INVESTIGATION OF THE ALLERGIC PATIENT: THE IMPORTANCE OF EARLY DIAGNOSIS

If specific diagnosis and intervention are instituted early, the 'allergic march' can be attenuated and even prevented.

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Allergic diseases have dramatically increased worldwide during the past 20 years. This increase has led to a prevalence in allergic symptoms in children which has increased by 200% when compared with the mid 1970s. In most developed countries 1 in 4 children are affected by allergies and in undeveloped countries the prevalence is also increasing rapidly. The main allergic diseases in infancy are atopic eczema and food allergies.

In young children, asthma, rhinitis and urticaria are increasingly diagnosed. This progression of allergic diseases, referred to as the 'allergic march', can be attenuated and even prevented either by new pharmacological medications or by using immunotherapy, if specific diagnosis and intervention are instituted early. The identification of specific allergen sensitivity in young infants has very specific diagnostic implications, not only in relation to allergen avoidance, but also as direct implications for preventive intervention.

New concepts in allergy diagnosis now focus on quantitative interpretation of the results of skin prick and Immunocap RAST tests. Food challenges and new tests for non-IgE-mediated sensitivity have improved diagnostic accuracy. New understanding and appreciation of immunological cross-reactivity has implications for selection of further allergy testing and prevention of inadvertent exposure to potentially dangerous allergens.

WHY EARLY DIAGNOSIS?

In the past, investigation of infants and very young children was discouraged, because it was considered that conducting and reading skin tests in infants was unreliable. Until fairly recently there were no available validated guidelines for the clinical significance of a specific IgE value for the common allergens to which young children develop positive test results. All of this has now changed.[1]

- **Cut-off values are now known**
  Early diagnosis is now possible because the 95% predictive values for clinical sensitivity have been determined in children with atopic eczema, for most of the common allergens. This applies both to skin prick tests and for Immunocap RASTs. The predictive values for tests are defined in Table I.

Table I. **Definitions of sensitivity, specificity and predictive values**

Positive predictive value	Proportion of true positive test results among all positive test results
Sensitivity	Proportion of positive results among patients with the disease
Negative predictive value	Proportion of true negative tests among all negative test results
Specificity	Proportion of negative results among healthy patients
Efficiency	The relative number of correctly classified patients

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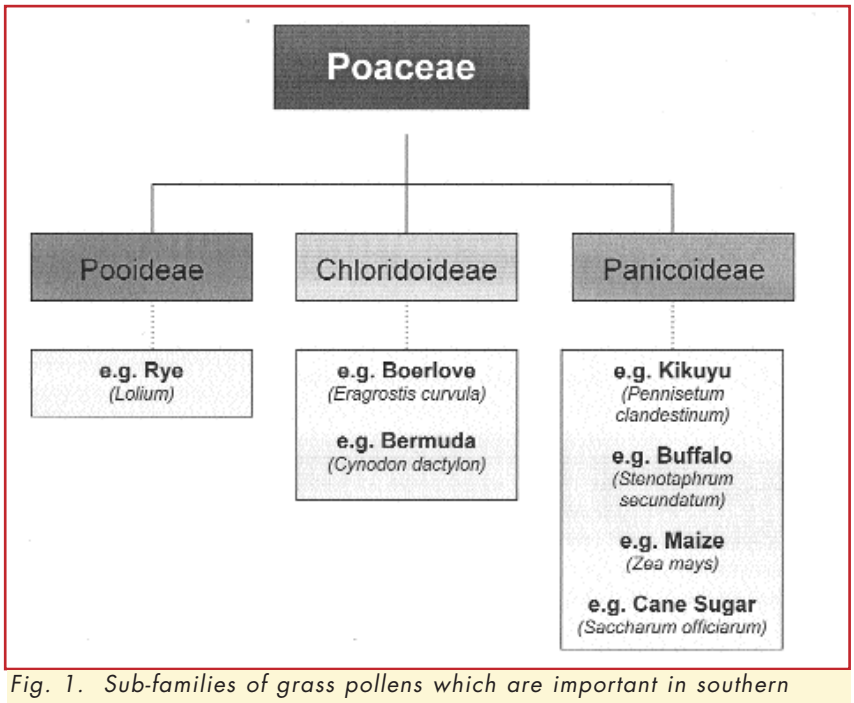

Fig. 1. Sub-families of grass pollens which are important in southern Africa.

- **To avoid clinical type I reactions**
  The second reason to make an early diagnosis of allergy in infants is to avoid clinical reactions to the food allergen (e.g. egg, peanut, milk, soya) which can be life-threatening for some infants.

- **To prevent eczema flare-ups**
  In infants with eczema allergy testing must be performed to identify those who have atopic eczema. Between 30% and 60% of infants with eczema are found to have food allergy and food exposure plays a significant role in the exacerbation of eczematous flare-ups. These intermediate reactions to food may manifest with early erythematous flaring of the skin with accompanying pruritus, which quickly progresses to eczematous flare-ups when the infants scratch.

- **To identify eczema children who will develop asthma**
  A fourth reason to diagnose allergies early is to identify the subgroup of eczema infants who will develop asthma and in whom prevention of asthma is possible using pharmacological treatment with cetirizine or ketotifen.[2] The ETAC study found that it was the subgroup of eczematous infants who had early house dust mite and grass pollen allergy in whom intervention produced a significant reduction in the development of asthma.

- **To select the subgroup who will benefit from immunotherapy**
  A fifth reason for the early diagnosis of allergies, particularly house dust mite and grass pollen allergies in young children, is to select these children for allergen immunotherapy, either via the injection route or via the sublingual route. In young children with rhinitic symptoms who have confirmed grass pollen allergy, specific immunotherapy will also reduce the expected development of asthma in this subgroup by 50%.[3]

- **To identify children in whom further allergic evaluation will be required**
  Confirmation of specific food allergy in infants identifies the infant in whom specific allergy testing for inhalant allergens should be conducted as the child grows older. New allergies may develop and clinical sensitivity to the food allergens will go away for most food allergens by the time the child goes to school. This would be confirmed by specific follow-up testing of the pre-school child.

KNOWLEDGE BASE FOR ALLERGY TESTING

Foods

A sound knowledge of the specific foods that are responsible for the majority of adverse reactions in infants, makes allergy testing both inexpensive and rewarding. A panel of 5 food allergens is all that is required in infancy. These include egg, milk, wheat, soya and peanut. These account for over 90% of allergies in infants. The fx5e is a useful screening RAST for food allergies in infants and young children.

In older children testing for fish and other allergens suggested by the history is important. In older children and adults crustaceans, molluscs, tree nuts and fruits (especially tropical fruits) are important food allergens. It is important to bear in mind that although peanuts are legumes and not true nuts, about 50% of peanut-sensitive patients will have concordant tree nut sensitivity. Nut sensitivity should be explored in peanut-sensitive children.

Inhalants

For inhalant allergens a knowledge of the environment in which the patient lives is essential. Important indoor environmental allergens include house dust mites (*Dermatophygoides pteronyssinus, Dermatophygoides farinae* and *Blomia tropicalis*), cockroaches, cats, dogs and fungal spores. Animal handlers or laboratory workers may also be exposed to latex, horse, cow, rat, guinea pig and even locusts in an indoor environment. These are important inhalant allergens.

Outdoor environmental fungal spores include cladosporium, alternaria, epicoccum and aspergillus. The grass pollens in southern Africa fall into 3 major groups (Fig.1). The major sub-families to test for inhalant pollen allergens are the *Pooideae*, of which *Lolium perenne*

(rye) is a good representative and the *Chloridoideae* represented by Bermuda grass.

Important indigenous grasses, such as Eragrostis, also belong to the *Chloridoideae* sub-family. A group of grasses of great regional significance are in the *Panicoideae* sub-family. These include buffalo (*Stenotaphrum*), maize (*Zea mays*) and cane sugar (*Saccharum officiarum*) (Figs 2 - 4).

Fig. 2. Buffalo grass (Stenotaphrum secundatum).

Fig. 3. Anther of kikuyu grass (Pennisetum clandestinum).

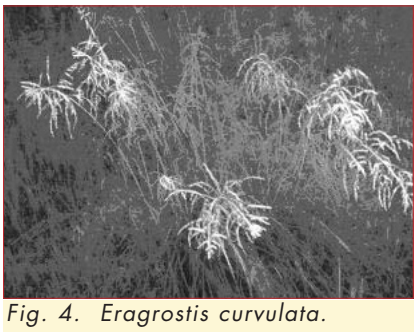

Fig. 4. Eragrostis curvulata.

Pollen allergies are acquired by the age of 3 - 5 years in 50% of children and by the age of 9 - 13 years in 90% of children attending an allergy clinic in Gauteng (M Groenewald (2000): personal communication).

In the Cape and KwaZulu-Natal about 40% of allergic children and young adults are allergic to pollen, but allergies to house dust mites are found in 60 - 80% of the allergic population. House dust mite and cockroach allergy is also more common in KwaZulu-Natal and in the Eastern Cape.

Tree allergies are found in Gauteng and also in the Cape. Important pollens include oak and plane trees. Eucalyptus, pine, Port Jackson and jacaranda pollens are often believed to be responsible for patient symptoms, but true allergy to these tree pollens is uncommonly confirmed. Allergy to weed and floral pollens is also less common but immune responses to cosmos, chrysanthemums and English plantain is also found, but is rather uncommon.

It is clear from the above discussion that an intelligent selection of relevant inhalant allergens for CAP RAST or skin prick tests depends on the geographical location of the patient within southern Africa.

HOW RELIABLE IS ALLERGY TESTING?

Labile versus stable allergens

The reliability of the specific test depends on the quality of the testing extract and the performance of the test.

For skin prick tests stable allergens are reliable skin prick testing solutions. Examples of these include egg, peanut, codfish, latex, house dust mite and grass pollens. A wheal of greater than 3 mm accompanied by a flare, is a positive result. A positive test result does not always correlate with clinical sensitivity to that allergen, although in general the larger the reaction the greater its clinical significance.

For drug allergies (e.g. penicillin) and certain occupational allergens (e.g. latex), a wheal of 3 mm is clinically significant.

For heat-labile allergens and for fruit allergens in which proteolytic activity may denature the allergens, skin prick testing with fresh extracts is more reliable (e.g. melon, kiwi, peach, apple). This is particularly relevant in the diagnosis of the oral allergy syndrome.

Cut-off values

Cut-off values for the predictive value of skin prick tests for clinical sensitivity to common food allergens have been determined by Sporik *et al.*[5] and are listed in Table II. Skin tests are the most reliable tests for the diagnosis of penicillin and cephalosporin allergy. For laboratory tests there is a wide range in the sensitivity, specificity and positive predictive value of the test depending on the allergen and the *in vitro* system.

Table II. **Predictive values for Immuno CAP RASTs**

	95% predictive value
Egg	6 Ku/l
Milk	32 Ku/l
Peanuts	15 Ku/l
Fish	20 Ku/l
Soy	65 Ku/l
Wheat	80 Ku/l
Negative predictive value = 95%	

The Pharmacia Immunocap system remains the gold standard for specific IgE determination and is the most widely used in South Africa. Using the Pharmacia Immunocap system, cut-off values for the 95% predictive value for the induction of a measurable clinical reaction when exposed to a given food have been determined (Table II).[4] There is a 95% risk of a clinical reaction to that food where values are greater than those listed in Table II. Predictive values for skin prick tests are listed in Table III.

Thus when investigating eczema patients, who often have many positive results, one can use the possible clinical significance of a test.

In young children allergies to foods wane with age and they may acquire inhalant allergies, as illustrated in a case

Table III. **Predictive values for skin prick tests**

	Positive challenges of wheal (100% of predictive value)	
	Over 2 years	Under 2 years
Cow's milk	> 8 mm	> 6 mm
Egg	> 7 mm	> 6 mm
Peanut	> 8 mm	> 4 mm

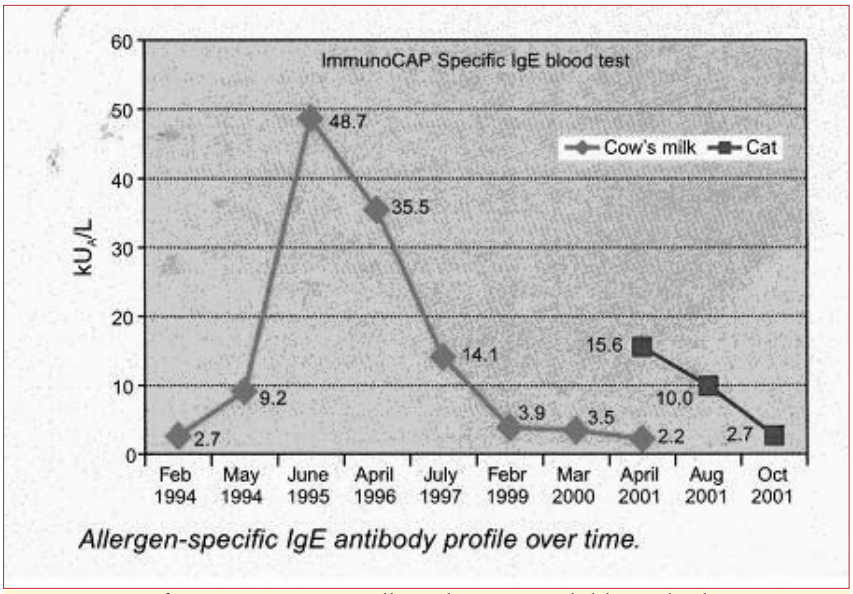

Fig. 5. Specific IgEs to cow's milk and cat in a child, studied over a 7-year period.

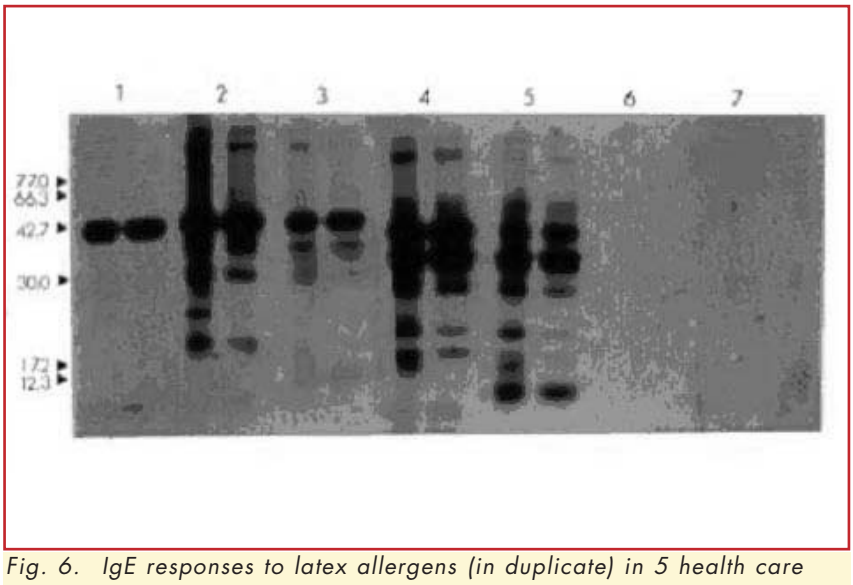

Fig. 6. IgE responses to latex allergens (in duplicate) in 5 health care workers using Western blot technique.

study shown in Fig. 5, in which the child lost clinical milk allergy but acquired cat allergy later on.

Rechallenging with foods

Monitoring the fall in specific IgE values for milk and egg is particularly useful in children under 6 years of age, where loss of sensitivity is expected, but guidelines are required as to when re-challenge with these foods is likely to be safe and appropriate.

For food allergies, a blinded or open challenge is the final arbiter as to whether a patient is truly allergic or not. Although the cut-off values are extremely useful, there are occasional patients who will react to a food challenge at levels below the cut-off values and thus food challenges should not be conducted at home, but under medical supervision.

Western blots

Western blots can be used to identify specific IgE responses to allergens which are not commercially available. This applies to many of the indigenous seafood allergens and may be useful for fine-tuning of the immune responses in a patient with allergy to indigenous inhalant allergens.

These are available through the UCT Allergy Diagnostic and Clinical Research Unit (ADCRU) in Cape Town which has been involved in pioneering work identifying the major allergens responsible for adverse reactions to indigenous species (Table IV). A Western blot showing IgE immune responses to latex allergies in 5 patients is shown in shown in Fig. 6.

Tryptase levels

A rise in mast cell tryptase levels following a severe adverse reaction (e.g. during anaesthetic) suggests that the reaction was indeed allergic and justifies specific IgE testing for the anaesthetic agents used.

Tryptase levels characteristically peak 30 minutes to 3 hours after a reaction and return to normal values 24 - 48 hours after a reaction. It is a stable test and can also be useful for forensic purposes if elevated following a fatal reaction (e.g. cot deaths, anaesthetic deaths).

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Table IV. **Indigenous allergens of southern Africa**

Plants	
Grass pollens	Eragrostis, kikuyu, buffalo
Floral pollens	African daisies
Tree pollens	Acacia, mesquite, imbuia
Contact irritants	Verbena hybrida, Rhodesian flame lilly
Plant extracts	Certain latex proteins
Insects	
Locusts	
Spider mites	
Psychoda fly	
Chemicals	
Platinum salts	
Foods	
Abalone	
Local fish allergens	
Reptiles	
Cobra venom (rinkhals)	

TESTING FOR NON-IgE-MEDIATED REACTIONS

A number of adverse reactions mimic allergic reactions in their clinical manifestations, but an IgE-mediated mechanism does not appear to mediate the reaction. Some of these reactions involve basophils and mast cells that are triggered via non-IgE-mediated pathways. These are sometimes referred to as pseudo-allergic reactions. 'Intolerance' reactions may be examples of such reactions.

Characteristic clinical features of intolerance reactions to proteins (e.g. wheat, milk) or food additives (e.g. sulphites and benzoates) is that they are dose-responsive, somewhat variable and often delayed (a few hours after exposure). The best test for food intolerance is an elimination challenge test with the suspected food but the period of observation post challenge should not be less than 8 - 10 hours.

Table V. **New technical cut-off values for the CAST test**

	Pg/ml
Sodium benzoate	90
Sodium metabisulphite	40
Food colourant	160
Latex	200
Lys aspirin	90
Amoxycillin	100

The CAST-2000 ELISA may be regarded as an *in vitro* allergy provocation test. Leukocytes are isolated, the basophils are stimulated and leukotriene release is determined using an ELISA assay. Although CAST assays are available for inhalants, venom, foods, antibiotics, occupational allergens and anti-inflammatory drugs, their most useful application in our experience is for the confirmation of food additive sensitivities. Leukotriene release is measured and new technical cut-off values for some of the CAST tests are listed in Table V. Values above these levels often correlate with clinical sensitivity. This has recently been validated at the UCT Allergy Diagnostic and Clinical Research Unit for Sulphites. A fresh sample of EDTA blood is required for the test.

ELIMINATION/CHALLENGE DIETS

It is not always possible to select appropriate IgE or non-IgE tests from the patient's history. The clinical relevance of different foods in a mixed diet can be explored using elimination/challenge diets.

One such basic diet includes rice, fruit (pear, apple and grapes), meat (lamb and chicken), vegetables (asparagus, beetroot, carrots, lettuce, sweet potato, potato, butternut, squash), black tea or rooibos, olive oil, sunflower oil, sugar and salt. No additives, preservatives or spices are permitted. The diet is dairy free, legume free and wheat free.

Patients who are allergic or intolerant to foods generally improve on this elimination diet and then, using a systematic challenge programme, introducing foods one by one, the culprit food can be identified and specific IgE or non-IgE test can be selected for confirmation of the sensitivity. Conducting and interpreting the results of elimination/challenge diets takes some skill and is best performed with the help of an allergy specialist.

References available on request.

IN A NUTSHELL

Allergy diagnosis is based on careful history taking and tests selected according to the age, geographical location, occupation and the clinical profile of the patient.

Early diagnosis (as young as 3 months of age) assists with prevention of severe type I reactions, the management of atopic eczema flares and the prevention of asthma.

Allergy tests for foods now have cut-off values that can predict with confidence a 95% chance of developing a clinical reaction to that food if challenged with it.

Inhalant allergy tests are selected based on the geographical location of the patient.

Testing for non-IgE-mediated reactions may be conducted using elimination challenge diets or using the CAST test for preservative sensitivities.

Elimination challenge diets have an important role to play in the selection of specific tests to identify foods responsible for adverse reactions.

Western blots and in-house ELISAs are important tools for the identification of specific IgE responses to indigenous allergens and 'now' allergens which are not yet commercially available.