



Diagnosing allergies in general practice...

**The evidence, the art of skin prick test
and specific IgE measurement, and the
interpretation of results**



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Diagnosing allergies is a three-stage detective procedure, where all the stages are vitally important. If the first two stages are done properly and the clues interpreted correctly, the third and final stage might not be necessary.

Stage one

The first stage is the gathering of the evidence for the case. If the right amount of time is spent gathering the evidence – taking a full, proper history – and the detective has some knowledge about the suspect's whereabouts, it will be much easier to find them.

Stage two

The second stage involves finding the suspects. In diagnosing allergies, this is done through skin prick testing or measuring specific IgE in the serum. Unfortunately, the detective will often find many suspects from his initial search. Now he has the task of figuring out which of these suspects are guilty of committing the crime. In some cases only one suspect is found and the evidence is overwhelming, so the case is cut and dry. For example, a child bites into a peanut butter sandwich and develops generalised urticaria, vomiting and wheezing within five minutes, which requires treatment with adrenaline by a doctor. This case is solved very easily by doing a skin prick test, which reveals a > 3 mm wheal diameter to peanut. There is no need to look for further evidence by feeding the child peanuts and watching for a reaction.

Stage three

The third and final stage in the diagnosis of allergies is the allergen provocation test. This is the gold standard for proving an allergy beyond the shadow of a doubt. In this case of the peanut reaction, an oral food challenge is not necessary. In fact it is not advisable as it would be considered too risky. In most cases diagnosing an allergy is not as cut and dry. This is especially the case when the evidence isn't collected properly and there are several likely suspects. For example, when there are several positive skin prick test responses there is the difficult task of finding the suspect. To further complicate this, the actual suspect might not be amongst those responses because it is hidden.

Detective work

Diagnosing allergies is no different from a detective solving a crime. The doctor must make the time to gather the evidence by asking the right questions, and knowing when to ignore misleading information volunteered by the patient. The doctor should have some basic background knowledge of the likely allergens present in the particular patient's diet and environment. A good history will also help to decide if a food reaction is likely to be IgE-mediated (if it occurs within one hour of eating the food) or non-IgE mediated (delayed in onset). The latter is more likely to be a food intolerance and measuring for IgE would not be the investigation of choice.

The second stage of the investigative process is probably the least important of the three stages, and the one which causes the most problems in the diagnosis of allergies. This is the measurement of specific IgE antibodies. This can be done in one of two ways, either the skin prick test (SPT) or measuring specific IgE in the serum, ImmunoCAP® (formerly RAST) test. A positive test at this stage only indicates sensitisation to that allergen and provides supportive evidence for the diagnosis of allergies. The skin prick test is the *in vivo* counterpart of the *in vitro* measurement of specific IgE (ImmunoCAP) in serum. Both tests give the same answer, with some minor differences. The most important difference is that the skin prick test is more sensitive than the specific IgE Immuno CAP if it is done properly and interpreted correctly. The newer methods of measuring specific IgE, like ImmunoCAP compared to the older RAST, is considered by some to be more specific than the skin prick test, but still not as sensitive as the SPT.

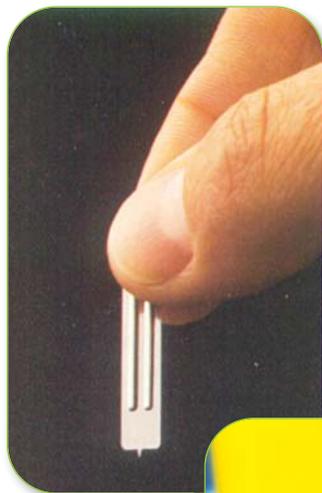
It is very important to remember that positive skin prick tests or positive ImmunoCAP results to a specific allergen demonstrate specific IgE sensitisation, but are not proof that the allergen is the cause of the clinical symptom. The specificity of both tests is very much dependent on the full history taken prior to the testing or pre-test probability.

Predictive values

The Pre-Test Probability of an Allergy diagnosis is defined as the probability of the allergic disorder being present before a diagnostic test result is known. This is useful in interpreting the results of all allergy tests or in deciding whether it's worth doing the allergy testing at all. A reaction occurring within one hour of eating a particular food, with a reliable witness observing objective signs of an allergic reaction (anaphylaxis), has a very high pre-test probability of a diagnosis of food allergy. Also, the presence of atopy (asthma, eczema and hay fever), a reaction to one of the eight common food allergens (milk, egg, peanut, tree nuts, wheat, soy, fish and shellfish), and when there is no other non-allergic explanation of the food reaction all add weight to the pre-test probability of a food allergy.

Traditionally, taken with a good clinical history, cut-off levels for SPT weal size of $> 3\text{mm}$ or serum-specific IgE $> 0.35\text{ kU/L}$ have been used to support a clinical diagnosis of an IgE-mediated allergy. However, if the history is weak a level $> 3\text{mm}$ may be irrelevant. In most centres throughout the world a skin weal diameter of 3mm has been recommended as a marker of hypersensitivity to foods. A 3mm weal has high sensitivity, but the corresponding specificity is too low (probably about 50 per cent) to be of value in identifying clinically relevant food allergy. Conversely a negative or $< 3\text{mm}$ weal is highly useful (> 90 per cent specific) in excluding IgE-mediated food allergy. Hugh Sampson, Mt Sinai School of Medicine, USA, in earlier studies⁽³⁾, reported that a 3mm weal had 96 per cent sensitivity in the diagnosis of peanut, milk and egg allergy. But 3mm cut-off is only about 50 per cent specific. In a study of children referred to the Royal Children's Hospital in Melbourne, Hill and Sporik⁽²⁾ did a prospective investigation of the results of SPT and 555

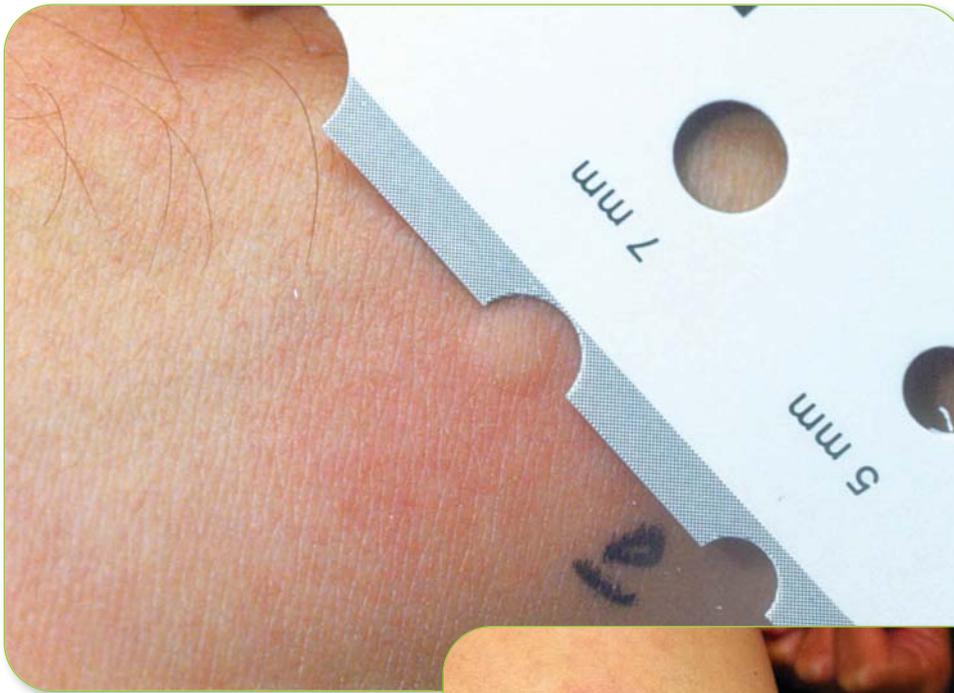
oral food challenges performed in 467 children (median age 3.0 years) over a nine-year period. They have found that a strongly positive skin reaction to cow milk ($> 8\text{ mm}$), egg ($> 7\text{ mm}$), and peanut ($> 8\text{ mm}$) was invariably associated with an adverse reaction on formal open food challenge. These results confirm and extend previous observations by Sampson and others. In addition, the results confirm observations by other groups that the presence of a positive allergen skin test, in itself, is a poor positive predictive marker of clinically relevant food allergy. It is only when the degree of sensitisation is taken into account that it is of value. This increased certainty of correctly identifying a child who would react adversely to food (gain in specificity) is invariably accompanied by a reduction in the number of children correctly identified (loss of sensitivity). This is of clinical use, however, in that it allows allergen skin prick tests to be used as a screening procedure; those with a strongly positive reaction do not require further evaluation. In conclusion, this study defined SPT weal diameters as '100 per cent diagnostic' by using 100 per cent specificity for Cow's Milk ($> 8\text{mm}$), Hen's Egg ($> 7\text{mm}$) and peanut ($> 8\text{mm}$). Therefore, they suggested that all children exceeding these limits should be considered allergic to this specific food without further investigation. For children two years of age or younger 100 per cent specificity was reached at lower SPT weal diameters, 6mm for cow milk, 5mm for egg, and 4mm peanut. In contrast for some unknown reason, in some plant-derived foods like wheat and soy the correlation of the IgE methods (SPT, specific serum IgE) and the outcome of oral food challenges was not as clear cut as with animal-derived foods (milk and eggs) and no such levels were found.



A skin prick test is normally done on the forearm after the individual is off antihistamines for a minimum of 72 hours.



The allergens, along with a negative saline and a positive histamine control, is applied to the forearms, pricked with a sterile lancet and then read in 15 minutes.



The size of the wheal is recorded by measuring the largest diameter.

For diagnosis of fruit and vegetable allergy in Oral Allergy Syndrome, the commercial extracts are unreliable because of the very short shelf life, and a prick-prick test is done. This is where you prick the food with a lancet and then immediately prick the forearm with the same lancet. This is sometimes done with fresh seafood, but there is a definite risk of anaphylaxis as the tests are non-standardised.



The British Society for Allergy and Clinical Immunology guideline for the diagnosis of egg allergy⁽¹⁾ proposes higher cut-off levels, which are associated with higher specificity and positive predictive values. Although in younger children (<2 years) smaller SPT wheals and lower serum-specific IgE are more likely to be predictive of egg allergy than in older children. For SPT to egg white, a weal size of 5mm or greater is associated with high specificity; smaller SPT wheals and lower serum-specific IgE are more likely to be predictive of egg allergy than in older children. For SPT to egg white, a weal size of 5mm or greater is associated with high specificity and in most cases there is no need to undertake oral challenge to confirm diagnosis. It is important to know that SPT weal size does not appear to correlate with clinical severity.

In a study by Verstege⁽⁴⁾ in Germany the predictive decision points for the SPT could also be calculated for egg and milk and predicted probabilities exceeding 99 per cent may render oral food challenges superfluous and indicate a therapeutic elimination diet. Similar to Hill and Sporok's study, smaller wheal sizes did not prove the absence of a food allergy with acceptable confidence. Interestingly, their data showed that the SPT offers advantages over the determination of specific serum IgE for the diagnostic work-up of suspected cow's milk allergy. Their study also subdivided children into those of below and above one year of age and resulted in different cut-off levels, with a tendency towards lower values in the younger children. This is in accordance with the results of Hill and Sporik showing lower cut-off levels in children below two years of age

Algorithm for diagnosis of peanut allergy in general practice

If a child gives a typical history of rapid onset of symptoms (urticaria, angioedema, vomiting abdominal pain, wheezing or breathlessness) after eating a peanut-containing product, the first test the child should have is a skin prick test to peanut. If the SPT wheal diameter is $>3\text{mm}$ peanut allergy is very likely. If the wheal is $>8\text{mm}$ peanut allergy is certain and an oral challenge is not necessary. If the SPT wheal diameter is $<3\text{mm}$ I would repeat it and if still $<3\text{mm}$ I would do ImmunoCAP specific IgE. If this is $<0.35\text{kU/L}$ then I would do an oral challenge. Specific IgE to peanut should not be measured in the absence of a history of peanut ingestion, as in this circumstance the test has poor sensitivity and low negative predictive value. However, if the doctor succumbs to parental pressure and it is done and found to be 2-4mm, an oral challenge is required to exclude peanut allergy. But if it is $>5\text{mm}$ peanut allergy is very likely. If it is 0-1mm peanut allergy is excluded. However, clinical allergy may be found in young infants with a SPT wheal diameter of 2mm, especially if there is an associated flare surrounding the wheal. A follow-up specific IgE ImmunoCAP to peanut is also normally done every one to two years to see if the patient belongs to the fortunate 20 per cent who will outgrow their peanut allergy.

The future of allergy testing

Each allergen (foods, pollen, dust mites etc) is composed of many different molecules that may cause sensitisation. A detailed picture of each patient's sensitisation pattern can be obtained by measuring IgE sensitisation to each of these allergen components. This type of testing, known as component resolved diagnostics (CRD), is useful in identifying the source of the allergens and also allows the clinician to predict the prognosis of the allergic disease. The new Phadia ImmunoCAP® Component Tests (ISAC) is very exciting because it will be able to help with one of the biggest diagnostic problem in food allergy, that of differentiating peanut sensitisation due to cross-reaction from birch pollen – which usually does not usually have a risk of a life-threatening reaction - from true primary peanut sensitisation, with the risk of a life-threatening reaction.



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