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Abstract

The newly revised Australian Infant Feeding Guidelines recommends that all infants, including those at high risk of allergy, be introduced foods traditionally considered allergenic (such as peanut butter, dairy, wheat and egg) within the first year of life. High-risk infants are considered those with early onset eczema (less than 3 months old) or with moderate to severe eczema not responding to treatment (less than 6 months old).

Eczema can also represent a symptom of allergy presentation and recommended introduction of some foods in this group may inevitably lead to allergic reactions at home. Although there have been no reported deaths from gradual food introduction to infants at home and cohort studies have only reported mild-moderate reactions, there is anecdotal evidence that more severe reactions can occur rarely. Allergic reactions, even if not life-threatening, can be a terrifying experience for parents.

Dermatologists play an important role when dealing with high risk infants in promoting the message of early allergenic food introduction yet also instigating appropriate allergy testing when necessary. This short review aims to provide an update to Australian dermatologists with regards to the newly revised Australian Infant Feeding Guidelines and provide a food allergy

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screening pathway for high risk infants prior to commencement of allergenic foods.

Introduction

The link between eczema and allergy

Atopic eczema is a common inflammatory skin condition in the Australian paediatric population.¹ Eczema is a known risk factor for the development of Immunoglobulin E (Ig E) mediated food allergy.² The exact pathogenesis of food allergy in atopic eczema is unknown. It has been postulated that epidermal barrier dysfunction arising from filaggrin mutations results in percutaneous entry of the allergen, which in turn causes early food sensitisation.³ However, early introduction of food protein can also induce oral tolerance. The timing and balance of cutaneous and gut exposure determines if the infant develops an allergy or food tolerance. This is also known as the “dual-allergen-exposure” hypothesis.⁴

The strong association between food allergy and eczema has been studied clinically as well. A recent Melbourne population-based study determined that over half of 12-months old infants with early onset eczema (before 3 months old) requiring topical steroids developed food allergy. Those with eczema were 6 to 11 times more likely to develop peanut or egg allergy respectively.² Overall, the most common allergenic foods are cow's milk, egg, soy, wheat, seafood and peanut. In a proportion of infants with eczema ongoing exposure to foods to which they are allergic may result in aggravation of eczema.³

The protective role and nutritional value of breastfeeding on a developing infant is well established and widely recognized.⁵ Breast milk confers passive immunity (via secretory immunoglobulin A and G) and also actively regulates the infant's immune system through other factors. As such, breast milk can impact on the development of the infant's immune system and risk of allergic conditions.⁶ There has been mixed evidence regarding the association between breastfeeding and the prevention of allergic conditions such as asthma, eczema and allergic rhinitis. Systematic reviews have concluded that

there is no significant evidence for the protective effect of breastfeeding against eczema or food allergies in children aged 5 years and below. They however identified that there is some evidence that breastfeeding confers protection for asthma in older children between 5 to 18 years old.^{5,6}

Breast milk has been found to contain food antigens from the maternal diet. As such, food allergens can be exposed to the breast-fed infant with the potential to cause food sensitisation, particularly in atopic infants.⁷ More recently, meta-analyses have reported that neither maternal dietary avoidance of allergenic food in the antenatal phase and during breastfeeding⁸ nor the use of partially hydrolysed formula (labelled as HA or hypoallergenic)⁹ has been effective in preventing the development of atopy or food allergy.

Infant Feeding Guidelines: Rationale for revision and relevance to Dermatologists

The prior approach towards food allergy prevention mainly targeted allergen avoidance during infancy.¹⁰ However, with more evidence arising from new studies, there has been a shift towards introducing allergenic food earlier. Multiple previous studies have determined an association amongst allergy prevention, timing of initiating complementary feed and type of foods introduced.^{2,10-12} In Australia, the National Health and Medical research Council (NHMRC) Infant Feeding Guidelines and the Australasian Society of Clinical Immunology & Allergy (ASCIA) infant feeding advice form the two key sets of infant feeding guidelines for the general population and infants at high risk of allergy respectively.^{13,14} However there has been an update in the evidence base and it was felt that a consensus position statement was required to ensure minimisation of confusion.

In May 2016 an Australian Infant Feeding Summit was hosted by the NHMRC funded Centre for Food and Allergy research and a broad range of key stakeholders was invited to participate. This included ASCIA, NHMRC, the Breastfeeding association and representatives from a range of bodies

including health professionals, allied health and State government health departments.

The newly revised infant feeding ASCIA guidelines in May 2016 summarises the new consensus reached that may reduce the risk of eczema and food allergies in infants. The three key recommendations states:

1. When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron rich foods, while continuing breastfeeding.
2. All infants should be given allergenic solid foods including peanut butter, cooked egg and dairy and wheat products in the first year of life (unless already allergic to that food). This includes infants at high risk of allergy.
3. Hydrolysed (partially and extensively) infant formula are not recommended for prevention of allergic disease.

ASCIA now encourage the early introduction of food allergens (particularly peanut) into the infant diet to reduce allergy risk.¹⁴ This was introduced following the release of new evidence from the LEAP study in 2015. This landmark randomised controlled trial compared early (4-11 months) with delayed (5 years) introduction to peanut in high-risk infants with atopic disease and/or food allergy. The investigators concluded that the early introduction of peanuts significantly reduced the frequency of development of peanut allergy amongst the high-risk cohort.¹⁵

High-risk infants defined by the LEAP trial criteria included those with severe eczema and/or egg allergy proven on skin prick testing.¹⁵ This definition should extend to include infants with early onset eczema (less than 3 months old) or with moderate to severe eczema not responding to treatment (less than 6 months old).^{2,16}

The revised ASCIA infant feeding guidelines is now applicable to all infants regardless of allergy risk. However, the introduction of highly allergenic food to high-risk infants is of particular interest for dermatologists who frequently

deal with this population. Eczema can be a manifestation of food allergy and ongoing exposure to these foods can exacerbate the condition, cause undue parental concerns and expose the child to the potential risk of anaphylactic reactions.¹⁷ The LEAP study reported mild to moderate reactions, such as urticaria and gastroenteritis, in those who consumed peanuts. There was no serious adverse reactions or deaths.¹⁵ Findings from Koplin et al also supported that peanut introduction in young infants resulted in mild reactions with no cases of anaphylaxis.¹⁹ However, caution is required as food allergy resulting in anaphylaxis and hospitalisation, although rare, has been reported to be increasing in prevalence particularly in children between 0 to 4 years old.¹⁸ The key food allergens identified in this age group have been peanuts, egg, milk and tree nuts.¹⁷

It is thus our recommendation that food sensitisation testing be considered in high-risk infants prior to the introduction of allergenic solid foods. This sentiment is supported by Martin et al. whose study concluded that infants with early onset (less than 3 months old) eczema were likely to develop challenge-proven food allergy and advocates for the increase awareness of food allergy risk and early testing.² However at this point, this issue remains controversial and is currently being debated around the world. Some advocate that testing of this group of infants could not be supported by the current work force. Others argue that without testing, parents of high-risk infants will continue to avoid allergens regardless of the new guidelines. Tey et al. showed that the Australian population responded to change in infant guidelines recommendations in 2008 with significantly earlier introduction of solids, including egg and peanut.²⁰ However it was notable that those with a family history of allergy (arguably those most requiring the recommendations) were twice as likely to delay the introduction of these allergens.

Controversy remains about how and when to test or screen for food allergy in high-risk infants and those with eczema prior to the commencement of allergenic solid foods. We propose a pathway for testing high-risk infants, specifically those with early onset eczema (less than 3 months old) or with moderate to severe eczema not responding to treatment (less than 6 months

old), prior to the introduction of allergenic solid foods to identify those infants who will benefit from a referral to an allergist (Figure 1).

Our proposed screening pathway (Figure 1) is in response to the food allergy screening guidance from the National Institute of Allergy and Infectious Disease (NIAID)'s Interim Consensus communication in this high-risk infant group²¹ and a recent large Australian epidemiology study which suggested that screening with food-specific IgE blood test could help to reduce the number of patients needing SPT and/or OFC.¹⁹

In Australia, the National Allergy Strategy, which is an initiative of the ASCIA and Allergy & Anaphylaxis Australia (A&AA), will be hosting a round table discussion on food allergy testing for high-risk infants in March 2017 (led by Chairman: Associate Professor Richard Loh and Deputy Chair: Ms Maria Said).

Types of Allergy Testing and Interpretation

1. Serological Immunoglobulin E (Ig E) testing (Total and Specific)

Food-specific serum Ig E testing can be a useful diagnostic tool when conducted appropriately. Screening is recommended for peanut only at this point in time since there is an absence of data on the protective aspect of early introduction of other foods.

The positive 95% predictive thresholds for food-specific serum Ig E testing have been formulated for egg (≥ 7 kUa/L, ≥ 2 kUa/L if less than 2 years old), milk (≥ 15 kUa/L, ≥ 5 kUa/L if less than 1 years old), soy (≥ 65 kUa/L), wheat (≥ 100 kUa/L), peanut (≥ 15 kUa/L) and fish (≥ 20 kUa/L).^{23,24} Generally, higher threshold levels are associated with increased probability of food reaction. However, these levels can vary between different populations and demographic groups.²³

It is crucial to note that food-specific serum Ig E testing should not be used as a sole diagnostic strategy for diagnosis of food allergy and a negative serological test does not exclude food allergy. A referral to an allergist is recommended

so that other tests such as the SPT or oral food challenge (OFC) can be appropriately performed if the clinical history is suggestive of food reactivity. The use of food-specific serum Ig E testing in non-high risk infants is not recommended as there is little evidence for this and there is a risk that it might result in unwarranted dietary limitation.²³

Total serum Ig E can be elevated in patients with an atopic diathesis and with food allergies. However, it is neither specific nor sensitive as an independent test for food allergy.

2. Skin Prick Testing (SPT)

Skin prick testing is a commonly utilised method amongst allergists and immunologists for testing Ig E sensitisation to specific food allergens. It is safe, effective and convenient to perform in an outpatient clinical setting. The prick-prick method is used to test food extracts on the skin. The results are compared to positive (histamine) and negative (saline) controls, which are introduced to the skin at the same time. A positive SPT result is defined as a wheal of 3mm diameter or larger measured 15 minutes after the prick is performed. The size of the wheal is positively associated with clinical relevance of a food allergen but not correlated with disease severity.²³ That is to say that the size of wheal predicts the likelihood of food allergy but not the severity of a reaction.

The SPT test is known to have a high negative predictive value over 90 percent. It is a helpful test to exclude Ig E-related food allergy. In one Australian based infant cohort, the SPT 95% predictive values for allergic reactions were as the following: egg ≥ 4 mm, peanut ≥ 8 mm and sesame ≥ 8 mm. However the SPT was reported to be a poor predictor of baked egg allergy.²⁵ It is important to note that the above cutoffs may not be universally applicable in the absence of a supportive history.

3. Oral food challenge (OFC)

The OFC, usually undertaken by an allergist/immunologist, can be conducted to assist with the diagnosis of Ig E-mediated food allergy. A standardised

protocol for conducting and interpreting the results of the OFC has been outlined in the PRACTALL consensus report.²⁶ This is now recommended to exclude a food allergy if the clinical history of food related anaphylaxis is unclear and when serum Ig E or SPT testing is negative or equivocal.²³

Approach to Equivocal results

Misinterpretation of allergy tests can result in over diagnosis of food allergy. False positive SPT or food-specific Ig E results can occur in the context of high total Ig E levels (particularly in atopic patients).²⁷ A positive result can also indicate food sensitisation (asymptomatic) rather than clinical reactivity. Therefore, the choice of food allergens tested and results need to be carefully correlated with the clinical history of reactivity.²³

It is also possible to have a negative allergy test result despite a strong clinical history of food reaction. This can occur if the food reaction is not Ig E mediated. In the case of SPT testing, a negative result can ensue if the protein that triggers Ig E mediated reaction is not present in commercially prepared food extracts (fruits and vegetables), with concomitant antihistamine usage or use of topical or oral corticosteroids.²³

A referral to an allergist/immunologist for further evaluation is recommended for high-risk infants with a positive food-specific Ig E levels.

Conclusion

Optimal introduction of allergenic foods, such as peanut butter, in the first year of life is now shown to be beneficial in food allergy prevention. However studies have also shown that eczema and food allergy are intimately linked. In the context of the newly revised Australian Infant Feeding Guidelines, the dermatologist has an important role in screening and further evaluation for food allergies prior to the commencement of highly allergenic foods in those infants at high risk of allergic disease. This is important to ensure optimal management of the infant's eczema, reduce the risk of serious allergic reactions, allay parental concerns regarding food allergy and also to reinforce the message of early introduction of allergenic foods.

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wheeze) gastrointestinal symptoms (diarrhoea, vomiting, bloody stools), failure to thrive or chronic respiratory symptoms. Rarely,

a Primary

Immunodeficiency

Disorder (PID) requires
exclusion in infants with
eczema and systemic
manifestations

Infants with recurrent
urticaria (or other
symptoms to suggest
immediate hypersensitivity

reaction such as vomiting,
cough,
wheeze) gastrointestinal
symptoms (diarrhoea,
vomiting, bloody stools),
failure to thrive or chronic
respiratory symptoms.

Rarely,

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Immunodeficiency

Disorder (PID) requires
exclusion in infants with
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Figure 1. Proposed food allergy screening algorithm in high risk infants prior to commencement of allergenic solid foods.

[#] as per LEAP trial⁴ and NIAD interim consensus communications¹⁹

[^] as per Koplin et al.²⁰

* Cow's milk is the commonest allergen in 1st year of life. However, testing is not indicated if the infant has been exposed to and is already tolerating cow milk formula.

^{^^} Tree nuts are one of the key food allergens in the Australian context so testing should be considered¹⁷

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