

The Australasian Society of Clinical Immunology and Allergy infant feeding for allergy prevention guidelines

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Allergic disease is common in Australian infants. Eczema affects 15–20% of infants.¹ Food allergy has been increasing in incidence worldwide,² with rates in Australia among the highest in the world. The Melbourne-based HealthNuts study reported 10% of infants under 1 year of age had a challenge-proven food allergy. Egg and peanut had an incidence of 8.9% and 3.0%, respectively.³ Egg, cow's milk, wheat, soy, peanut, tree nuts, fish and shellfish constitute the most common food allergens in Australia. About 30% of cow's milk and egg allergy persists into adulthood, whereas peanut, tree nut and seafood allergies are persistent in the majority.¹ In Australia, emergency department presentations for anaphylaxis and fatalities from food-induced anaphylaxis continue to rise.^{4,5} While peanut is the most common cause of death from anaphylaxis in Australian children, cow's milk is now the leading cause of food anaphylaxis fatalities in the United Kingdom. There are no reliable data on the most common food triggering anaphylaxis among Australia children.

There is an urgent need to prevent food allergy as there is no current cure. As such, any measures which have proven efficacy in primary prevention should be given significant consideration in public health policy. The Australasian Society of Clinical Immunology and Allergy (ASCIA) has developed primary prevention guidelines that may help reduce eczema and food allergy.⁶ This article summarises the basis of these guidelines and their key recommendations, and discusses controversies and knowledge gaps (Box 1). Recommendations for the prevention of asthma and allergic rhinitis are not discussed but are well covered by the National Asthma Council recommendations.⁷

Background and methods

The current ASCIA guidelines for infant feeding and allergy prevention were developed by the ASCIA paediatric committee and are intended for use by parents and carers of all children, regardless of their allergy risk.⁸ They were not designed for use in treatment of existing specific food allergies.

The Centre for Food and Allergy Research (CFAR) assisted in creating the guidelines. We performed a literature search of PubMed, Medline, Web of Science and EMBASE spanning the years 2000–2016. Where possible, CFAR carried out a meta-analysis of data from single studies.⁹ Evidence was graded by the ASCIA paediatric committee according to National Health and Medical Research Council (NHMRC) criteria and then assessed using the GRADE approach.¹⁰ Level of evidence and a further risk/harm assessment was used to arrive at an overall recommendation (strong, moderate, weak, poor or no recommendation).

Guidance for health professionals for prevention of peanut allergy was published in 2017, based on emerging evidence and issues specific to our region.^{11,12}

Abstract

Introduction: The Australasian Society of Clinical Immunology and Allergy, the peak professional body for clinical immunology and allergy in Australia and New Zealand, develops and provides information on a wide range of immune-mediated disorders, including advice about infant feeding and allergy prevention for health professionals and families. Guidelines for infant feeding and early onset allergy prevention were published in 2016, with additional guidance published in 2017 and 2018, based on emerging evidence.

Main recommendations:

- When the infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods. (This is not a strict window of introduction but rather a recommendation not to delay the introduction of solid foods beyond 12 months.)
- Introduce peanut and egg in the first year of life in all infants, regardless of their allergy risk factors.
- Hydrolysed (partially and extensively) formula is no longer recommended for the prevention of allergic disease.

Changes in management a result of the guidelines: The guidelines specifically recommend introducing solid foods at around 6 months of age and introducing peanut and egg in the first year of life in all infants to prevent allergy development. Hydrolysed formula is no longer recommended for prevention of allergic disease. A new document outlining the reasons for and the method of peanut introduction to high risk infants is available for health professionals.

Over the past decade, infant feeding guidelines for primary prevention of food allergy have changed dramatically in response to a significant rise in food allergy. The reasons for the rise in food allergy are complex and still not well understood. Previous recommendations were that certain allergenic foods should be avoided in early childhood. During the 2000s, multiple cohort studies reported finding no evidence that delayed introduction of allergenic foods was associated with reduced rates of food allergy. In 2008, a cross-sectional study reported that the prevalence of peanut allergy was 10-fold higher among children in the UK (where infant peanut avoidance was recommended) compared with Israeli children of similar ancestry (where peanut is usually introduced at around 6–7 months).¹³ Interest developed in examining the effects of early introduction of solid foods in an interventional clinical trial setting. Good evidence, albeit from a single large randomised clinical trial (RCT), has now been published regarding the early introduction of peanut, especially in infants with severe eczema and/or egg allergy.¹²

Maternal diet during pregnancy and breastfeeding

The ASCIA guidelines recommend a healthy balanced diet. Exclusion of any particular foods (eg, peanut) from the maternal diet during pregnancy or breastfeeding is not recommended, as this has not been shown to prevent allergies.^{14,15}

1 Key recommendations for allergy prevention in the Australasian Society of Clinical Immunology and Allergy guidelines

Recommendation	New	GRADE quality of evidence	Type of evidence
During pregnancy			
No restriction of maternal diet	No	Low	Meta-analysis
Up to three serves of oily fish/week	Yes	Low	Meta-analysis
No probiotic supplementation	Yes	Low	Meta-analysis
During breastfeeding			
No restriction of maternal diet	No	Low	Meta-analysis
Breastfeed for at least 6 months (where possible)	No	No evidence	Observational study
For infants			
Introduce peanut and egg before 1 year of age	Yes	Moderate	Randomised controlled trial, meta-analysis
Do not use soy or hypoallergenic formula (for primary prevention)	Yes	Moderate	Meta-analysis
Do not use probiotics	Yes	Low	Meta-analysis

Omega-3 rich fish

Up to three serves of oily fish per week may be beneficial on the basis of low grade evidence that omega-3 fatty acids (found in oily fish) during pregnancy and breastfeeding may help prevent eczema in early life.¹⁶ Although synthesised evidence does suggest a benefit of omega-3s, the individual studies have largely used proxy markers for allergic disease, such as sensitisation, rather than allergic disease itself. Effects have been largely confined to sensitisation to egg and peanut.¹⁶

Omega-3 supplementation is not recommended, but rather the inclusion of healthy food in moderate proportions, consistent with general recommendations for fish consumption during pregnancy (for benefits unrelated to prevention of allergic disease).^{17,18}

Probiotics

The evidence for probiotics in pregnancy/breastfeeding for preventing eczema is graded as low because the data are heterogeneous.^{19,20} The most recent Cochrane review (2007) does not recommend their use;²¹ however, it does not include many studies assessed in the more recent World Allergy Organization review.¹⁹ Additionally, optimal species and doses of probiotics are still not well defined. Recommendations about probiotic supplements cannot be made as yet and more research is required.

Breastfeeding and infant formula

Breastfeeding

Consistent with NHMRC recommendations,²² breastfeeding is recommended for at least 6 months, for as long as mother and infant wish to continue. While there is no consistent evidence

that breastfeeding is effective in preventing allergic disease, it is recommended for the many benefits it provides to mother and infant.²³

There is controversy surrounding the overall benefits of exclusive breastfeeding for 6 months compared with 4 months in Australia, with relatively low incidence of infectious disease and high prevalence of allergic disease. Breastfeeding when solid foods are first introduced may help reduce the risk of infant allergies, although evidence for this is weak.²⁴

Infant formula

Standard cow's milk formula (but not regular cow's, goat's, soy or nut milk under 12 months of age) can be used if breastfeeding is not possible. There is no evidence that soy or goat's milk formula reduces the risk of allergic disease when used in preference to cow's milk based formula.²⁵

The most recent systematic review in this area reported no consistent convincing evidence to support partially or extensively hydrolysed formulas for primary prevention of eczema, food allergy, asthma or allergic rhinitis in infants or children.²⁶ This is at odds with a now outdated 2006 Cochrane review²⁷ and a withdrawn 2017 Cochrane review.²⁸ The updated ASCIA guidelines do not recommend the use of these formulas for prevention of early onset allergic disease. Some countries have not yet adopted ASCIA's position in this area. The United States Food

and Drug Administration has granted qualified health claim status for risk reduction of eczema to a single formulation of partially hydrolysed (whey) formulation for infants with a family history of allergic disease. The risk reductions appear small, and supporting evidence relied on per-protocol analysis rather than intention-to-treat analysis.²⁹ The most recent meta-analysis noted a high or unclear risk of bias and risk of conflict of interest in most included studies for allergic outcomes.²⁶

Introduction of solid foods

Solid food introduction is recommended at around 6 months, but not before 4 months, and preferably while breastfeeding.³⁰ This is a deliberately flexible, rather than narrow, window that discourages delayed introduction of solid foods. Thus, the focus is on prevention of delayed introduction. The timing is consistent with current NHMRC recommendations for introduction of complementary food at around 6 months of age.²² The optimal timing of introduction of certain foods (eg, cow's milk) for allergy prevention is not known and may even be earlier than 4 months, although the evidence for this is very limited.³¹ This is discussed further below and is consistent with other international guidelines.^{32–34}

Although the World Health Organization guidelines recommend exclusive breastfeeding for 6 months,³⁵ they were not specifically formulated for allergy prevention. The main benefits of exclusive breastfeeding, such as prevention of gastroenteritis, may be more important than food allergy prevention in certain areas of the world, and the ASCIA guidelines must therefore be taken in their intended context. Limited data indicate that there is no difference in duration of breastfeeding between infants who are introduced to solid foods early and those are not.^{12,31}

Introduction of specific allergenic foods

Only peanut and egg have levels of evidence sufficient to merit specific introduction recommendations. Optimal timing of introduction of cow's milk, wheat, soy and tree nuts is not known. Thus, specific recommendations (except not delaying introduction) are not made because of this knowledge gap. Observational cohorts have suggested an association between delayed introduction of common allergenic foods such as wheat, cow's milk and fish with a higher incidence of food allergy; however, further evidence is required to clarify optimal timing for the introduction of these foods.⁸ Based on the GRADE approach, there is moderate evidence that introduction of cooked egg at around 6 months of age prevents the development of egg allergy.^{31,36,37}

Infants with severe eczema and/or egg allergy are at high risk of peanut allergy.³⁸ There is now moderate evidence that regular peanut intake before 12 months of age can reduce the risk of developing peanut allergy. The Learning Early about Peanut Allergy (LEAP) trial randomised 640 children between 4 and 11 months of age with severe eczema, egg allergy, or both, to consume or avoid peanut-containing foods until 60 months of age, at which time a peanut oral food challenge was conducted.¹² Among the 540 infants in the intention-to-treat group with a negative skin prick test (SPT) result, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group ($P < 0.001$). In the intention-to-treat group, among those who initially had a positive SPT result, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P = 0.004$), with an 86.1% relative reduction in the prevalence of peanut allergy at 60 months in the consumption compared with the avoidance group.

Infants with SPT results of ≥ 5 mm to peanut at screening were not included in the LEAP study and this is one of the main limitations of the data. Although the results from LEAP and its follow-on study, LEAP-On, are compelling, the GRADE level of evidence is moderate as it was a single RCT and the control group had an unrealistic 5 years of avoidance.³⁹

In contrast, the Enquiring about Tolerance (EAT) trial, which examined introduction of multiple allergenic foods (including peanut) between 3 and 6 months of age in a large unselected population, did not find a significant difference in rates of peanut allergy in infants exposed to peanut compared with those who avoided peanut until at least 6 months of age by intention-to-treat analysis. Per-protocol analysis did suggest a possible effect for egg (1% v 5.5%) and peanut allergy (0% v 2.5%) in infants and families who managed to achieve at least 75% of the recommended dose for five of the allergens.³¹

Based on these findings, ASCIA guidelines note that if infants already have an egg allergy or severe eczema, they are at increased risk of peanut allergy. The guidelines recommend that parents should introduce peanut before 12 months (but not before 4 months) and suggest discussing how to do this with the child's doctor.

How to introduce peanut into the diet in high risk infants

Infants with moderate to severe eczema and/or egg allergy are at high risk of developing peanut allergy;³⁸ however, such infants are the most likely to benefit from early introduction of these allergens. Some infants will already be allergic to the food (and thus experience an allergic reaction on introduction), but the majority may benefit from early introduction.

Screening programs to identify pre-existing IgE sensitisation to peanut for infants with severe eczema and/or egg allergy before introduction of peanut (ostensibly to improve safety) have been proposed by the US National Institutes of Allergy and Infectious Diseases.⁴⁰ Although this appears superficially to be a sensible approach, it raises several important issues.^{9,41} Firstly, sensitisation is not clinical allergic disease. Moreover, within Australia and New Zealand, SPT is not readily available for most infants in a timely manner, and interpretation of results requires experienced clinicians. Serum-specific IgE tests may not be suitable for screening infants under 12 months, as there are insufficient data in this group to interpret their predictive value.⁴² Finally, referring to specialists on the basis of sensitisation may lead to delayed introduction of peanut, which is counter to the intended outcome.

We acknowledge that there is a cultural fear of peanut introduction. This does need to be balanced by a practical approach whereby infants have access to introduction of peanut in a timely fashion. It is somewhat reassuring that there have been no reports of fatalities to peanut under 12 months of age anywhere in the world, even in countries that have practised early introduction of peanut (eg, Israel) for many years.

ASCIA guidelines therefore recommend either home or office introduction of peanut to all infants (unless they have had an allergic reaction to peanut) without prior screening. For infants at high risk of peanut allergy, step-by-step advice for health care professionals has been formulated (Box 2).¹¹ Once the foods are introduced, the guidelines recommend including these on a regular basis (twice weekly) in the infant's diet so that tolerance is not lost.

Ongoing issues and knowledge gaps

The guidelines recommend the introduction of common allergenic foods within the first year but acknowledge that the optimal timing of introduction of most foods is currently not known. Foods should be continued on a regular basis; however, the quantities required to sustain tolerance of the food are also not known. In the LEAP study, infants were required to eat the equivalent of

2 Suggested procedure for introduction of peanut before 12 months (not before 4 months) under medical supervision (eg, in general practitioner rooms) or at home (when the infant is developmentally ready for solid food)

- Rub a small amount of smooth peanut butter/paste on the inside of the infant's lip (not on skin).*
- If there is no allergic reaction after a few minutes, feed the infant ¼ teaspoon of smooth peanut butter/paste (as a spread or mixed into other food that the infant is already eating or mixed with a few drops of warm water) and observe for 30 minutes.
- If there is no allergic reaction, give ½ teaspoon of smooth peanut butter/paste and observe for a further 30 minutes.
- If there is no allergic reaction, parents should continue to include peanut in their infant's diet in gradually increasing amounts at least weekly, as it is important to continue to feed peanut to the infant as a part of a varied diet.
- If there is an allergic reaction at any step, stop feeding peanut to the infant and seek medical advice (if at home).
- An allergic reaction should be treated by following the ASCIA action plan: <https://www.allergy.org.au/anaphylaxis>.

* This is to exclude a contact reaction to the skin, which is not a test for food allergy. Many infants will have erythema to many different foods on direct skin contact. Mucosal contact will give a low dose exposure of the allergen to the infant. Additional reference: Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016; 4: 196-203; quiz 204. ♦

three teaspoons of peanut butter a week,¹² which may be difficult for many families.

The most compelling evidence for introduction of peanut is based on high risk populations,¹² and the evidence for the general population (largely from the EAT study) is less compelling.³¹

There are practicalities regarding introduction of allergenic foods in anxious families or high risk infants, which may limit translation into clinical practice. Medical practitioners may be asked to give infants peanut (or other allergenic foods) in their rooms and the demand may increase their workloads. There are no Medicare item numbers to cover the increased work that this will entail. While the guidelines do provide a step-by-step guide,¹¹ some health professionals may not be comfortable with the process. In addition, not all infants will react on first exposure, such that a single observed feeding of peanut without incident does not guarantee no reactions in the subsequent exposures at home. In the LEAP study and the egg-introduction RCTs, allergic reactions in the first week of exposure were reported but rare.^{12,36}

The LEAP study was a large RCT conducted in infants from well educated, largely ethnically homogeneous families.¹² Translation of results to different populations with diverse racial backgrounds has not been assessed.^{41,43}

Guidelines require ongoing evaluation to assess their efficacy and safety. There are efforts to disseminate and assess the guidelines through ASCIA, CFAR and the National Allergy Strategy. It is hoped that current ASCIA guidelines will assist in reversing the upward trajectory of early onset allergy disease in Australia, and that further research will continue.

Competing interests: Preeti Joshi is currently the chair of the ASCIA paediatric committee and the deputy chair of the National Allergy Strategy allergy prevention project. Sandra Vale is coordinator of the National Allergy Strategy. Jill Smith is the ASCIA CEO and company secretary. Dianne Campbell was chair of the ASCIA paediatric committee from 2011 to 2017, has received funding for unrelated research from the NHMRC, the Allergy and Immunology Foundation of Australasia and the Australian Food Allergy Foundation, and has received travel expenses to attend investigator meetings from DBV Technologies.

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