Is allergy testing cost effective?

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ABSTRACT

This article reviews the evidence for and against specific IgE testing in allergy management prior to pharmacotherapy ('testers' versus 'treaters'). While the value of combining results of both Phadiatop inhalant and fx5 food allergy screening may improve our ability to predict clinical allergic asthma, rhinitis and eczema, evidence suggests that the cumulative load of environmental allergens to which an individual is sensitised may help to determine when allergen tolerance or clinical allergic diseases such as asthma and rhinitis are likely to occur.

'TESTERS' VERSUS 'TREATERS'

Medical opinions are divided between the 'testers' who investigate before therapy is instituted and' treaters' who do not investigate to save costs. The 'treaters' have suggested that allergy testing is *not* always necessary in patients with allergy symptoms and prefer to treat with pharmacotherapy without identification of specific triggers. An example of this is a recent editorial in this journal in which Lalloo[1] expressed the view that specific IgE testing is overused and most diagnoses and therapeutic decisions are not influenced by this test.[1] The controversy is whether specific allergy testing is an essential diagnostic resource or an unnecessary expense.

'Testers' will argue that it is incorrect to blindly engage in various pharmacotherapies and that these trials of therapy will outweigh the initial cost of allergy diagnostic testing. 'Testers' will argue further that treatment can then be more focused and this could include specific allergen avoidance, appropriate pharmacotherapy and occasionally desensitisation immunotherapy. This is supported by rhinologists who will stress that even in mild to moderate hay fever it is essential to identify specific seasonal triggers in order to plan prophylactic treatment each year. Atopic patients endure mite and pet exposure which triggers their persistent symptoms of asthma, rhinitis and eczema, and targeted lifestyle changes can lead to a significant improvement in symptoms.[2] A recent general practice study conducted in The Netherlands revealed that asthmatic patients were highly unlikely to be told whether their asthma was allergic or non-allergic suggesting that no diagnostic testing was done.[3] In fact very few persistent asthmatics ever see an allergist or have allergen skin-prick testing done, despite half of all asthma sufferers being sensitised to house dust mites.[3] Nasser[2] points out that allergic sensitisation is central to the underlying mechanisms of atopic asthma judging from the success of anti-IgE therapy (Xolair) in patients with severe persistent asthma.

Although theoretically only a controlled allergen challenge can confirm the causal relationship between allergen exposure and clinically relevant allergic symptoms, in routine day-to-day allergy practice, it is common to use a positive skin-prick test or the presence of serum specific IgE antibodies to relevant environmental allergens plus a suggestive clinical history as proof of allergy-induced disease. Moreover, the higher the level of specific IgE antibodies present, the stronger the association with clinical allergic disease.[4] According to the European Academy for Allergology and Clinical Immunology (EAACI), it is essential to establish an early diagnosis of allergy in young children with precise identification of the offending allergens. In addition, there may be merit in periodically quantifying the levels of specific IgE so as to reassess clinical reactivity and perhaps detect development of allergen tolerance.

Allergy testing using the skin prick method, specific IgE estimation or allergen challenge is pivotal to good allergy practice particularly in the initial management of children with asthma, rhinitis, eczema and food allergies.

Symptoms do not always *mean allergy*

The real value to patients of having a 'tester' as opposed to a 'treater' as their medical advisor lies in the following data. In infants with atopic dermatitis approximately one-third will have a specific food allergy as an eczema trigger, while at 4 years of age, 43% of children with eczema will have developed allergies to house-dust mites, grass pollen and cats.[5] Asthma that commences in early life is often atopic and associated with IgE sensitisation to common foods (particularly egg) and inhalant allergens (predominantly house-dust mite and pet).

However, not all early wheezing is associated with allergy and only about one-third of infants with virus-induced wheeze are allergic.[6] The majority (70%) of young children with wheeze will in fact be symptom-free by school age.[7] Here negative results to allergy testing are helpful in determining those children unlikely to develop asthma and in reassuring their parents of this low risk.[8] The converse is true in older children; about two-thirds will have a specific allergy as a cause for their persistent wheezing or cough. Non-allergic causes of asthma-like symptoms in children should be considered and these include gastro-oesophageal reflux disease (GORD), infective rhinosinusitis, vocal cord dysfunction and the highly prevalent 'crèche syndrome' with its troublesome post-viral cough.

Allergy testing helps predict the 'allergic march'

It is common for children to progress over time from one allergic manifestation to another in a predictable manner. The path of the 'allergic march' begins with food-related allergies and eczema in infancy and progresses to predominant inhalant allergies with wheezing, asthma and rhinitis in the middle childhood years. Symptoms of asthma often settle by adolescence but tend to recur again in middle age. Food-allergic children may show declining levels of food specific IgE and subsequently develop tolerance to many foods by about the age of 5 years, particularly if their food specific IgE

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antibody levels were initially low.

Concomitant factors that promote the 'allergic march' in children include a combination of:

- less early exposure to infectious diseases (a cornerstone of the 'hygiene hypothesis')
- prolonged indoor environmental exposure
- and adopting a sedentary lifestyle.

Platts-Mills[9] feels that the current predisposition to minimal outdoor physical activity during childhood (with TV, computer games and fear of crime) leads to obesity which is strongly associated with the development of asthma. The value of seeing a 'tester' is that the information from investigations will help predict which patients with this type of lifestyle are at risk of developing allergic diseases.

Allergy testing is now recommended from infancy

All patients with severe, persistent or recurrent allergy-like symptoms and those with a need for ongoing 'preventer' treatment should be tested for specific allergies irrespective of their age.[4] Children may be allergy tested from 4 months of age or even younger, particularly if food allergies are suspected to cow's milk, hen's egg, and peanut allergens. There is no longer a lower age limit for performing skin-prick tests or specific IgE antibody estimation. Specific IgE is produced by the fetus during the last trimester of pregnancy and is well established in the neonatal period. The lower age limit of 3 years for allergy testing which was incorrectly promoted in the medical literature was without any evidence base.

Young children may present with many allergic signs and symptoms such as eczema, rhinitis, asthma and food allergy and it is imperative to identify specific trigger allergens as early as possible. Individuals with insect venom allergy, latex allergy and oral allergic symptoms as a result of cross-reactivity between pollens and fruits will also benefit from confirmation of their specific IgE-mediated allergic hypersensitivity.

Studies show that elevated specific IgE antibodies to allergens such as hen's egg and cow's milk in infancy can predict sensitisation to inhalant allergens and the development of allergic asthma by 7 to 10 years of age.[10,11] However it is imperative that any allergy testing should be preceded by a comprehensive allergy history to guide the practitioner in identifying the trigger allergens. Tests that measure specific antibodies should be chosen on the basis of local and seasonal allergen knowledge and should focus on those local allergens that are statistically more likely to cause symptoms.

The extent of each allergy test profile will depend on the individual's age, geographic region, positive family allergy history and the character of their symptoms.

Allergy testing should help identify infants at risk for the development of subsequent allergic diseases and also guide specific treatments such as secondary allergen avoidance, effective pharmacotherapy and specific allergen immunotherapy.

ALLERGY TESTING AND ITS PREDICTIVE VALUE

Which allergy test?

Allergy testing using the allergen skin-prick method with commercial allergens is simple and relatively inexpensive. However, allergens need to be carefully stored; have a limited shelf-life and testing needs to be conducted by a practitioner experienced in interpreting the wheal and flare reactions. Serum specific IgE antibody testing is arguably more cost-effective at the initial assessment of the allergic patient who presents with persistent respiratory, dermatological and food-related symptoms.

The ImmunoCAP® or CAP RAST multi-channel analysing system is now widely accessible via pathology laboratories throughout Southern Africa. These tests have replaced the earlier RAST (radio-allergo sorbent tests) which utilised a radio-label to measure specific IgE to various inhalant and food allergens in the patient's serum. The ImmunoCAP is highly reliable for identifying typical IgE-mediated allergy when accurate skin-prick testing (SPT) is not readily available. A number of ImmunoCAP screening panels have been developed for local inhalant allergens such as house-dust mites, pet danders, local pollens and mould spores, and also for common offending food allergens. Both SPT and ImmunoCAP RAST have good positive predictive values (can identify those with a specific allergy) and negative predictive values (can identify those with no allergy). One should not forget the value of a negative allergy test, which can liberate the anxious patient and the parent from unnecessary house-dust mite or pet avoidance practices and dietary manipulation.

Accurately predicting the probability of an allergic disease

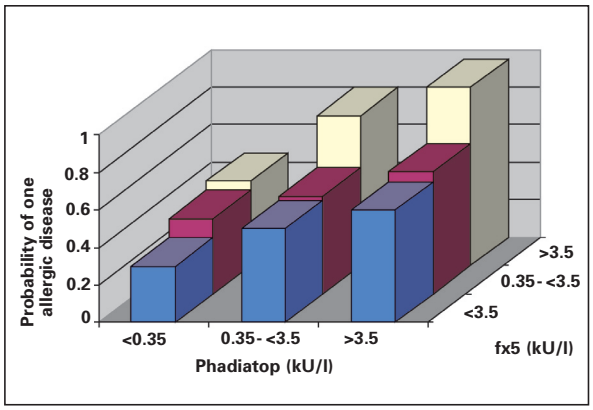
Elevated total serum IgE is a non-specific phenomenon and is of minimal value in identifying a specific allergy. Total IgE normally increases with age from infancy to plateau in the teenage years and may be non-specifically raised with extensive eczema. Furthermore, a normal total IgE (less than 100kU/l in adults) does not rule out specific allergy but makes it less likely, especially if the level is below 10kU/l.

While the higher the level of serum specific IgE antibodies, the stronger the likelihood of clinical allergic disease, the clinical relevance of specific IgE values less than 3.5kU/l (RAST grade 2) is of limited value. These slightly raised levels of specific IgE to common food and inhalant allergens are common, especially in early childhood and may have no clinical significance

Blood testing using the *Phadiatop (Pharmacia)* is an excellent baseline inhalant allergen screen if no one particular allergen is initially suspected. This screen in South Africa includes allergens such as house-dust mite *(Dermatophagoides pteronyssinus)*, cat dander, dog dander, horse hair, tree pollen (silver birch), grass pollen (Bermuda and timothy), mould spores (cladosporium) and weed pollen (mugwort).

The *fx5 paediatric food allergen screening panel (Pharmacia)* includes cow's milk, hen's egg, wheat flour, soy protein, cod fish and peanut. These six food allergens account for over 90% of relevant paediatric food-allergy-related problems.

Wickman *et al.*[12, 13] in the Scandinavian BAMSE birth-cohort study demonstrated that the presence of IgE antibodies greater than 3.5kU/l for both Phadiatop and fx5 measured in combination in 4-year-old children could indicate a 97.4% predictive likelihood of a suspected allergic disease (asthma, rhinitis, eczema or food allergy) (Fig. 1). In the same study, the presence of IgE antibodies greater than 3.5kU/l to either Phadiatop or to fx5 used as a single test was less efficient in predicting any allergic disease (71%). Custovic *et al.*[14] in the Manchester Asthma and Allergy Study found a similar predictable value for asthma development if a summation of house-dust mite and cat allergen specific IgE levels was utilised and not merely the identification of antibodies.



Wickman *et al.* then looked at sensitisation to 14 individual allergens contained in the screens including Phadiatop inhalants (*D. pteronyssinus*, cat, dog, horse, silver birch, timothy, cladosporium and mugwort) and

Fig. 1. Probability of development of at least one of four allergic diseases (asthma, eczema, allergic rhinitis and food allergy)

fx5 foods (cow's milk, egg white, wheat, soy protein, codfish and peanut). They noted that if the sum of allergen specific IgE antibody levels to their selected profile of 14 allergens was greater than 34kU/l or more than 4 of the 14 allergens tested were positive, then this indicated a 75% or greater probability of an allergic disease being present or developing (Figs 2 & 3).[13] Thus testing a certain profile of airborne and food allergens and utilising the sum of IgE antibody levels in combination with the number of allergens that elicit a positive test result may represent a more efficient diagnostic tool than using individual positive IgE antibody results only.

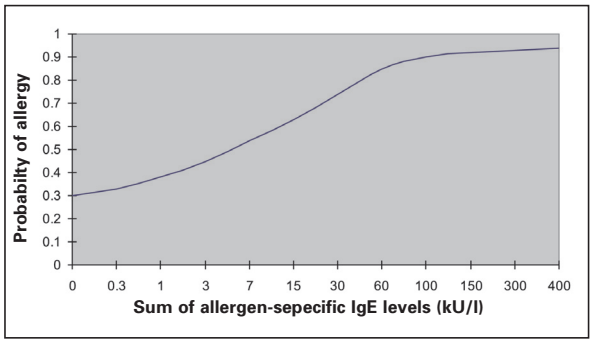


Fig. 2. Probability of allergic disease based on sum of allergen specific IgE levels.

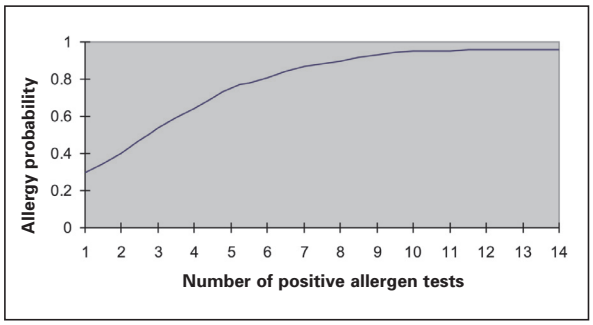


Fig. 3. Probability of allergic disease based on number of positive allergen tests.

Sampson *et al.*[15] looked at individual food allergens in an attempt to quantify specific IgE cut-off points for allergy diagnosis in children in the USA (Table I). They have produced data on specific IgE levels for cow's milk, hen's egg, cod fish and peanut, above which food allergy has a 95% probability.

Table I. Food specific IgE concentrations (RAST) predictive of clinical reactions

Food allergen	Decision point (kU/l)	Positive predictive value (%)
Cow's milk		
• < 2 years	5	95
• > 2 years	15	95
Hen's egg		
• < 2 years	2	95
• >2 years	7	98
Peanut	14	100
Tree nut	~15	~95
Fish	20	100
Wheat	26	74
Soya	30	73

Reproduced from: Sampson *et al.*[15]

Testing a select profile of airborne and food allergens and then utilising the sum of IgE antibody levels in combination with the number of allergens that elicit a positive test result may represent a more efficient diagnostic tool than using individual positive IgE antibody results alone.

IMPACT OF THE ALLERGEN 'LOAD'

Some patients may be sensitised to an allergen on testing but paradoxically remain asymptomatic, suggesting the involvement of both tolerance mechanisms and a threshold above which clinical disease will manifest. Others, at modest levels of pollen exposure, will experience upper respiratory, ocular and nasal symptoms only, but at higher ambient pollen levels will in addition experience lower respiratory symptoms with wheeze and develop asthma.

Furthermore, patients may be asymptomatic on exposure to a specific allergen, but become symptomatic when concurrently exposed to additional allergens to which they are sensitised. Thus several different allergens (the *allergen load* (Fig. 4)) may act synergistically to exceed an individual's reaction threshold. But if the allergen load is reduced through avoidance of one or more of the allergens (to which they are sensitised), they may experience fewer symptoms and a reduced need for pharmacotherapy.

To further illustrate this point, consider an individual sensitised to both cat and grass pollen, who may have

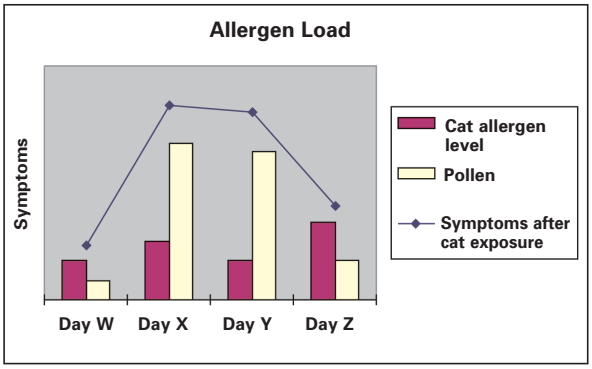


Fig. 4. Allergen load.

no symptoms on cat exposure in winter, but in summer with the higher pollen load displays troublesome symptoms if re-exposed to cats. This paradoxical reactivity may occur with various combinations of house-dust mite, pollen, pet dander and mould spore exposure.[12] The clinical course of asthma is usually characterised by periods of symptom-control and is then interrupted by unexplained asthma exacerbations. Using knowledge of local 'allergen load' may help us predict these exacerbations and any sudden deterioration in asthma.

It is therefore fundamentally important to test and identify the exact nature of allergens to which the individual has allergic sensitisation, so that planning and allergen avoidance can be implemented to reduce the allergen load and improve overall rhinitis, asthma and even eczema management.

Practice points

- Children with persisting/recurrent/severe allergy symptoms should all be allergy tested.
- Many infant wheezers do not have allergies or asthma and will outgrow their symptoms.
- A negative allergy test will liberate the individual and their care-givers from unnecessary avoidance measures.
- Infants tend to develop transient food allergies while older children develop persistent inhalant allergies.
- In sensitised individuals, the cumulative sum of the allergen 'load' will determine when symptoms occur.
- The more allergens that test positive and the greater the sum of specific IgE antibodies present, the greater the probability of an allergic disease being present.
- In children, specific food allergies can now be predicted using cut-off points for specific IgE, thus reducing the need for food challenge testing.

ImmunoCAP multi-channel analyser

House-dust mite

Skin Prick Test (SPT) solutions

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