



REVIEW ARTICLE

Role of food allergy in childhood atopic dermatitis

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Abstract: The interplay between atopic dermatitis (AD) and food allergy is complex and subject to significant misconceptions both by the general public and the medical community. Childhood AD is a very prevalent disorder. In its moderate and severe forms, AD is a challenging disorder to manage from the perspective of the child, parent and treating doctor. As AD is one of the disease manifestations of atopy, it is unsurprising that many children with AD also have a coexisting IgE-mediated food allergy. It is a common misconception that food allergy is causal in the setting of AD. However, in a proportion of sufferers, food allergy does play a role in triggering or exacerbating pre-existing AD by immune-mediated mechanisms and potentially by non-immune mechanisms. It is, therefore, important to differentiate causality, co-existent disease and disease modifiers in this context. This paper seeks to clarify the role of food allergy in childhood AD, and to outline a rational framework for the diagnosis and approach to food allergy in the context of the management of a child with problematic AD.

Key words: atopic dermatitis; eczema; elimination diet; food allergy.

Introduction

Childhood atopic dermatitis (AD) is a common disorder with an estimated prevalence of up to 20% in infants and young children in Australia.¹ Moreover, prevalence is increasing in both developed and developing nations, unlike atopic disorders such as asthma which have shown some evidence of plateauing in developed nations over the past decade.^{2,3} Although a proportion of childhood AD is mild, transitory and relatively simple to manage, at least 20% of AD may be classified as moderate or

moderate to severe in terms of disease activity,⁴ and causes significant burden of disease, stress⁵ and decreased quality of life.⁶

It is estimated that up to 40% of children with moderate AD⁷ and possibly a greater proportion of those with severe AD⁸ have a concomitant IgE-mediated food allergy. An even higher proportion of children with AD have been demonstrated to produce IgE to common food allergens.⁹ However, only a proportion of these children have clinical reactions on exposure to these foods, and there is poor correlation between IgE food allergen sensitisation and both immediate and delayed eczematous reactions in childhood AD.¹⁰ Furthermore, other testing methods to identify potential food allergens in AD such as atopy patch testing (APT) have not been shown to have value in predicting delayed reactions to foods resulting in flaring of AD.¹¹

Despite evidence to the contrary, it remains a commonly held belief that removal of one or two offending allergens from the child's diet or environment will lead to resolution of their symptoms or cure of their AD.^{12,13} Moreover, exclusion of foods from the diet of children with AD based upon IgE sensitisation alone has been shown to have unintended consequences such as nutritional deficiencies,^{12,13} failure to thrive¹⁴ and risk of anaphylaxis on re-exposure to previously 'tolerated' foods.¹⁵

The following paper will review the evidence for diagnosis of food allergies, both IgE mediated and delayed, and of dietary manipulation in the context of childhood AD.

Atopy, Food Allergy and AD: – Chicken or Egg?

Immunologists and allergists have long regarded AD as a cutaneous manifestation of the atopic state, with changes in skin histopathology and microstructure believed to be secondary to

Key Points

- Atopic dermatitis and food allergy are co-associated, but food allergy does not cause atopic dermatitis
- Foods may trigger exacerbations of atopic dermatitis
- *In vitro* specific IgE measurement and allergy skin tests have poor positive predictive value in identifying offending foods which may be exacerbating atopic dermatitis
- Food allergy is more likely to play a role in atopic dermatitis in infants and young children with severe disease
- Foods should not be removed from the diet of a child with atopic dermatitis without determining a specific clinical outcome and a clear plan for reintroduction
- Foods should be re-introduced within 3–4 weeks of removal from the diet if no clinical effect has been observed
- An observed blinded or open food challenge is the most appropriate way to identify food as a trigger for problematic atopic dermatitis

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the deregulated inflammatory process ('inside–outside' theory). There is now significant evidence to suggest that the reverse may well be true, with the 'outside–inside' hypothesis gaining support: that is, AD is the primary insult, which allows for the development of the food allergy.¹⁶

It is likely that genetic skin barrier defects, such as the filaggrin protein deficiency, are the key primary insult in the pathogenesis of AD (reviewed in reference¹⁷). A defective skin barrier may be central to developing food and aeroallergen sensitisation, with primary exposures to these antigens occurring via the epicutaneous route rather than the 'normal' oral/inhalation route. This might generate aberrant 'Th2'-type responses in genetically atopic predisposed individuals, which manifest as food and respiratory IgE-mediated allergy in the context of AD. In animal models of filaggrin deficiency, spontaneous eczema may be observed, and sensitisation via the epidermis to environmental allergens is enhanced.¹⁸ There are also epidemiological data to suggest that children with filaggrin protein defects and AD have enhanced IgE sensitisation to cat¹⁹ and food allergens²⁰ where the primary sensitising route is epicutaneous.

In keeping with this theory is the sequencing of the 'atopic march', where AD is usually the first clinical evidence of atopy, followed by food allergies and then respiratory disease (reviewed in reference²¹). Thus, the 'outside–inside' model supports the existing evidence that food exclusion cannot influence the natural history of AD or result in long-lasting disease remission but may reduce the severity of disease in selected individuals.

Clinical Approach

Clinicians are frequently confronted with infants and children covered in poorly controlled AD, and asked to determine the extent to which a food allergy may be contributing to the disease. In this setting, it is imperative to ensure that the parents and child (if age appropriate) understand that moderate-to-severe AD is a chronic, relapsing and remitting disorder, which will not be cured by any form of dietary manipulation. However, AD can be significantly improved with an individualised management plan, which may include dietary manipulation in some children. The age of the child, severity of the AD and the history of past IgE-mediated and delayed reactions to foods (urticaria, angioedema, cough, wheeze) will determine how likely it is that foods may be exacerbating the AD. Delayed eczematous reactions to foods are harder to identify from history and are likely to be significantly less frequent than co-existing IgE-mediated food allergy.^{22,23}

Children may have already had determinations of IgE to foods performed by either skin prick test (SPT) or *in vitro* specific IgE measurement (formerly radioallergen sorbent tests (RAST)). Except in the presence of a reliable history of recent immediate IgE mediated-type food reaction, these are of little value in further management. If there is a reliable history of immediate allergic reaction to the food and confirmatory IgE sensitisation, the offending food is likely to have been already eliminated from the diet, and standard food allergy management with an

anaphylaxis plan should be provided. These are clearly not causing the AD in the child as they are being avoided and 'trace amounts' in manufactured goods are generally unlikely to account for significant persistent symptoms.

Table 1 outlines the suggested approach to likely scenarios of exposure to foods and history in childhood AD and is based on synthesis of the evidence as follows.

AD and Positive SPT and/or *In Vitro* Specific IgE

Between 40 and 90% of infants with moderate-to-severe AD may have positive SPT to one or more common food allergens (such as egg, milk, peanut, wheat, potato, soy or fish).^{26,27} However, the likelihood of a child with AD reacting with either an immediate or delayed reaction in an observed food challenge (OFC) is reported to be only 27–60% of these IgE-sensitised children.^{7,8} Differences in reported frequency of reactions to OFC depend upon the inclusion criteria of the study for food challenge, the age of the patients and the type of reactions which were considered positive (immediate and/or delayed flaring of AD). Overall, it is estimated that only 30–40% of children with at least moderate AD attending a specialist service with a positive IgE to a particular food will have a positive challenge to that food under double-blind, placebo-controlled conditions.²⁸

In general, most reported reactions from OFC studies in AD are immediate IgE-mediated reactions, and therefore not likely to be an unidentified allergen in a diet causing flaring of AD. Studies which include younger children with more severe AD and do not exclude children with a history of IgE mediation reactions to the foods report higher proportions of children with positive challenges.²⁹ The negative predictive value of a SPT in the setting of AD is high³⁰ and is a good predictor that children who have never been exposed to a food will not have an immediate allergic reaction on initial exposure.

Component-resolved diagnostics (CRD) are increasingly being used in the setting of IgE-mediated food allergy and have the potential to assist in the identification of specific food epitopes to which the subject has become sensitised. A detailed account of CRD is beyond the scope of this review; however, they have potential value in identifying specific characteristics of the food allergy, such as likelihood of persistence of allergy and cross reactivity with other foods and aeroallergens (reviewed in reference³¹). Their utility in the diagnosis of food allergens relevant in AD is yet to be defined.

Summary and recommendation:

- SPT sensitivity does not equal clinical reactivity, and most food challenges detect immediate, not delayed, eczematous reactions to the offending foods. Overall, a positive SPT in the presence of past known ingestion without immediate reaction has a very poor positive predictive value for identifying food allergens triggering AD.
- Children who have IgE sensitisation (positive SPT or *in vitro* specific IgE) and a history of tolerating the food without immediate reaction should not have the food excluded from the diet until an observed challenge clearly confirms a delayed eczematous reaction.

Table 1 Approach to the child with atopic dermatitis and suspected food allergy

Possible scenarios	SPT/RAST	Food strategy	Additional management	Reintroduction
Eaten the food/s previously with immediate IgE reaction	Yes	Avoid food	As per ASCIA for food allergen avoidance	Not until tolerance established
Eaten the food/s previously with observed delayed reaction	No	Remove from diet for short period of time (3–4 weeks) if AD moderate-severe	Eczema diary – daily skin score† OFC if significant improvement Only continue exclusion following positive OFC	Reintroduce if no improvement after 3 weeks Reintroduce food with caution if removed for long period of time
Eaten the food/s previously – No observed immediate or delayed reaction	No	Do not remove from diet		
Eaten the foods previously – No observed immediate or delayed reaction SPT/ <i>in vitro</i> specific IgE positive			OFC	Reintroduce food with caution if removed for long period of time
Never eaten the food	No – unless high index of suspicion of food allergy or very severe disease	Slow introduction of foods	OFC if SPT/ <i>in vitro</i> specific IgE performed and positive – as below	
Never eaten the food SPT/ <i>in vitro</i> specific IgE positive	Confirm positive test		OFC unless SPT or <i>in vitro</i> specific IgE >95% PPV for IgE-mediated reaction ^{24,25}	

†Parents record daily parental/child assessment of AD on a scale of 1–10, new foods introduced or foods removed are recorded. ASCIA, Australian Society for Allergy and Clinical Immunology; OFC, observed food challenge; RAST, radioallergosorbent tests; SPT, skin prick test.

Are There Other Tests which are Better than RAST or SPT to Identify Food Allergy in AD?

APT, where allergens are directly applied to the skin under an airtight chamber and subsequently examined for delayed eczematous reactions at 48–72 h, has not been shown to significantly increase the predictive value of OFC in identifying food allergies in children with AD.^{11,32} The test relies on non-standardised reagents, is time consuming, requires an experienced evaluator for reliability and has no current defined role in the clinical setting for AD management.³³ *In vitro* T cell proliferation assays³⁴ and food-specific *in vitro* activation tests³⁵ remain a research tool at this stage (reviewed in reference ³⁶).

The current best practice for determination of food allergy in AD is an observed double-blind, placebo-controlled food challenge, which includes evaluation of the child on the day of and at least the day after the challenge.^{28,37} For practical purposes, most food challenges are performed as open, unblinded challenges. Where results are equivocal in an open challenge, a blinded placebo-controlled challenge can follow. Blinding of foods, especially for infants undergoing a food challenge, can be problematic, and capsule challenges for older children (except for additives such as colours and preservatives) are generally not in use in Australian centres. Food challenges should be carried out in a setting with appropriate protocols and anaphylaxis preparedness.

Summary and recommendation:

- A blinded, placebo-controlled oral challenge is the gold standard for establishing food allergy in AD; however, observed open challenges are usually adequate in the clinical setting.

Exclusion Diets for AD

Exclusion diets for children with AD may consist of the removal of individual single foods; removal of common allergens such as eggs, milk, wheat, nuts, soy and fish; a 'few foods diet' (quite a restricted diet); or an elemental diet (elemental formula only). A 2008 Cochrane review found insufficient evidence to support egg- and milk-free diets, elemental or few foods diets in unselected participants with AD.³⁸ The review identified a total of nine randomised controlled trials that were considered suitable for meta-analysis. There was some evidence for removal of egg in infants with moderate or severe AD and IgE sensitisation to egg, where significant improvement but not resolution of AD was observed.³⁹ It is likely that this study identified largely concomitant IgE-mediated egg allergy as 85% were positive on OFC with immediate reactions to egg and all reported ingesting small amounts of egg in their regular diet.

In the absence of a clear history of IgE-mediated reactions, many other exclusion diets have not been shown to improve the severity of AD. In a study of Sinagra *et al.*, 80% of children on a milk-free diet for AD control had positive SPT and/or RAST to milk; however, only 4% were noted to react on open challenge.⁴⁰ A similar study examining milk exclusion in children with AD found that only 9% of the children had clinical deterioration of their dermatitis on reintroduction of milk.⁴⁰ Hanafin *et al.*⁴¹ found only one in 58 eczematous reactions after reintroduction of previously removed common foods (eggs, milk,

wheat, soy, peanut, fish) from the diet of children with severe AD at OFC. Published studies suggest that young infants with moderate and severe disease may respond more readily to an elimination diet than older children.⁴²

Maternal Exclusion Diets in Breastfeeding Infants

Exclusion of foods from the maternal diet in breastfeeding infants with AD is frequently recommended, but well-conducted studies to support its use are lacking. Maternally ingested food allergens are known to be present in breast milk.⁴³ A recent Cochrane review on this subject states, 'Dietary antigen avoidance by lactating mothers of infants with atopic eczema may reduce the severity of the eczema, but larger trials are needed.'⁴⁴ These recommendations are based upon a study which examined 17 infants in a crossover study. There was no significant difference in severity of AD between the dietary exclusion groups and the normal maternal diet groups; however, soy was used as the milk replacement for the mothers, which may have interfered with the intervention. Of note, the authors reported that improvement in AD was unrelated to known IgE sensitisation status of the infants.⁴⁵ Other observational cohort studies, without control groups, crossover or randomisation, have reported conflicting results in the improvement of AD in breastfed infants using maternal elimination diets.⁴⁶

The role of breastfeeding and type of formula in the primary prevention of AD is beyond the scope of this review, but, again, strong evidence for manipulation of the maternal diet is lacking in this setting.⁴⁴

Summary and recommendation:

- The evidence for the efficacy of elimination diets in children with AD is poor.
- Exclusion of foods is more likely to be useful in young infants, those with clinical history of reactions and those with severe disease.
- Maternal exclusion diets in breastfeeding infants may reduce the severity of their AD, but good evidence is lacking.

Risk of Anaphylaxis on Re-exposure to Previously Tolerated Foods in AD

There have been several disturbing reports of children with moderate or severe AD experiencing anaphylaxis on re-exposure to foods that they had previously tolerated in their diet.^{13,15,47} These foods had generally been removed on the basis of IgE sensitisation (SPT or *in vitro* specific IgE measurement) for long periods of time, usually greater than 3–6 months. Children with moderate-to-severe AD appear to be at particular risk and, consequently, foods which have been strictly avoided for a long period of time (>3–6 months) should be reintroduced cautiously under challenge conditions with appropriate emergency provisions.

There is no good evidence for the optimal time for the safe removal and subsequent reintroduction of allergenic foods in the management of AD. It is suggested that 3–4 weeks is sufficient to observe significant clinical improvement and short enough to prevent the loss of tolerance to previously ingested

food allergens. In cases where removal of foods under suspicion is equivocal, due to other environmental or infectious triggers of the AD, foods should be reintroduced and then again removed when the exacerbation has been controlled.

When significant improvement is observed and the foods are withdrawn for long periods of time, reintroduction of the foods at a later stage (sometimes years) should be undertaken with caution, in an appropriate setting. The history of the absence of immediate IgE-mediated symptoms on ingestion in the presence of IgE sensitisation (tolerance) should not be assumed to have persisted.

Colour, Preservative and Additive-Free Diets in AD

The association between additives, colouring agents and preservatives in the diet and AD is controversial, and weaker than that for chronic urticaria, where improvement following strict additive-free diet is reported in 10–20% of adolescent and adult patients with chronic urticaria.⁴⁸ These reactions are typically associated with itch and urticaria and are likely related to mast cell degranulation by non-IgE mechanisms.

No randomised controlled trials have addressed this issue in AD. Fuglsang *et al.*⁴⁹ examined a heterogeneous group of atopic subjects which included AD, asthma, allergic rhinitis and urticaria with an additive-free diet and OFC. Sixteen of 23 positive challenges out of a total challenge of 355 were reported as AD exacerbations. Vieluf *et al.*⁵⁰ reported on single-blind additive challenges in a group of adults and children with severe AD. Fourteen of 26 positive reactions resulted in exacerbations of AD. Others have described clinical improvement in 23/50 adults with AD placed on an additive-free diet but were not able to show associated positive challenges to the excluded additives on reintroduction.⁵¹

There is no role for skin or pathology tests in identifying potential additive triggers. If an additive diet is considered for a child with AD, a standard low additive diet, such as outlined by Reese *et al.*⁵² is recommended. The diet should be for a short, defined period of time (usually 3 weeks) and if no significant improvement in AD is observed, the diet should be immediately normalised. If significant improvement has been observed, a series of blinded, placebo-controlled additive challenges should be performed. These are very time-consuming and difficult to interpret given the fluctuating nature of AD and the delayed nature of possible reactions. An additive-free diet should not be attempted without the supervision of an experienced paediatric dietitian. Given the difficulty of compliance with the diet, it should only be attempted when clinical suspicion is high and the parents and patient are enthusiastic.

Summary and recommendation:

- High-quality evidence is lacking for additive-free diets in AD. They are time consuming, unpalatable, largely unproven and should not be undertaken without expert dietitian input.

Summary

The relationship between food allergy and AD is complex. Many children with moderate or severe AD will have a co-existing IgE-mediated food allergy which will have been identified by a

typical immediate allergic reaction. These food allergies do not cause the AD, although will trigger significant exacerbations and their removal has not been shown to alter the natural history of the disorder. SPT and *in vitro* specific IgE measurements have poor predictive capabilities for both immediate and delayed eczematous reactions, especially in the context of a prior history of no immediate reaction to the food.

In infants and children with severe disease, exclusion diets might play a role in managing the disease, but they require careful planning, expert dietitian support and clear plans for reintroduction of eliminated foods. Care must be taken not to leave children on nutritionally inadequate or overly restrictive diets when no significant improvement in their dermatitis has been observed. Any elimination of foods should be coupled with an exit strategy, which should include clinical and time end points, an OFC and a clear plan for reintroduction.

Multiple Choice Questions

- 1 A 7-year-old boy presents for assessment of his atopic dermatitis and food allergies. He has been on a restricted diet for 2 years, following results of *in vitro* specific IgE measurement that showed sensitisation to egg and cows milk. He had previously tolerated milk and egg in his diet without any obvious reaction and his eczema has gradually improved over the past 2 years. He was noted to have positive SPT to cows milk and egg 6 months ago.

Which one of the following is the most appropriate management for his diet?

- A Continue to exclude egg, milk and peanut.
- B Repeat *in vitro* specific IgE measurement to egg and cows milk.
- C SPT to other commonly ingested foods in current diet.
- D Observed food challenge.
- E Introduce small amounts of milk and egg in baked form.

Answer: D

Following long-term exclusion from the diet, children with AD have been reported to have severe allergic reactions on re-exposure to previously tolerated foods, presumably related to a loss of tolerance. SPT and IgE measurement are unlikely to be of significant assistance in this boy in the absence of a clinical reaction and the most appropriate management is a supervised observed food challenge.

- 2 A 12-month-old infant presents with a history of intermittent flexural and truncal eczema. She gets redness but no urticaria around her mouth after eating strawberries and tomato, but has had no other reactions to foods and has an unrestricted diet.

Which one of the following is the most appropriate management?

- A SPT to strawberry and tomato.
- B SPT to common panel of food allergens.
- C Observed food challenge.
- D Colour and preservative free diet trial.
- E Reassurance only.

Answer: E

Infants with AD commonly have irritant reactions to foods that come into contact with the skin such as tomato, strawberry and citrus fruits. In the absence of angioedema, urticaria or other

IgE-mediated symptoms, true allergy to these types of foods is very rare. If the reactions are transient and no residual facial eczema is apparent, no dietary exclusions are necessary. Often, simple application of thick emollient to the face and perioral area prior to meals will help with the irritant reactions.

3 A 9-month-old infant presents with widespread eczema with crusting and weeping lesions over the face, arms, legs and trunk. He is obviously uncomfortable and itchy and he wakes frequently over the night. He is breastfed and has had solids including wheat, modified cows milk and baked egg in his diet for the last 3 months. His mother is unsure whether he reacts to these foods as he seems to be constantly red and itchy. He is being managed with mid-potency topical steroids once daily.

Which one of the following is the most appropriate first step in management of this infant?

- A SPT to wheat, milk and egg.
- B Elimination diet.
- C Trial of elemental formula.
- D Intensification of topical therapy.
- E Elimination of egg, milk, wheat from maternal and infant diet.

Answer: D

This infant has moderate/severe AD and his skin needs to be under improved control before assessment of whether foods might be playing a role. The first step would be to intensify his topical regime with a mid/high potency steroid at least twice daily and wet wraps. He might also have an added staphylococcal super-infection that needs to be treated with oral antibiotics, such as flucloxacillin or cephalexin. Foods might well be playing a role in this infant as he is young with severe disease. Once his skin is under maximal therapy for a 2–3-week period, he should be reassessed for a history of immediate reactions to his current diet. He might require a short elimination diet (3 weeks) and then OFC to assess potential food allergies. Food exclusions and intensification of the topical regime +/- oral antibiotics should not be performed simultaneously during a flare, as it will not be clear which strategy has been successful in improving his AD.

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