31} Delayed introduction of certain foods beyond 6 months may also be associated with an increased risk of development of autoimmune disease.³² Introduction of complementary feeds while breastfeeding may favour development of tolerance.³³

Further research is required to determine whether earlier introduction and regular exposure to highly allergenic foods may reduce the risk of specific allergies to these foods and/or the risk of developing other allergic diseases. There are currently studies underway in the United Kingdom to evaluate the role of early rather than delayed introduction of peanuts to prevent peanut

allergy. The results of this and similar studies are awaited with much interest.

Introduction of solids should be delayed to 4–6 months of age. There is no evidence to suggest that delaying the introduction of solids past 4–6 months has a protective effect against allergic disease and there is emerging evidence that it may actually increase the risk of food allergy and autoimmune diseases such as coeliac disease

Smoking

Maternal smoking during pregnancy has been associated with impairment of fetal lung development.³⁴ The relationship between in utero and early childhood exposure to cigarette smoke and atopy is not yet clear. However parental smoking has been associated with an increase incidence of early childhood wheeze.³⁵

Women should be advised not to smoke during pregnancy
A smoke free environment should be recommended for all children

Probiotics and microbial exposure

Microbial organisms may possibly have an important effect on atopic sensitisation and induction of tolerance. There is mounting evidence that probiotics – live bacteria that colonise the gastrointestinal tract and provide a health benefit to the host – may prevent development of eczema. Differences in intestinal microflora have been identified between atopic and nonatopic children. These differences include greater levels of intestinal colonisation with pathogenic bacteria and lower levels of intestinal colonisation with probiotic bacteria in children with allergic disease. Furthermore, these differences can be demonstrated in the first weeks of life before the development of allergic disease, suggesting a role in development of disease. It has therefore been postulated that modification of the infant intestinal microbiota by promoting probiotic bacterial colonisation may protect against the development of allergic disease.^{36,37} There is growing evidence that administration of probiotics – *Lactobacillus GG* alone or in combination with other probiotic strains and prebiotics or *Lactobacillus reuteri* – to mothers in the last weeks of pregnancy and then to babies or breastfeeding mothers in the first 6 months postnatally may protect against development of atopic dermatitis at 2 years.^{38–40} These protective effects may persist to 7 years of age.⁴¹ However, administration of *Lactobacillus acidophilus* LAVRI A1 postnatally for the first 6 months of life failed to provide any beneficial effects against the development of allergic disease and was instead associated with increased risk of sensitisation.⁴² This latter finding suggests that either the probiotic strain and/or the timing of administration may be important for efficacy in prevention of allergic disease. It is well known that different probiotic strains and species can have widely different immunological effects. A recent Cochrane review analysed the effect of probiotics given to infants and



found that although there was a reduction in risk of eczema in infants that were given probiotics, the effect was not consistent between studies, leading to the conclusion that there is currently insufficient evidence to recommend the addition of probiotics to infant feeds for the prevention of allergic disease. Further research in this area, particularly into the specific effects of selected probiotic species/strain, dose and timing of administration, is required before definitive recommendations can be made.

There is currently insufficient evidence to recommend addition of probiotics to the maternal or infant diet for allergy prevention

Polyunsaturated fatty acids

Epidemiological studies have shown an association between intake of oily fish – rich in omega 3 fatty acids – and a reduced risk of allergic disease in childhood.^{43,44} A similar association between maternal fish intake during pregnancy and reduced risk of eczema at 1 year, wheeze at 6 years and sensitisation to house dust mite at 6 years of age, has been reported.⁴⁵ However, evidence from randomised intervention trials remains lacking. An Australian study of dietary supplementation with omega 3 fatty acids from 6 months of age found no beneficial effect on atopy or allergic disease in children.^{9,46} Fatty acid dietary supplementation cannot currently be recommended for the primary prevention of allergic disease. There is some evidence that the pattern of long chain polyunsaturated fatty acid exposure in pregnancy can influence neonatal cytokine production, however the relevance of this is not yet clear.⁴⁷

Resource

The Australasian Society of Clinical Immunology and Allergy (ASCIA)
www.allergy.com.au.

Case study 1

Melissa is 18 weeks pregnant with her first child. She comes for a repeat prescription of her asthma medications. Melissa asks how likely it is that her child will have asthma and what can be done to prevent her child developing asthma.

As Melissa has asthma, her children are considered at high risk of having allergic diseases, including asthma, but also allergic rhinitis, atopic dermatitis and food allergy. The risk of her children having an allergic disease is 50–60%, although it may or may not be asthma. The risk for her child having an allergic disease increases further to 60–80% if the child's father also has an allergic disease (eg. asthma). To minimise the risk of her child developing an allergic disease, Melissa could not smoke during pregnancy and provide a smoke free environment for her baby once he/she is born, breastfeed exclusively for 4–6 months, and use a partially hydrolysed formula if supplementary formula is used. Even if all of these measures are implemented, her child may still develop an allergic disease.

Case study 2

Tommy is 3 months of age. He has a brother with egg allergy and atopic dermatitis. His mother asks what she can do to minimise the risk of Tommy developing egg allergy and eczema like his brother. She asks if she should delay the introduction of highly allergic foods such as egg and peanut? Tommy is at high risk of developing allergic disease because there is a family history of allergic disease in a sibling. There is no evidence that specific allergic conditions are inherited by mendelian inheritance. There is however an increased risk of allergic disease if there is a family history in a first degree relative. General guidelines for prevention should be recommended (as in Case 1). Complementary feeds should be delayed for 4–6 months. There is no evidence that delayed introduction beyond 6 months has any beneficial effect for the prevention of allergic disease, and some emerging evidence that there may even be an increased risk of food allergy. Foods, including the common allergens egg, milk, and peanut, can be introduced after 4–6 months. There is some evidence that introduction of complementary foods while still breastfeeding may promote the development of tolerance.

Case study 3

Leo is 3 months of age. He has atopic dermatitis. His father asks what he can do to minimise the risk of Leo developing further allergic diseases. He asks if he should delay the introduction of highly allergic foods such as egg and peanut.

The usual prevention strategies have not been shown to be effective for secondary prevention of allergic disease, ie. progression to other allergic conditions. Some studies suggest that allergen specific immunotherapy for allergic rhinitis has been shown to reduce the risk of developing asthma. However further evidence is required before this is recommended as a routine management approach. Solids should be started between 4–6 months. Dad should be alert to the possibility of foods causing a flare in atopic dermatitis. In children the most common foods that cause a flare of atopic dermatitis are eggs, milk, peanuts, soybean and wheat.

Case study 4

Simone comes to her GP for a pre-pregnancy consultation. She is worried about the rise of allergy in children and wants information on prevention. Neither Simone nor her partner have a past history or family history of atopic diseases.

At this point her future children are not considered at high risk of allergic disease, with a risk of about 20% of developing one of the atopic diseases. Simone can minimise the risk by not smoking during pregnancy, providing a smoke free environment and breastfeeding until 4–6 months. No maternal dietary restrictions, beyond routine pregnancy and breastfeeding recommendations, are suggested. Additional prevention strategies are not recommended (eg. hydrolysed formulas).



Conflict of interest: none declared.

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