In a child with atopic dermatitis, parents and the treating doctor may desire or need to consider the potential role of allergic triggers. The role of allergens in atopic dermatitis and the available and appropriate allergy testing methods are discussed in this article.

A topic dermatitis (AD) is a common affliction of children and both its diagnosis and management provide concerns for patients and their medical advisors. Children with AD often have other atopic (immunoglobulin E [IgE]-mediated) disorders, such as asthma, food allergies and allergic rhinitis. AD is also often referred to as ‘eczema’; although AD is technically a subtype of eczema, in common practice the terms are used interchangeably. Allergic contact dermatitis, however, is different to AD, usually manifesting within days (rather than minutes or hours) of exposure in areas of skin directly in contact with the allergen.

The clinical manifestations of AD are skin changes characterised by erythema, scaling, weeping and pruritus. The distribution of skin lesions in AD varies with the patient’s age: typically infantile AD involves the face, scalp, arms and legs, whereas in older children lesions are often prominent on flexor surfaces of the extremities. Onset of AD is primarily before the age of 5 years, and often before 1 year of age. The impact of this condition can be severe, particularly because of the accompanying intense pruritus, which often has a significant impact on a child’s functional ability and can cause major sleep disturbance. The consequences of AD are not limited to the child as family members also suffer major effects and incur significant personal and financial costs.

The aetiology of AD is related to an underlying defective skin barrier with altered immune responses to environmental allergens, skin irritants and micro-organisms. Multiple genetic abnormalities have been identified in patients with AD, with most evidence linking AD with a mutation in the FLG gene, which encodes for filaggrin (derived from ‘filament-aggregating protein’). Filaggrin assists in the strength and structure of skin and aids in epidermal hydration. Defective filaggrin expression has been widely demonstrated in people...
with AD, asthma and allergic rhinitis, suggesting that impaired skin barrier function has a significant role in atopic diseases as a whole.1,6

The usual recommendations for treatment of AD can be summarised by the following steps:

- Education regarding the aetiology and natural history of AD
- Consideration of triggers and exacerbating factors (including a discussion of the possible partial and variable role of allergic triggers)
- Reduction of irritant exposures
- Maximising the barrier function of the skin by moisturising (i.e. appropriate use of emollients)
- Appropriate use of topical corticosteroid and anti-inflammatory therapies
- Consideration of antimicrobial or adjunctive modalities.

This article focuses on the assessment of the allergic triggers that can cause AD. A careful history of allergy should be obtained in children with exacerbations of atopic dermatitis, and children with severe or refractory AD should be further investigated. This investigation is discussed below, and the flowchart provides a useful pathway to guide this process.

**ALLERGIC TRIGGERS IN AD**

The triggers that may exacerbate AD via an allergic (immune) mechanism include food proteins, aeroallergens and excipients contained in topical products. Testing for allergies involves serology or skin prick testing to detect allergen-specific IgE (in immediate-type hypersensitivities), epicutaneous patch testing (in delayed-type [type 4] hypersensitivities) and provocative oral challenges, usually to foods.

Any form of allergy testing, however, can only be correctly interpreted in conjunction with the clinical history. This is best illustrated by considering testing for food allergen-specific IgE, which can determine sensitisation but not necessarily allergy. This is so because many children with AD are likely to be sensitised to a suspected food trigger (e.g. cow’s milk), and therefore have raised levels of IgE specific to that food and yet are not allergic to it (i.e. they are able to tolerate the food when it is ingested).

**Food allergens**

The prevalences of both food allergy and AD continue to rise in developed countries. In addition, both food allergy and AD have their highest prevalence in preschool-aged children, and both conditions are often seen in the same child, with AD being an important risk factor for the development of a food allergy.

Although exact mechanisms linking atopic dermatitis and food allergies are poorly defined,
there is widespread belief that a late phase IgE response may be the source of eczematous reactions to food. Additionally, there is supporting evidence that transdermal sensitisation by environmental food allergens may be a contributing factor.

The foods most commonly implicated in allergies and AD flares are hen’s eggs, cow’s milk, wheat, soy and peanuts. Because AD and food allergy frequently coexist in the same child, the issue of allergy testing in children with AD is often raised by parents and healthcare providers.

**Aeroallergens**
The aeroallergens most commonly implicated as triggers in AD are house dust mite, cockroach, pet dander and pollen. House dust mites and cockroaches produce airborne allergens that act as proteases, directly disrupting the skin barrier. Pet danders and pollen both act via IgE-mediated allergy, resulting in the release of histamine from mast cells and stimulation of an inflammatory response.

**ALLERGEN-SPECIFIC IGE TESTS**

**Serology**
Measurement of allergen-specific IgE levels is very useful in assessing IgE-mediated allergy. The most commonly used method is Immunocap (also known as UniCap), which has replaced RAST (the radioallergosorbent test). The patient’s serum is incubated with a known allergen and then enzyme- or fluorescent compound-labelled antibodies specific for human IgE are added, allowing detection of allergen-specific IgE.

Serological IgE testing should be reported with quantification of the level of specific IgE in International Units (IU) per litre, reflecting the level of sensitisations of the patient to each allergen. If an allergen-specific IgE is detected, this result must always be correlated with the history to assess the clinical relevance of the sensitisation. In general, the higher the level of specific IgE then the greater the positive predictive value will be for the child having an IgE-mediated food allergy. Predictive curves for common food allergens are available.

The nondetection of allergen-specific IgE on this test (the lower sensitivity of conventional assays is reported as less than 0.35 IU/L) carries a high negative predictive value. However, false-negative results can occur. Anaphylaxis may lead to a transient fall in specific IgE levels, or levels may decline to very low over time following exposure, despite the patient having an ongoing clinical allergy. Also, the allergens used for testing can break down (this is particularly so for food allergens), thus providing additional potential for false-negative results.

There is no indication to test for a food allergen mix as results are less sensitive than testing for single allergens and results are more difficult to classify. Considerable variability between allergen preparations leads to inconsistency with laboratory reporting. This variability is even higher with allergen mixes.

**Skin prick testing**
Skin prick testing is another useful way of assessing IgE-mediated allergy, the wheal size indicating the response. Skin prick testing is usually performed on the forearm, and occasionally on the back. Allergen extract is placed on the skin, and a small prick in the skin is made with a sterile lancet through the allergen droplet, allowing the allergen to enter the skin (Figure 1a). The results are read after approximately 15 minutes, with a positive result indicated by the presence of a wheal greater than 3 mm at the test site (Figure 1b).

The procedure is generally well tolerated by children and can be performed in infants if indicated. Local itch and swelling at the site usually subside within one to two hours after testing. Patients must not take antihistamines for three days before skin prick
testing as mast cell histamine release is an integral part of the reaction in those with positive results.

The interpretation of skin prick testing results follows similar principles to that of serology; that is, a determination needs to be made of the positive and negative predictive value of the test to each allergen. The particular benefit of skin prick testing is that it has high negative predictive value (more than 90%) for excluding IgE-mediated food allergies. Thus, in the setting of a positive serological test without a clinical history of food allergy, a negative skin prick test may play a role in excluding IgE-mediated food allergy.11

Skin prick testing in Australia is generally performed in allergy centres as part of a consultation, as it requires standardisation of technique and personalised interpretation of the results. Children in whom allergy testing is required therefore require specialist referral.

**USING ALLERGEN-SPECIFIC IGE TESTS FOR FOOD-RELATED ALLERGIES**

**Indications for food-specific IgE testing**

When reviewing a child with AD, it is recommended that any suspected adverse reactions to food be investigated. The history should include whether the child has ever had a generalised allergic reaction to food, including an anaphylactic reaction (e.g. immediate skin rash, vomiting, cough, shortness of breath or collapse). If a history of anaphylaxis is present, referral to an allergist or general paediatrician is warranted for further evaluation, education about food avoidance and management such as the possible need for an adrenaline auto-injector.

Food-specific IgE testing (serological or skin prick testing) is not required for children with mild to moderate AD without a clear history of exacerbation by food. Testing should, however, be considered for all infants (less than 12 months of age) with severe eczema and in children with moderate to severe eczema that does not respond to standard topical treatment. A study on the epidemiology of food allergy and AD has reported that the relative risk of an infant with AD having an associated food allergy increased with the severity of the eczema.12

**Interpretation of food-specific IgE tests**

It is important for all practitioners to recognise that positive serum IgE titres or positive skin prick tests do not necessarily indicate a food allergy. Positive results obligate consideration of oral challenge tests and, if a food allergy is confirmed, involvement of a dietitian with expertise in paediatric food allergy. Restrictive diets based on serum IgE or skin prick test results alone may be unnecessary and can be harmful to children.13 Furthermore, strict food avoidance may contribute to more severe anaphylactic reactions on subsequent exposure.14 The role and risks of graded food exposure to induce tolerance is controversial and the subject of intense current research.

Decision cut-off points have been proposed for food-specific IgE levels to help interpret the significance of serum IgE results in symptomatic children and adolescents.15 Individuals with food-specific IgE levels for the four major food allergens eggs, cow’s milk, peanuts and fish above the values listed below were shown to have a 95% probability of reacting (immediate hypersensitivity) to a food challenge:15

- eggs, 6 kUa/L
- cow’s milk, 32 kUa/L
- peanuts, 15 kUa/L
- fish, 20 kUa/L.

In the same study, the positive predictive values for two other major allergens were 100% for wheat at a decision cut-off point of 100 kUa/L, and 86% for soy at a cut-off point of 65 kUa/L.15

Although these decision points are of great assistance in interpreting serum IgE test results, it must be noted that they were proposed for immediate skin reactions and not for delayed eczematous reactions to foods. The positive predictive value of food-specific IgE for late AD flares is significantly low, at 33%.5 This low specificity reflects the large numbers of patients who are sensitised to certain foods but are asymptomatic. Furthermore, the above positive predictive values were based on a study performed in the USA and thus may not apply to all populations. Variations in the prevalence of different allergens in specific populations around the world have been well documented.

**Confirming a food allergy – oral food challenge test**

An oral food challenge test may be indicated to confirm a food allergy in any child. This test may be the only way to document a food allergy in a child who is sensitised to one or more foods. For some children, an oral food challenge will need to be done in a medical setting, usually in hospital, because of the risk of anaphylaxis.

A positive result on oral food challenge indicates the need for ongoing avoidance of the food. Patients with positive results should be referred to a dietitian for ongoing nutritional support, and have follow up by an allergist. Exclusion diets to investigate food allergy are recommended only under the supervision of both a medical practitioner and a dietitian.16 Management of AD with an exclusion diet that is not based on a clear history and/or supportive testing is not recommended.

**USING ALLERGEN-SPECIFIC IGE TESTS FOR AEROALLERGEN-RELATED ALLERGIES**

The role of aeroallergens in AD has been less studied than that of food allergens, but research has demonstrated a subset of patients with AD who have exacerbations of their disease secondary to exposure to aeroallergens. As mentioned earlier, the airborne proteins most commonly implicated are from house dust mites and cockroaches, and others include proteins from pet dander and pollen.15

Interventional studies have looked at the role of prevention of atopic disease in children through early avoidance of allergens. The Isle of Wight Allergy Prevention
Study demonstrated a reduction in childhood atopic disease (to the age of 8 years) through the use of food allergen and house dust mite allergen avoidance in infancy. This, however, has not been demonstrated in all studies: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study showed an inverse relationship between house dust mite exposure and AD in infancy. Given the conflicting results of existing research, further studies into the role of aeroallergens and atopic dermatitis are warranted.

### Indications for aeroallergen-specific IgE testing
Aeroallergen-specific IgE testing with skin prick testing and serum IgE levels is indicated in children with AD unresponsive to conventional management and a concomitant diagnosis of asthma and/or allergic rhinitis. Infants rarely develop specific IgE to aeroallergens and thus testing in this age group is often negative. Testing is further supported by a history of seasonal exacerbations of AD and/or AD in an air-exposed skin distribution (face, neck, arms and lower legs, with sparing of the trunk).

### Interpretation of aeroallergen-specific IgE tests
The interpretation of aeroallergen testing results is a contentious area, with limited supporting evidence. Many children with eczema will have specific IgE to one or more aeroallergens.

Exposure to house dust mite can be reduced and a trial of reduction may be indicated in children with AD; a response to avoidance suggests a house dust mite allergy. Many children with AD have perennial allergic rhinitis triggered by house dust mite, and avoidance measures would be indicated for management of the rhinitis. Studies to support this are limited, with poor evidence for definitive recommendations, but there appears to be no adverse outcomes from a trial of house dust mite reduction. Exposure to seasonal aeroallergens (pollen and moulds), however, cannot be avoided.

### Allergic contact dermatitis
Allergic contact dermatitis may mimic or complicate AD. However, it usually manifests within days (rather than minutes or hours) of exposure in areas of skin directly in contact with the allergen, although in severe cases it can extend beyond the area of contact. The delayed response of allergic contact dermatitis reflects its aetiology as a type 4 hypersensitivity reaction. Also, it may present with localised erythema, papules and vesicles on inflamed skin, as opposed to a generalised erythematous, pruritic reaction with AD.

The agents most commonly implicated in allergic contact dermatitis in children are nickel and cobalt, but reactions to topical therapies (especially to the preservative and fragrance components), plants, rubber chemicals, dressings and numerous other agents may be responsible. Although allergic contact dermatitis has previously been thought to be uncommon in children, recent studies have shown an incidence of about 8% in adolescents in Denmark (diagnosis confirmed by clinically relevant patch testing).

### Testing for allergic contact dermatitis
Epicutaneous patch testing is useful in children with localised or regional dermatitis or suspected allergic contact dermatitis where the trigger is not obvious. Usually undertaken by dermatologists, patch testing assesses delayed type hypersensitivity, with allergens selected from a large range of possible agents including metals, preservatives, plants, components of creams and environmental exposures. The usual procedure involves application to the individual’s back of 20 to 40 known and standardised antigenic substances, which are retained with adhesive tape for 48 hours. Readings are required two and four days after initial application, and positive reactions (localised erythema, induration or vesicles) require careful and experienced interpretation. Specialised dermatology input is required if allergic contact dermatitis is suspected.

Patch testing may be considered or undertaken when the history suggests topical exposures or contacts aggravate eczema, or when the distribution of eczema is characteristic (examples of patterns include predominant hand dermatitis, rashes in areas of metal exposure, scalp and eyelid dermatitis and foot dermatitis).

### Conclusion
There are numerous potential allergens involved in the exacerbation of atopic dermatitis in children. A careful history of allergy should be obtained, and children with severe or refractory AD should be further investigated. Specialist referral and assessment may be required for further management and investigation, based on interpretation of eczema flares after allergen exposure, clinical manifestations (including the pattern and regions affected) and response to treatments.

### References
A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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Allergy testing in paediatric atopic dermatitis

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