

REVIEW ARTICLE

Food allergy testing in infantile eczema: A clinical approach and algorithm

Kate Newland,¹ Lachlan Warren¹ and Michael Gold²

¹Department of Dermatology, Women's and Children's Hospital, and ²Discipline of Paediatrics, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia, Australia

ABSTRACT

The complex relationship between food allergy and infantile eczema has prompted divergent approaches to investigating potential food triggers in eczematous patients. It is well recognised that a significant proportion of infants with eczema have immunoglobulin E-mediated food allergy, reported to range between 20–80%. Determining whether certain foods trigger an eczematous flare in individual infants with eczema is difficult. For all infants with eczema, good skin care is the mainstay of treatment but identifying and avoiding triggers (both allergic and non-allergic) is important in some infants. Given this, we have developed an algorithm that can be used by dermatologists in the investigation and management of food allergies in infantile eczema. Issues such as patient selection, investigation and elimination diets are addressed, with reference to relevant evidence in the literature. Our aim is to provide dermatologists with a framework to manage food allergies in infantile eczema, allowing the problem to be addressed with confidence.

Key words: atopic eczema, food allergy, immunoglobulin E serological testing, skin prick testing.

INTRODUCTION

Atopic eczema is a chronic inflammatory skin disease, commonly beginning in infancy at under 12 months of age. It is reported to affect 28% of Australian infants and makes up a significant proportion of referrals to dermatologists.¹

Adverse reactions to food are frequently reported by parents of children under 3 years of age. In considering potential adverse reactions to food it is important to differentiate between food allergy and food intolerance (Fig. 1). In this review we highlight immunoglobulin-E (IgE)-mediated food allergy. The role of food allergy and its significance in eczema management is commonly raised by parents and thus needs to be addressed with confidence. It can be difficult for dermatologists to determine which infants should be investigated for a suspected food allergy, which tests are appropriate and how to manage a food allergy. In this article we aim to provide dermatologists with a framework for investigating and managing food allergies in infants with atopic eczema, and review relevant issues from allergy, immunology and dermatology literature sources.

There are two important considerations in the relationship between allergy and eczema. Firstly, most infants and children with food allergies have eczema,² which often develops in early infancy and may pre-date the presentation of a food allergy. Thus, infants with eczema are at increased risk of food allergies. Secondly, some infants and children with eczema and food allergies may have their eczema exacerbated by their continued exposure to the allergenic food.³

Is food allergy associated with atopic eczema?

The prevalence of food allergy in infants with atopic eczema is reported to range from 20 to 80%.³ Hill and colleagues have extensively investigated the relationship between atopic eczema and food sensitisation, finding that 80% of infants referred to a dermatology department with moderately severe eczema had immunoglobulin E (IgE)-mediated food sensitisation to cow's milk, eggs, or peanuts.⁴ Food allergies to more than one of these food proteins often

Correspondence: Dr Kate Newland, Women's and Children's Hospital, 72 King William Road, North Adelaide SA 5006, Australia. Email: kmnewland@live.com.au

Kate Newland, MBBS. Lachlan Warren, FACD. Michael Gold, FRACP.

Submitted 15 October 2011; accepted 26 February 2012.

Abbreviations:

DBPCFC	double-blind, placebo-controlled food challenge
IgE	immunoglobulin E
PID	primary immunodeficiency disorder
SPT	skin prick testing

occur. The reasons why infantile eczema is a risk factor for food allergy is unknown, but one hypothesis that is supported by ecological evidence is that transdermal sensitisation by environmental food allergens may be a facilitating factor.⁵ Thus, a proportion of infants and children presenting to a dermatologist will have an associated food allergy, including some who have experienced food anaphylaxis. A suggested approach is to ask a basic question about the infant's past ingestion of the six common foods that are potentially allergenic (cow's milk, soy, eggs, wheat, seafood and peanuts). Our approach is to ask, 'Has your child ever had immediate (within 60 min) skin rash (usually urticaria) with or without vomiting, cough, difficulty breathing or collapse after exposure to one of these foods?' It is important to ascertain whether there was a history of anaphylaxis and, if so, to initiate a referral to an allergist or general paediatrician. The aim of this would be to educate the parents on food avoidance and establish a management plan that may include access to an adrenaline auto-injector (for infants whose weight exceeds 10 kg).

Food allergy as a trigger for atopic eczema: what is the evidence?

While the association between eczema and immediate food allergy has been well documented, it has been more difficult to demonstrate that ongoing exposure to food in the infant diet may exacerbate eczema.⁶ Eczematous reactions to food are delayed reactions in which eczema flares within hours to 2 days after a food challenge.⁷ The evidence that food may trigger eczema is based on laboratory evidence and clinical studies. These studies have used different methodologies including a double-blind cross-over trial (Atherton and colleagues), a randomised controlled trial (Lever and colleagues) and a number of retrospective reviews of oral food challenges (Sampson and Scanlon,

Sampson and McCaskill, Sampson and Metcalfe, Eigenmann and colleagues Niggemann and colleagues).^{8–15} Breuer and colleagues found that more than 50% of all positive oral challenges in children suffering from atopic eczema were associated with an exacerbation of eczema.¹⁴ Niggemann and colleagues observed late reactions in 25% of positive provocation tests¹⁵ (Table 1). It is proposed that a late phase IgE response may be implicated in eczematous reactions to food,¹⁶ with homing of food-responsive T-cells to the skin.¹⁷ Certainly, there is mounting evidence that foods exacerbate eczema in young children through both IgE-mediated and non-IgE-mediated mechanisms.

Which infants with eczema should be tested when considering a food allergy trigger?

Eczema commonly appears in the first 4–6 months of life, often coinciding with the introduction of solids. This leads many parents to believe, often incorrectly, that their child's eczema is triggered by a food allergy. Since not all infants with eczema have a food allergy and universal IgE testing (either serological or skin prick testing [SPT]) of eczematous infants is not recommended, the following guidelines are suggested for identifying which infants with eczema may have a food allergy and triggers investigated further.

Infants with severe eczema

An Australian study assessed 141 infants with atopic eczema using SPT and found that the relative risk of an infant with eczema having a food allergy increased with the severity of eczema.¹⁸ Most articles suggest that those with persistent severe atopic eczema who do not respond to proper skin care should be investigated.

There are different methods by which the severity of eczema can be quantified. These include scoring methods such as the scoring atopic dermatitis index,¹⁹ the six-area, six-sign atopic dermatitis severity score²⁰ and the eczema severity score.⁴ However, we appreciate that in practice most dermatologists do not use these scoring systems and assess eczema severity based on their clinical experience. Thus, the diagnosis of severe eczema is at the dermatologist's discretion for the purpose of this algorithm. Factors such as continuous symptoms, significant sleep disturbance, large body surface involvement, failure of response to topical steroids (including wet wraps) and requirement for hospital admission may indicate increased eczema severity.

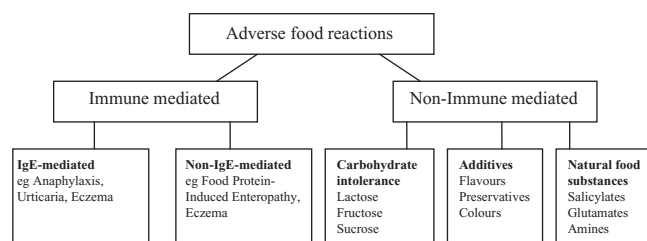


Figure 1 Types of adverse food reactions.

Table 1 Reactions in double-blind placebo-controlled food challenges (DBPCFC) to soy, wheat, cow's milk and eggs in infants and children with atopic eczema (*n*, %)

	Study methodology	DBPCFC (<i>N</i>)	Positive reactions	Immediate reactions	Late reactions (eczematous)	Combined immediate + late reaction
Breuer and colleagues	Retrospective	106	49 (46)	21 (43)	6 (12)	22 (45)
Niggemann and colleagues	Retrospective	259	131 (51)	91 (70)	33 (25)	6 (5)

Immediate reactions include urticaria, angioedema, erythema, gastrointestinal and respiratory symptoms.

It is our proposal that allergy testing be considered in all infants with severe eczema under the age of 6 months. Infants with moderate to severe eczema who do not respond to standard topical therapy (soap substitutes, emollient, mild to moderate topical steroids with or without wet wrapping) should be considered for allergy testing.

Infants with eczema plus urticaria or systemic symptoms, or both

Infants with recurrent urticaria (or other symptoms to suggest immediate hypersensitivity reaction such as vomiting, coughing and wheezing; gastrointestinal symptoms such as diarrhoea, vomiting and bloody stools; failure to thrive or chronic respiratory symptoms in addition to their eczema should undergo food allergy testing. Rarely, a primary immunodeficiency disorder (PID) requires exclusion in infants with eczema and systemic manifestations. A PID should be considered when there is parental consanguinity, an onset of eczema in the neonatal period, erythroderma, large and multiple lymphadenopathy, alopecia, opportunistic or severe infections, failure to thrive, lymphopaenia or thrombocytopaenia. In the above situations, urgent referral to an allergist or immunologist, paediatrician, or both, is appropriate.

Positive history of food reactions

Parents may give a history of an immediate or delayed reaction to certain foods. Eczematous reactions to foods are usually delayed (hours to 2 days),¹⁴ which make attributing certain foods to a flare of eczema difficult. However, if a parent gives a convincing history of either an immediate or delayed reaction to staple foods (e.g. milk, eggs and wheat), then allergy testing is recommended. Niggemann and colleagues found that children of parents with a specific suspicion of food-related symptoms showed positive results to food challenge significantly more often than children without parental suspicion.¹⁵

Which testing method should be used for IgE-mediated food allergy?

A double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard for diagnosing a food allergy.²¹ However, this is a time-consuming investigation that often requires a hospital admission. Considering this, serological IgE (UniCap previous known as RAST testing) or SPT are useful in the determination of an IgE-mediated food allergy. When testing, it is important to remember that a positive SPT or serum food-specific IgE test result indicates sensitisation but not necessarily a clinical allergy. This is often a source of confusion and it is vital to assess the significance of these tests in light of the clinical history.

Specific IgE serological testing and total IgE

In regards to specific IgE serological testing, Sampson and colleagues proposed that the quantification of food-specific

IgE is a useful test for diagnosing a symptomatic allergy to eggs, milk, peanut, fish, soy and wheat. Those with a positive serological test (using decision points as proposed by Sampson and colleagues) to eggs (6 kUa/L), milk (32 kUa/L), peanuts (15 kUa/L) and fish (20 kUa/L) have a 95% probability of reacting to a food challenge.²¹ The positive predictive value for soy (65 kUa/L) was found to be 86%, while using the decision point 100 kUa/L for wheat, the positive predictive value is 100%.²¹ Additionally, increasingly higher concentrations of food-specific IgE levels correlate with an increasing likelihood of a clinical reaction. However, they do not predict the reaction severity, such as the risk of anaphylaxis.²¹

It must be noted that these decision points proposed by Sampson are for immediate reactions and were not designed to predict late eczematous reactions to foods.²² The positive predictive value of food-specific IgE in eczematous reactions is 33%.⁵ The low specificity of serological testing is due to a large number of patients with asymptomatic hypersensitivity, that is, 'sensitisation'.¹⁵ Serological testing has a relatively high negative predictive value, estimated to be 75%.²² However, this implies that 25% of IgE-mediated food allergies will not be detected by serological testing. Therefore, negative serology should be interpreted with some caution.

Despite the limitations of specific IgE serological testing, the Australian Society of Clinical Immunology and Allergy advises that specific IgE serological testing in children with eczema can help to identify possible food trigger(s).²³

Hen's eggs, cow's milk, soy, wheat and peanuts account for most allergenic foods in children with atopic eczema.^{3,4} We therefore recommend serological IgE testing for these five foods in infants with severe atopic eczema as the first step in the evaluation of food allergy.

The measurement of total IgE levels is a non-specific and non-sensitive investigation. IgE concentrations are age dependent and overlap widely between atopic and non-atopic populations.²⁴ It is therefore our recommendation that total IgE levels not be tested in children with atopic eczema unless as part of investigation for a PID.

Skin prick testing

SPT in Australia is most commonly performed by allergists and detects IgE sensitisation to common specific food allergens. An increasing SPT wheal size is associated with an increased likelihood of a clinical allergy.¹⁷ Hill and colleagues found that SPT is more sensitive in diagnosing allergies to eggs and peanuts than serological testing, but is similar in the diagnosis of cow's milk allergy.²⁵

A number of studies have confirmed that negative SPT responses have excellent negative predictive values (>90%) for excluding the presence of an IgE-mediated food allergy and is superior to that of serological testing. Thus, in the presence of a positive serology test without a clear history of allergy, a negative SPT could be used to exclude an IgE-mediated food allergy.¹⁷

Alternative methods of food allergy testing

Atopy patch testing is performed by placing foods and aeroallergens under patch testing chambers in the same way that skin testing is performed for contact allergens. This method of testing is not used to diagnose IgE-mediated food allergy and is still not generally recommended for the routine diagnosis of food-induced eczema (which may be non-IgE-mediated).^{7,26} A recent study involving a large number of children concluded that atopy patch testing does not lead to a significant reduction of the need for oral food challenge when food-induced eczema is suspected.²⁷ Hence, atopy patch testing is not included in our algorithm.

Food specific-IgG and IgG4 antibodies were historically believed to be useful diagnostic tools in the investigation of food allergies.²⁴ However, these antibodies have never shown a correlation with the diagnostic results of DBPCFC. The current recommendation is that food-specific IgG and IgG4 antibodies are not useful in the investigation of a food allergy.²⁴

Recommendation

In summary, both serological IgE testing and SPT can be useful in the investigation of food allergy in infantile eczema. Serological IgE testing has the benefit of being easily accessible to dermatologists and thus the patients under their care. SPT has the advantage of having a higher negative predictive value (>90% *vs* 75%) than serological IgE testing and is more sensitive in the diagnosis of egg and peanut allergies.^{17,22,25} The disadvantage of SPT is that it is performed by allergists or immunologists and is not immediately accessible to many dermatologists wanting to investigate food allergies in patients with infantile eczema. Both serological IgE testing and SPT decrease the number of DBPCFC performed, making them cost effective investigations.

What is the role of elimination diets in the management of atopic eczema?

Unnecessary diets that are not based on a precise diagnosis can lead to additional parental stress and malnutrition in patients with atopic eczema.^{7,28} They are commonly initiated by parents, often with minimal evidence supporting their use. However, elimination diets do have a role to play in the assessment and management of infants with atopic eczema. A positive serological test in the setting of a strong clinical suspicion should be followed by a 2-week diagnostic elimination diet with dietician support, if required. Dietetic support ensures that parents have been educated in removing the triggering food(s) from the diet and that the diet remains nutritionally adequate. If the eczema improves during the elimination period (as assessed by the treating dermatologist and reported by parents in regards to decreased itch, improvement in sleep and less requirement for topical steroids) the infant should continue to avoid the

offending food. Ideally, at this stage the infant should be referred to an allergist for consideration of an oral food challenge, along with a dietician for nutritional support, if such specialists are not already involved.

If the elimination diet does not result in a reduction in the eczema, the probability that the suspected food allergy is clinically relevant is low. In this case, food challenges are unnecessary, as are dietary restrictions and the food can be added back to the diet.²⁶ There have been a number of case reports of more severe allergic reactions, including anaphylaxis, following the re-introduction of food following an elimination diet.²⁹ It is unclear how frequently this occurs but parents should be instructed to cease re-introduction if allergic symptoms occur. In addition, a graded introduction of the food could be considered with clear instructions to stop the food if allergic symptoms occur such as generalised urticaria, vomiting or any respiratory symptoms.

Does the maternal diet need to be altered in breast-fed infants with a food allergy?

There is a large amount of evidence supporting breast-feeding in infants. However, it must be remembered that all food proteins may pass from the maternal diet into breast milk. If a food allergy is identified in breast-fed infants it may be necessary to modify the mother's diet, with the support of a dietician.^{6,30} This should be done as a 2-week trial only.

It is our suggestion that the same principles of allergy testing be applied to both breast-fed and formula-fed infants, obviously with the consideration of maternal diet in breast-fed infants. In some infants an extensively hydrolysed or an amino acid formula is used in the setting of a cow milk allergy.

CONCLUSION

Our suggested algorithm for the investigation of food allergies in infants with infantile eczema (Fig. 2) has limitations, particularly in the case of non-IgE-mediated food allergies, which are estimated to affect about 10% of infants and children with eczema.³¹ Given that a significant percentage of infants with atopic eczema have a food allergy, it is important that dermatologists feel confident in the initial stages of assessment, even if the food allergy is not triggering the eczema. We accept that there is debate as to the role IgE-mediated food allergy plays in eczema exacerbation. It is our belief that food allergies do play a role in triggering eczema in some individuals. The focus of management in infants with eczema should remain on good skin care but in some infants investigation for a food allergy is recommended. We believe that this algorithm provides dermatologists with a framework to investigate food allergies, offering clarification of the role of food allergy in individual infants with eczema, a decrease in parental concern, reduction of unnecessary exclusion diets and enhanced eczema management.

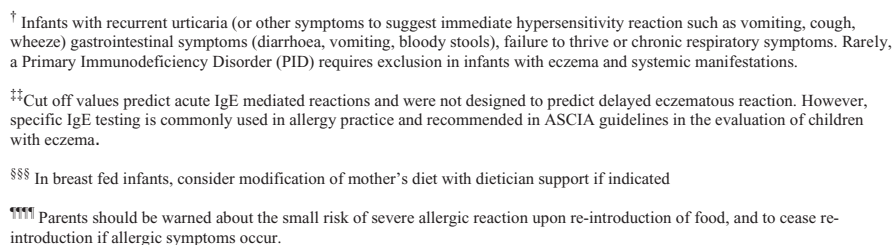


Figure 2 Algorithm for the investigation and management of food allergies in infantile eczema.

REFERENCES

- ## REFERENCES
1. Hill DJ, Hosking CS, de Benedicts FM *et al.* Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin. Exp. Allergy* 2007; **38**: 161–8.
 2. Leung DYM, Sampson HA, Geha RS *et al.* *Pediatric Allergy: Principles and Practice*. St Louis, MO: Mosby, 2005: 558.
 3. Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr. Opin. Allergy Clin. Immunol.* 2004; **4**: 379–85.
 4. Hill DJ, Heine RG, Hosking CS *et al.* IgE food sensitization in infants with eczema attending a dermatology department. *J. Paediatr.* 2007; **151**: 359–63.
 5. Worth A, Sheikh A. Food allergy and atopic eczema. *Curr. Opin. Allergy Clin. Immunol.* 2010; **10**: 226–30.

6. Rance F. Food allergy in children suffering from atopic eczema. *Pediatr. Allergy Immunol.* 2008; **19**: 279–84.
7. Werfel T, Ballmer-Weber B, Eigenmann PA *et al.* Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy* 2007; **67**: 725–8.
8. Atherton DJ, Sewell M, Soothill JF *et al.* A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; **1**: 401–5.
9. Lever R, MacDonald C, Waugh P *et al.* Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr. Allergy Immunol.* 1998; **9**: 13–9.
10. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J. Pediatr.* 1989; **115**: 25–7.
11. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 115 patients. *J. Pediatr.* 1985; **107**: 669–75.
12. Sampson HA, Metcalfe DD. Food allergies. *JAMA* 1992; **268**: 2840–4.
13. Eigenmann PA, Sicherer SH, Borkowski TA *et al.* Prevalence of IgE mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; **101**: E8.
14. Breuer K, Heratizadeh A, Wulf A *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin. Exp. Allergy* 2004; **34**: 817–24.
15. Niggemann B, Sielaff B, Beyer K *et al.* Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin. Exp. Allergy* 1999; **29**: 91–6.
16. Lever R. The role of food in atopic eczema. *J. Am. Acad. Dermatol.* 2001; **45**: S57–60.
17. Sicherer SH, Sampson HA. Food allergy. *J. Allergy Clin. Immunol.* 2010; **125**: S116–25.
18. Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiological study. *Pediatr. Allergy Immunol.* 2004; **15**: 421–7.
19. Kunz B, Orange AP, Labreze L *et al.* A clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; **195**: 10–9.
20. Berth-Jones J. Six-area, six-sign atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br. J. Dermatol.* 1996; **135**: 25–30.
21. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J. Allergy Clin. Immunol.* 2001; **107**: 891–6.
22. Suh KY. Food allergy and atopic dermatitis: separating fact from fiction. *Semin. Cutan. Med. Surg.* 2010; **29**: 72–8.
23. Australasian Society of Clinical Immunology and Allergy – ASCIA (internet). . (Updated 3/11/2011) Available from URL: <http://www.allergy.org.au/content/view/175/148>. (Accessed 16 Dec 2011)
24. Hamilton RG. Clinical laboratory assessment of immediate-type hypersensitivity. *J. Allergy Clin. Immunol.* 2010; **125**: S284–96.
25. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr. Allergy Immunol.* 2004; **15**: 435–41.
26. Werfel T, Erdmann S, Fuchs T *et al.* Approach to suspected food allergy in atopic dermatitis. Guideline of the Task Force on Food Allergy of the German Society of Allergology and Clinical Immunology (DGAKI) and the Medical Association of German Allergologists (ADA) and the German Society of Pediatric Allergology (GPA). *J. Dtsch. Dermatol. Ges.* 2009; **7**: 265–71.
27. Mehl A, Rolinck-Werninghaus C, Staden U *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J. Allergy Clin. Immunol.* 2006; **118**: 925–9.
28. Bath-Hextal FJ, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. *Cochrane Database Syst. Rev.* 2008; (1): CD005203. doi: 10.1002/14651858.CD005203.PUB.2.
29. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch. Dis. Child.* 1984; **59**: 985–6.
30. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database of Systemic Reviews* 2006; (3): CD000133. doi:10.1002/14651858.CD000133.PUB.2.
31. Niggemann B, Reibel S, Roehr CC *et al.* Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J. Allergy Clin. Immunol.* 2001; **108**: 1053–8.