The diagnosis of IgE-mediated allergy is based on the confirmation of a typical history of allergic symptoms by diagnostic tests. *In vivo* and *in vitro* tests are used in the diagnosis to detect free or cell-bound IgE, the major isotype of anaphylactic antibodies.

The diagnosis of allergy has been improved by allergen standardisation, which provides satisfactory extracts for both *in vivo* and *in vitro* tests for most inhalant allergens, and the introduction of recombinant allergens. Nasal, bronchial and conjunctival challenge tests are used in research and to a lesser extent in clinical practice, but they may be particularly important in the diagnosis of occupational allergies. They deserve a special chapter.

**Skin tests**

Immediate-reading skin tests are widely used to demonstrate an IgE-mediated allergic reaction and represent a major diagnostic tool. If properly performed, they yield useful confirmatory evidence for a diagnosis of specific allergy. The modified prick test introduced by Pepys is the current reference method. Various devices were introduced to decrease the variability of prick tests. Opinions concerning these so-called standardised methods vary according to the skill of the investigator.

They are highly reproducible. Prick tests should be 2 cm apart. Prick plus prick tests with fresh foods, mainly fruits and vegetables can be used
when commercial extracts are not sufficiently sensitive or are not available. In some instances (e.g. weak allergen solution), intradermal skin tests may be employed. Although they are more sensitive than prick tests, they may induce some false positive reactions and correlate less well with symptoms.

Intradermal tests are less safe than prick tests, since, although rarely, systemic reactions may occur. Intradermal tests are not considered useful for the diagnosis of inhalant allergy when standardised extracts are available.

As a general rule, the starting dose of intracutaneous extract solutions in patients with a preceding negative prick test should range between 100- and 1,000-fold dilutions of those used for prick-puncture tests.

Because of inter-patient variability in cutaneous reactivity, it is always necessary to include negative and positive controls. The negative control solutions are the diluents concerned. Any reaction at the negative control test sites will hinder interpretation of the allergen sites.

Positive control solutions are used to detect possible suppression by medication or disease, exceptional patients who are poorly reactive to histamine or variations in technician performance. The usual positive control for prick-puncture testing is histamine dihydrochloride (1 or 10 mg/mL). Mast cell secretagogues such as codeine phosphate 9% may also be used. Histamine-induced skin reactions reflect vascular reactivity and are useful to determine whether histamine antagonists are present, while codeine skin reactions are a function of both mast cell reactivity and vascular responsiveness.

Recombinant DNA technology allows production of pure biochemically characterised proteins. Skin tests with recombinant allergens have been available since the 1990s for pollens, moulds such as Aspergillus, mites, venoms and latex. Skin tests with recombinant and natural allergens have a similar value if
the recombinant allergens have been well selected and represent all or most epitopes of the natural allergen. They would allow the detection of IgE to non-panallergenic molecules using skin tests and/or serum IgE, which is of importance in polysensitized patients. Recombinant allergens should also be useful for the diagnosis of food allergy.

Skin tests should be read at the peak of their reaction by measuring (in mm) the wheal and the flare approximately 15 minutes after the performance of the tests.

For prick tests, when the control site is completely negative, small wheals of a mean diameter of at least 3 mm of the negative control represent a positive immunological response, but these reactions do not necessarily imply the presence of a clinical allergy.

Skin reaction is dependent on a number of variables that may alter the performance of skin tests:

- The **quality of the allergen extract** is important.
- **Age** is known to affect the size of the reaction, but positive skin prick tests can be found early in infancy. In old age, the size of skin tests decreases.
- **Seasonal variations**. Skin sensitivity increases after the pollen season and then declines.
- **Drugs** affect skin tests and it is always necessary to ask patients about the drugs they have taken. Discontinuing other H1-antihistamines one week before is required.
• Patients with dermographism (urticaria) or widespread skin lesions should not be tested by prick puncture tests. Intradermal tests with the proper negative control are often feasible.

Serum specific IgE assays

Sometimes identification of the causal factors is not easy because of the high number of allergens and the fact that not all allergies are IgE-dependent.

In vitro tests are of great interest in order to establish the culprit agent and to avoid provocations, especially for patients exposed to several allergens simultaneously or with histories of life-threatening reactions. Only specific IgE assays will be covered here, but new tools (basophil activation tests and micro-arrays) are being evaluated.

The discovery of IgE in 1967 was a major advance in the understanding and diagnosis of allergic diseases. In normal subjects, levels of IgE increase from birth (0-1 KU/l) to adolescence and then decrease slowly and reach a plateau after the age of 20-30 years. In adults, levels of over 100-150 KU/l are considered to be above normal. Allergic and parasitic diseases as well as many other conditions increase the levels of total IgE in serum. Thus, the measurement of total serum IgE is barely predictive for allergy screening and should no longer be used as a diagnostic tool.

In contrast to the low predictive value of total serum IgE measurements in the diagnosis of immediate type allergy, the measurement of allergen-specific IgE in serum is of importance. The first technique used was the RAST (radioallergosorbent test). New techniques are now available using either radio- or enzyme-labelled anti-IgE. Specific IgE measurements are not influenced by drugs or skin diseases. As for skin tests, the quality of allergens is of critical importance and, when possible, only standardised extracts or more recently recombinant allergens should be used.
Several studies have shown that serum specific IgE results correlate closely to those of skin tests and nasal challenges. As in skin tests, the presence or absence of specific IgE in the serum does not preclude symptoms, and some symptom-free subjects have serum specific IgE.

Although a low specific IgE titre may not be clinically relevant, the titre of serum specific IgE is usually unrelated with symptoms. When using single allergen tests, the cost of serum specific IgE measurement is high and only a selected list of allergens can usually be tested.

Some methods use either a mixture of several allergens in a single assay or test several different allergens during a single assay. These tests can be used by non-allergists as screening tests for the diagnosis of allergic diseases. It has been shown that their efficiency (specificity and sensitivity) in allergy diagnosis is often over 85%. However, using these tests, the patient is defined only as sensitized or non-sensitized and more extensive investigations are needed if the test is positive.

**Clinical value of allergy tests**

The diagnosis of allergy is based on the correlation between the clinical history and diagnostic tests for allergy. It is not possible to diagnose allergy based solely on responses to skin tests, *in vitro* tests, or even challenges.

**Diagnosis of respiratory allergy**

Skin tests represent the primary diagnostic tools used for immediate-type hypersensitivity. Comparisons between the measurement of specific IgE and skin tests depend on the quality and standardisation of the allergens used in both types of tests and, to a lesser extent, on the method of skin testing used. For standardised allergens, challenges are usually not necessary to confirm the diagnosis of allergy. Positive responses to skin tests and serum-specific IgE can be found in totally symptom-free subjects with a similar prevalence. Correlations between responses to skin tests and to the measurement of allergen-
specific IgE with inhalation challenges are less consistent because of the nonspecific hyper-reactivity.

**Diagnosis of food allergy**
The diagnosis of IgE-dependent food allergy is complicated, because allergen extracts and the test reagents currently available are not standardised and their stability is poorly determined.
The presence of food-specific IgE in serum or a positive skin test to a foodstuff does not always correlate with a food allergy since some patients outgrow their allergy with age and not all patients with food-specific IgE have a clinical sensitivity. In many instances, the diagnosis has to be confirmed by a double-blind food challenge, which should be carried out under precisely specified conditions and by staff who have the competence to manage anaphylactic reactions.

**Diagnosis of occupational allergy**
In practice, interviews concerning the causal relation, frequency, latent period, and atopic disposition often provide suggestions, but sometimes give unreliable evidence for diagnosing occupational respiratory allergy.
Therefore, examinations such as skin tests, provocation tests, and determination of the IgE antibody level are necessary to confirm the causality between the disease and the work exposure.

**Diagnosis of drug allergy**
The diagnosis of drug hypersensitivity is often difficult since patients may be allergic to one of the drug metabolites, there is a lack of standardization, and non IgE-dependent mechanisms may be involved.
With a few exceptions, skin tests in drug allergies are of poor predictive values. With complete allergens such as myorelaxants or chymopapain intradermal or prick-puncture tests can detect an IgE-mediated allergy.
In penicillin allergy, the haptens that have been generally used are benzylpenicilloyl-poly-L-lysine (PPL), a mixture of minor determinants (MDM) and penicillin G, amoxicillin, ampicillin and any other relevant β-lactam and skin tests are of major importance.
When negative, they need to be followed by a provocation, which should be carried out under hospital surveillance.
Diagnosis of venom allergy
Skin tests with venoms provide useful confirmatory evidence of an IgE response.
Intradermal tests are preferred.
At the concentration of 1 µg/ml, about 30% of patients with systemic reaction have a negative intradermal test and one fourth of nonallergic subjects have positive results, because of mast cell degranulating compounds contained in venoms.
Specific IgE are always measured and equally helpful.

References


