

# Allergic evaluation and management of the atopic patient

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## Abstract

Atopy is defined as an inherited predisposition to produce immunoglobulin E (IgE) antibodies in response to natural exposure to minute quantities of environmental allergens, manifesting clinically with atopic diseases. These include food allergy, eczema, asthma, seasonal and persistent rhinitis and urticaria. Not all allergic diseases are atopic in nature.

Examples of non-atopic allergic diseases include allergy to drugs (e.g. penicillin), venoms (e.g. bee sting allergy) and some occupational allergies.

The cornerstone of the clinical diagnosis of any atopic disease is a detailed history, followed by specific IgE sensitivity testing. This requires knowledge of the patient's presenting symptoms, his family history and a careful knowledge of the environment in which the patient lives or works.

History taking is time consuming, but always rewarding and the most cost effective part of the clinical evaluation. The history guides the clinician as to the most appropriate clinical or laboratory test and can save the patient and health funder unnecessary expenses since there are hundreds of allergen sensitivities which can be tested.

In clinical practice, it is important to distinguish those patients with eczema, rhinitis, asthma and adverse food reactions who are truly allergic or "atopic" from those who are not. This distinction has a direct bearing on the treatment options for the patient (Figure 1). There are a number of unscientific and unvalidated tests which attempt to identify allergic factors playing a role in the patient's disease, but many of these are expensive and those which do not specifically determine IgE levels or evidence of mast cell or eosinophil activation are not recommended by allergologists.

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## Evaluation of allergy in patients with eczema

The term eczema describes an aggregation of several skin diseases with common clinical characteristics, which involve a genetically determined skin barrier defect.

The prevalence of atopic eczema (AE) has risen significantly during the past few decades.<sup>1</sup> A recent study among Xhosa children<sup>2</sup> found a point prevalence of dermatologist diagnosed eczema in 0.7%, 1.1% and 3.7% in rural, peri-urban and urban settings respectively.

In children and young adults the inflammatory component of the eczema is triggered by immunoglobulin E in more than 50% of cases. In such patients the term atopic eczema is applied. Other children and most adults do not have an "atopic" component to the eczema, as evidenced by absence of a family history of atopic diseases, normal IgE levels and no documented specific IgE sensitivities detected by skin or Immunocap RAST testing. The diagnosis of "atopic" eczema thus cannot be made without confirmation of an atopic immune

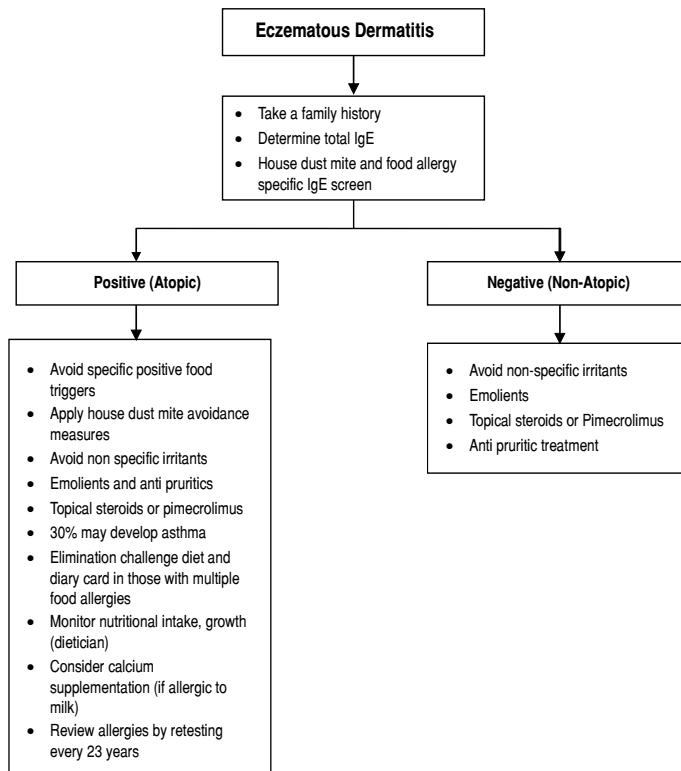
response by confirming that the patient has elevated total IgE levels or specific IgE antibodies to environmental allergens.

The younger the child, the more likely the eczema is to have an atopic basis and younger patients benefit more from allergic (usually dietary) intervention. Diet has almost no place in the management of "non-atopic" eczema, except for a recommendation to avoid non-specific possible triggers of pruritis such as preservatives in processed foods and acidic or irritant foods. These are also irritant if applied directly to the skin since the barrier function is deficient (See Figure 1).

In view of the known barrier dysfunction in all patients with eczema, antigens can also penetrate the skin directly and cause irritant or eczematous reactions. This applies particularly to creams with preservatives (e.g. para amino benzoic acid), soaps with fragrances and also to antigens in house dust.

In eczema patients who are atopic, IgE sensitisation via the inhaled route may have resulted in sensitivity to house dust mites.

Figure 1: Approach to eczema in infants



Eczematous reactions can be triggered via exposure via the cutaneous route or inhaled route and in these patients with strong specific IgE responses to house dust mites. These will benefit from mite avoidance procedures such as mite impermeable bedding, hot washing (60°C) of the sheets and blankets and removal of carpets from the patient's room. Such patients may react with cutaneous itching even to inhaled house dust mite exposure, e.g. at night in their beds.

There is now sufficient evidence that in some communities exclusive breast-feeding of high risk infants for at least four months prevents the development of atopic eczema.<sup>3</sup> However a recent study by Obihara et al<sup>4</sup> demonstrated that the protective effect of breast-feeding for six months was more significant when the mother was not atopic herself.

Benefits of breast-feeding were lost in infants of the highly atopic mothers suggesting that strong genetic factors override any benefit of breast-feeding. It is well known that cow milk and egg antigens may pass through the breast milk to the nursing infant. If mothers are unable to breast-feed, a hypo allergenic extensively hydrolysed formula may be given to the infant (e.g. Alfare, Nutramigen). If this is not possible a partially hydrolysed formula such as NAN-HA is recommended in the guidelines.<sup>1</sup> There is no evidence that substitution of breast milk with soya formulas will prevent allergic diseases, through soya may be used as an alternative in infants who have confirmed cow milk allergy who are skin test or Immunocap test negative to soya.

In the general population true food allergy has a prevalence of between 1–4%, whereas up to 80% of young infants with atopic dermatitis will have positive food allergy tests.

Food allergy testing is thus an essential part of the management of the infant with atopic dermatitis/eczema.

### Skin prick tests

Skin prick tests are inexpensive and cost-effective and can be done in infants as young as three months of age. Children must be off antihistamines for at least 72 hours and the test requires some co-operation in young children, but is simple to perform.

They may be done on the back or the forearm. Positive (histamine) and negative (saline) controls must be included. A wheal of greater than 3 mm with an accompanying flare represents a positive test result, provided that the reaction to saline is negative and that the histamine positive control wheal response is 3 mm in diameter.

Skin prick tests are easy to conduct and should be read within 15–20 minutes. For infants a small panel including milk, egg, wheat, soya, peanut, codfish and house dust mites is recommended.

The more difficult part for the clinician is the interpretation of the tests. Where only one or two allergens are positive and these reactions are strong, elimination of the culprit food is nearly always beneficial.

In some infants however, “weak positive” wheals and flares are observed for all agents tested and questions as to the significance of a non-specific false positive result arise. In these cases the larger the wheal and flare the more likely the result is a true positive and cut off values for skin prick test results for children with eczema have been published by Hosking and Hill.<sup>5</sup>

The cut off values predict greater than 95% reaction to the food if the child is challenged with the food. They serve as guidelines as to whether the child could safely be carefully challenged and exposed to the food following an elimination diet. In cases where the levels are below the 95–100% predictive values it is recommended that the food is eliminated for two weeks and then to carefully challenge the child with the suspected food. This may be done as a careful graded open challenge in the doctor's rooms, or as a formal double blind placebo controlled food challenge (DBPCFC) by a trained allergologist in a facility where full resuscitation equipment is available.

### Immunocap RASTS

In children with atopic eczema, the paediatric food mix Fx5e blood test is a useful screen for possible food allergy. If positive, specific IgE sensitivity for egg, milk, soya, wheat, fish and peanut may be requested by the doctor. An elimination challenge diet is recommended for two weeks followed by challenges to confirm sensitivity. Challenges such as these are only advised if non-life threatening reactions have been the problem (i.e. there has been no oral, pharyngeal or respiratory involvement following ingestion of any foods). Sampson and Ho<sup>6</sup> have published IgE values giving predictive levels for a 95% positive challenge to a food: 6Ku/L for egg, 32Ku/L for milk, 15Ku/L for peanuts and 20Ku/L for fish. More importantly and clinically useful is that the negative predictive value of both blood and skin tests is greater than 95%. Thus careful testing is always useful.

### Atopy patch tests

Patch tests have conventionally been used for the diagnosis of contact dermatitis. These are well standardised and often employ Finn Chambers. More recently patch tests have been studied to

detect delayed immunological responses to food allergens in atopic dermatitis. Some researchers have found useful positive results, especially when conducted and interpreted in association with the results of skin prick tests. The interval between the last exposure and reaction to a particular food is important. The interpretation remains difficult for the average clinician and clearer guidelines are awaited before they can be generally recommended for food allergy diagnosis in the clinic.

### Evaluation of patients with inhalant atopic diseases

The two most important inhalant atopic diseases in which allergies may play a pivotal role are asthma and rhinitis.

#### Asthma

In asthma, sensitisation and early exposure to high levels of house dust mites is known to predict the development of house dust mite driven inflammation of the airways in later life and avoidance of early exposure is recommended.

The association between cats, in patients with indoor asthma, and pollens in patients with outdoor asthma, is also well known and a definite indication for allergy testing (for skin test or RAST). In the case of mono allergies immunotherapy may be curative.

The role of allergens in chronic asthmatics with year round persistent asthma is also important, but appears to be less well understood.

In these cases a chronic constant exposure to the small allergens (less than 5 microns in diameter) which penetrate the lower airways, and are broken down into sub-micronic particles contribute to the ongoing mast cell activation and production of leukotrienes, chemotactic factors, chemokines and other inflammatory molecules resulting in chronic disease and airway remodelling. Important allergens promoting chronic asthma include house dust mites (*Der-p-1*, *Der-f-1* and *Blomia tropicalis*), cockroaches (German, Oriental and American species), (particularly in those with inner city asthma) and the fungal spores (*aspergillus*, *cladosporium*, *alternaria* and *epicoccium*).

It is now well known that having a specific fungal allergy is a risk factor for more severe asthma and also for hospitalisation with asthma when the atmospheric fungal spore counts are high.

Diagnosing indoor allergens in persistent asthmatics is important for the implementation of avoidance of exposure measures (as outlined above in the section on atopic eczema), as well as providing an option for curative treatment for asthma in the form of allergen immunotherapy via the sublingual or via the subcutaneous routes. Allergen immunotherapy should be considered for mild to moderate persistent asthmatics whose forced expiratory volume (FEV) is above 75% who have no other risk factors for life threatening asthma events. Immunotherapy is given in combination with inhaled steroids, leukotrienes and/or long acting beta-2 agonists as a curative therapy for asthmatics with mono allergens to house dust mites, grass pollens and occasionally for cat or horse allergy.

Allergen immunotherapy is a particularly important additional option for cure in those asthmatics who also have persistent allergic rhinitis. Patients selected thus and treated with immunotherapy for three years or longer, can expect a 10–15 year lasting beneficial effect of sublingual immunotherapy, many of whom will go into complete remission of their asthma.<sup>7</sup>

#### Rhinitis

When assessing patients for evaluation of rhinitis, it is important to decide from the history whether or not the patient is suffering from non-

allergic or vasomotor rhinitis. These patients do not benefit from allergy test evaluations. Typical findings from the history of a non-allergic rhinitis patient are “sensitivity to perfumes and fragrances”, reactions to air-conditioning and gaseous irritants such as diesel exhaust fumes, cigarette smoke, stuffy environments and changes in temperature. By contrast, patients with allergic seasonal (intermittent) or persistent rhinitis invariably give a history of seasonal variation. Their symptoms are characteristically worse at a particular time of the year, e.g. autumn (house dust mites) or spring (grass or tree pollens) or summer (grass pollen) or following exposure to damp and changes in the weather (fungal allergies), exposure to animals (horses, cats, dogs, pets) or worse in the work environment (e.g. baker’s flour, isocyanates, latex products or pharmaceutical products). A good or positive response to antihistamines or intranasal steroids is also a good pointer to “allergy” being an underlying cause of the rhinitis. Twenty per cent of allergic patients also may complain about sensitivity to sulphur dioxide or sulphites in alcoholic beverages or cooldrinks. Such a history, in addition to a positive family history and a history of eczema as an infant, is a good indication for careful allergy testing tailored to the patient’s individual profile.

Testing should be guided by the history, the geographical location of the patient (e.g. city or farm environment), seasonality of the symptoms (summer, autumn, spring), age of the patient (foods are an extremely unusual cause of rhinitis symptoms in adults), and the patient’s occupation.

There is no such thing as a standard allergy panel of tests for allergies for all South Africans, bearing in mind the biodiversity of the country and its peoples and likelihood of exposure (Table I). A few common allergens should be included and supplemented according to history or location of the patient.

**Table I:** Recommended screening for inhalant allergens in South Africa (RAST or skin prick test)

| REGIONS           | ALLERGENS   |
|-------------------|---|
| All regions       | House dust mites (Der p 1 and Der f 1)<br>Rye and Bermuda grass<br>Aspergillus, alternaria, cladosporium<br>Cat and dog |
| Western Cape      | Add: Oak, Plane pollen, <i>Blomia tropicalis</i><br>Epicoccium fungal spore<br>Cockroach                                |
| Gauteng           | Add: Tree pollens including Cypress   |
| Farming areas     | Add: Zea Mays pollen<br>Horse<br><i>Blomia tropicalis</i>   |
| Healthcare worker | Add: Latex  |
| Grain industry    | Add: Storage mites, wheat and rye   |

Common inhalants which should be included are house dust mites (*Der p 1*, *Der f 1* and *Blomia tropicalis*), grass pollens (rye or Timothy plus Bermuda), cockroach, cat, dog, maize, *alternaria*, *aspergillus* and *epicoccium*. Test selection is guided by the locality of the patient and seasonality of symptoms. In practice it is very unusual to test for more than 12 inhalants and four or five food allergens in any given patient. Skin tests are cheaper and quite reliable, but for many Immunocap RASTs are often more convenient. There is a very wide range of Immunocaps, but if carefully selected, by the history, laboratory testing can work out less expensive than a “thoughtless panel” of inhalant skin prick tests.

There are a few patients who have both allergic and vasomotor components in their symptom profile. These patients are “difficult to

treat" and are usually not selected for allergen immunotherapy. The patients who do the best on allergen immunotherapy are those who are monosensitive to grass pollens (Bermuda and rye) or house dust mite allergens (Der-p-1 and Der-f-1).

A three year desensitisation programme should be offered to all such patients and will dramatically improve their quality of life, requirements for antihistamines and intranasal steroids, hospitalizations for asthma exacerbations and abuse of over the counter decongestants and sedating antihistamines.<sup>8</sup>

### Is allergen avoidance worthwhile?

Common sense dictates that a patient who is not exposed to an allergen will not have specific mast cell activation by IgE cross linking. While avoidance is unquestioned for bee venom, latex drug allergy and many food allergies (e.g. peanut, crustacean or tree nuts), the role of "allergen avoidance measures", in patients who on skin prick testing or RAST testing are shown to have an array of weakly positive results, has been questioned. In the case of eczema the true value of the test result may only be confirmed by elimination/challenge diets, with careful symptom diary scoring.

For inhalants and aero allergens, it is a fact that some allergens are impossible to avoid (e.g. fungal spores in the atmosphere in autumn and winter, pollen grains at the height of the pollen season in spring) and in some situations, house dust mites present all the year round. Because of the seeming impossibility of avoiding these allergens in such polysensitive patients, one has to rely on pharmacotherapy above to control symptoms, as such patients also do not respond to allergen immunotherapy, in its present form.

By contrast for monosensitive patients with persistent rhinitis or asthma, known to be allergic to house dust mites, house dust mite avoidance is unequivocally beneficial. This recommendation stands in spite of recent reviews and a meta-analysis which did not find a beneficial effect.<sup>9,10</sup> The meta analysis has been judged to be of poor quality (personal communication, Prof T Platts-Mills, ALLSA Congress, May 2008, Sun City) and only included a very small number of subjects (122).

The meta analysis did conclude however that it is possible to reduce the load of house dust mites using such control measures. Different individuals vary in their threshold of reactivity to house dust mite allergens and further studies are required to determine the optimal level, or threshold, below which mite sensitive individuals will not react clinically. At a clinical level, a reduction in the stimulus for inflammation in the airways is an essential part of the patient's management. Updated recommendations for house dust mite reduction are listed in Table II and have also been published for cat and pollen.<sup>11</sup>

**Table II:** House dust mite avoidance measures

|    | Avoidance measures  |
|----|---|
| 1. | Encase mattress and pillow and duvets completely in mite impermeable fabric (e.g. Allerbed, Dream Guard, Medibed) |
| 2. | Hot washing of bedding at 60°C  |
| 3. | Replace carpets with wooden or tiled or linoleum floors   |
| 4. | Remove dust collecting objects from the room (blankets, fluffy toys, etc.)  |
| 5. | Cover furniture with leather or vinyl or plastic  |
| 6. | Keep the room well ventilated with average humidity below 60%   |
| 7. | Use vacuum cleaners which have HEPA filters   |
| 8. | Wipe down bedroom surfaces with damp cloth, but dry properly  |

|     |   |
|-----|---|
| 9.  | A good down or feather pillow with a good quality cover is just as good as a synthetic pillow |
| 10. | Stay off carpets in living rooms or TV rooms or school rooms                                  |

### Evaluation of the patient for adverse reaction to foods

Adverse reactions to foods occur in about 20% of the population. The majority of these are not IgE mediated. They may be toxic (e.g. food poisoning), due to the chemical content of the food (e.g. tyramine or serotonin) or food intolerance reactions. The latter account for the majority of adverse food reactions. The history is the most important part of the investigation. IgE mediated true allergic reactions are typically rapid in onset, reproducible and manifest with swelling of the mouth, urticaria, angioedema, bronchospasm and hypotension.

Non-IgE mediated reactions are typically delayed and may involve the mouth and face, but more often involve the gastrointestinal tract and are often accompanied by non-specific symptoms such as bloating, cramps, tiredness, headache and lassitude. Typically with food intolerance, patients report variable and sometimes inconsistent reactions to the suspected foods.

In many cases intolerance reactions are due to food preservatives such as sodium metabisulphite (or SO<sub>2</sub>) or sodium benzoates. Some of these reactions can be confirmed by demonstrating that the patient's circulating basophils are sensitive to these preservatives in the test tube, releasing sulphido leukotrienes when exposed to them in the laboratory. The CAST (Cellular Activation Sulphido Leukotriene Release Test) has been found to be a useful indicator of sensitivity to some of these preservatives.

For true food allergies mediated by IgE and mast cells, it is important to consider the nature of the food, its storage and transport, processing by the body and its preparation. All of these factors may influence its allergenicity. For example, heating peanuts increases its allergenicity by trimerisation of the Ara-h-1 peanut allergens. Other allergens such as chitinases may be removed by peeling the fruit.

Another example of the effect of processing foods influencing its allergenicity occurs with hazel nuts. Raw hazel nuts cause the oral allergy syndrome in 100% of sensitive individuals, but roasting reduces the allergenicity. The Bet-v-1 (Birch) protein in hazel nuts is destroyed by roasting, but not the Lipid transfer protein (LTP). For some foods, allergenicity is reduced by boiling, if the allergens are water soluble, whereas for other foods interaction with oils enhances allergenicity and may concentrate the allergen.

There is an important distinction which must be made between "sensitisation" and "allergenicity". In practice the negative predictive value of a skin prick test or RAST is more useful than the finding of a low positive result.

In general, the higher the specific IgE value the greater the correlation with a positive food challenge to that allergen. Cut off IgE values<sup>6</sup> predicting a positive challenge are applicable for children with eczema for four allergens, but further studies are required for areas of the world which have high levels of parasite infestation. Cut off values are not known for all the other food allergens. The Immunocap RAST appears to have a good positive predictive value for stable allergens (e.g. fish Gad C1 in cod and peanut Ara-h-1) for unstable fruit allergens, e.g. apple (Mal-d-1) and tropical summer fruits, the CAP RAST sensitivity is low and skin prick tests with fresh fruit extracts are more sensitive in confirming Type I allergy in patients with the Oral Allergy Syndrome.

Another factor which adds to the diagnostic complexity in food allergy is "cross-reactivity". Many foods contain common proteins such as profilins, chitinases and lipid transfer factors, in addition to their major allergens, which may cause significant clinical co-sensitivity, but may also give rise to positive specific IgE results to other allergens, even from unrelated families.


An example of a relevant stable cross reactive allergen is tropomyosin found in molluscs, shellfish and house dust mites. By contrast profilins present in grasses, wheat and summer fruits do not appear to be clinically allergenic, but may account for "false positive" laboratory specific IgE tests. In these cases often the patient has had a "screen" for food allergens and although a number of borderline or low grade positive test results are obtained on the Immunocap only a few are clinically relevant. An example of such a result is obtained in some peanut allergic subjects who, despite also having a positive RAST to soya, can eat soya without ill effects.

Thus the interpretation of the results of food allergy testing in the laboratory is not simple and requires knowledge of food families, cross reactive allergens, cut off values for the "paediatric" food allergens such as milk, egg, peanut, fish and wheat, knowledge of the interval between the previous clinical reaction and the current positive test result.

IgG testing for food allergies is not clinically useful. Healthy individuals without food allergies make IgG antibodies to ingested foods as well as allergic individuals. There are no cut off IgG values predicting sensitivity to a particular food. Conversely, the higher the IgG to a food the more likely the patient is to tolerate the food. Food specific IgG is an index of exposure to a food protein in the diet, rather than an index of allergy.

Elimination challenge testing remains the gold standard for food allergy diagnosis, but should not be conducted when there has been a recent history of a significant systemic reaction to the food or anaphylaxis. Since the natural history of paediatric food allergies is to "grow out of" the allergy, follow up testing can guide the clinician as to whether rechallenging with a particular food is likely to be safe or not. If in doubt, or unable to conduct a controlled or blinded challenge, a positive test should be regarded as confirmatory, the patient should wear a Medic Alert bracelet and exposure to the food should be avoided definitely or until formal reassessment by an allergologist can be arranged.

In the future, the use of recombinant allergens of multiple proteins in foods using micro array technology, will refine specific food allergy diagnosis to the level of confirming a diagnosis, detecting cross

reactive sensitivities and predicting a clinical phenotype based on IgE profiling and genotyping. Studies using the new technology are already underlying at the University of Cape Town Centre for Proteomic and Genomic Research (CPGR) in collaboration with the Allergy Diagnostic and Clinical Research Unit (ADCRU). 

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