



GUIDELINE

Diagnostic testing in allergy

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1. Definitions

Atopy. Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, such individuals can develop the typical symptoms of asthma, rhinoconjunctivitis or eczema.¹

Allergy. Allergy is a hypersensitivity reaction initiated by immunological mechanisms. Allergy can be antibody- or cell-mediated. In the majority of cases the antibody typically responsible for an allergic reaction belongs to the IgE isotype, and these individuals may be referred to as suffering from an IgE-mediated allergy.¹

Atopic individuals must have clinical symptoms. Some 30 - 40% of individuals in developed countries are allergic, but only a proportion of these have atopic diseases, which include asthma (5 - 10%), rhinitis (10 - 20%) and food allergy (1 - 3%). In population studies allergic diseases peak at different ages. Food allergy and atopic eczema are predominant in early childhood, whereas asthma shows a biphasic peak and rhinitis peaks in the second or third decade.

Atopic diseases manifest as hyper-responsiveness in the target organ, whether skin, nose, lung or gastrointestinal tract. This hyper-responsiveness (allergy) may have both IgE-mediated and non-IgE-mediated components. The situation is further complicated because allergen exposure in allergic subjects may increase target organ hyper-responsiveness, which results in exaggerated symptoms on exposure to nonspecific irritants (tobacco smoke, changes in temperature, etc.) in allergic subjects. Only a proportion of atopic subjects develop disease, and atopic individuals may have casual factors in their disease independent of their atopic status. Furthermore, increased nonspecific responsiveness lowers the threshold for symptoms on subsequent allergen exposure.

2. Diagnostic approach

Allergy diagnosis depends primarily on the clinical history. The history, aided by a physical examination, guides objective tests of IgE sensitivity. Either skin tests or allergen-specific serum IgE measurements (RAST) are used to focus on the following questions:

- Is the patient allergic?

- Does allergy contribute to the patient's symptoms?
- What are the clinically relevant allergens?

There should be a high index of suspicion of allergy in patients presenting with symptoms of asthma, rhinitis or eczema, particularly if there is an associated personal or family history of other atopic disease. On the basis of a positive initial history, a limited number of skin-prick tests (SPTs) and possibly specific IgE measurements (radio-allergosorbent tests – RASTs) to commonly prevailing aero-allergens (Table I) or foods should be performed to confirm or exclude atopy. Few foods commonly provoke allergic reactions; they include cow's milk, egg and peanut in infants and young children, and fish, shellfish, peanuts, tree nuts, fruit and spices in older children and adults. Physical examination may determine which organ or organs is or are involved. When both the clinical history and results of SPTs (or specific IgE) are negative, one can exclude allergy with a high degree of confidence and no specific treatment for allergy is indicated. A positive history and positive tests help in rationalising treatment, initiating specific allergen avoidance measures and selecting appropriate immunotherapy.

Table I. Prevailing aero-allergens in South Africa¹⁸

All regions	House-dust mites (Der p 1 and Der f 1) Rye and Bermuda grass <i>Aspergillus</i> , <i>Alternaria</i> , <i>Cladosporium</i> Cat and dog
Western Cape	Add: Oak and plane tree pollen, <i>Blomia tropicalis</i> <i>Epicoccium</i> fungal spore Cockroach
Gauteng	Add: Tree pollens including cypress
Farming areas	Add: <i>Zea mays</i> pollen Horse <i>Blomia tropicalis</i>
Health care worker	Add: Latex
Grain industry	Add: Storage mites, wheat and rye

2.1 Skin-prick testing

SPTs with allergen extracts are the favoured method of *in vivo* testing for IgE-mediated sensitivity. Testing for a limited number of common allergens (Table I) may confirm or exclude atopy. The quality of extracts is important for reliable results. Standardised extracts are currently available for most common inhalant allergens and for some food allergens. Many patients with documented food allergy fail to react to commercial

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extracts but react to fresh extracts of the food,^{2,3} e.g. fruits,³ celery,⁴ shellfish and fish.^{5,6} Interpretation of SPTs may also be difficult in children younger than 2 years because of reduced reactivity to histamine in this age group.⁷ Results of SPTs must always be expressed in a quantitative manner that can be interpreted by other practitioners. SPTs must be performed in a setting where personnel and equipment are available for resuscitation (because of a very low but definite risk of anaphylaxis⁸).

2.2 Blood tests (*in vitro*)

Total IgE was initially used as a diagnostic marker of allergic disease, but it has limitations: IgE is elevated in allergic diseases and in non-allergic conditions, e.g. parasitic infestation, and half of IgE-mediated allergic patients have a total IgE within the normal range.⁹ The predictive value of this test is therefore rather limited in allergy diagnosis.

Specific IgE (RAST) measures allergen-specific IgE to allergens in patient serum. In the case of inhalant allergens a level of >0.35 kU/l is considered positive (sensitivity 60 - 80%, specificity 90%); for food allergy, the cut-off values for positive (indicating clinical reactivity) appear to be much higher (Fig. 1).¹⁰ The respective advantages of SPTs and specific IgE are shown in Table II.

2.3 Multi-allergen IgE antibody screening assays

These are useful when a patient provides an equivocal history for allergic disease (making it difficult to pinpoint with reasonable certainty the appropriate allergens to test for). The multi-allergen screen for aero-allergens is the Phadiatop¹² (Phadia, Uppsala) and for foods the Fx5 (Phadia, Uppsala). Phadiatop is usually reported as positive or negative. A positive

test indicates that the patient may be sensitive to one or more of the following inhalants: *house-dust mites, grass, mould, cat, dog*. The laboratory should then contact the doctor to discuss testing for the relevant allergen(s). The Fx5E is a quantitative test; a level of >0.35 kU/l is considered positive and indicates that the patient may be sensitive to one or more of the following foods: *cow's milk, egg white, fish, wheat, peanut, soya*. The laboratory should contact the referring doctor to discuss further testing. A negative multi-allergen screen reduces the probability that IgE-mediated allergic disease is the cause of the patient's clinical problems.

2.4 Mast cell tryptase

The serum level of β -tryptase can be useful as a marker of mast cell activation in the definitive diagnosis of anaphylaxis.¹³ Tryptase levels peak at 45 - 60 minutes and may remain elevated for several hours (up to 24 hours).¹⁴ Ideally, three serial measurements should be performed: the first soon after the reaction, the second a few hours later, and a baseline level 24 hours later.

2.5 CAST testing

Some patients may develop symptoms due to sensitivity to various food additives (colourants, flavourants or preservatives) or medications, which are not IgE mediated. These chemical sensitivities may be confirmed by CAST testing (cellular antigen stimulation test) and should be discussed with a specialist.

An algorithmic approach to testing for inhalant and food sensitivities is outlined in Figs 1 and 2.

2.6 Unproven diagnostic tests

There are many allergy 'diagnostic' tests performed by ecologists and alternative practitioners. These tests are of unproven value, are often time-consuming and expensive, and are not to be recommended (Table III).¹⁵⁻¹⁷

References

1. Johansson SG, Bieber T, Dahl R, *et al.* Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113(5): 832-836.
2. Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy* 1983; 38: 167-172.

Table II. SPT compared with specific IgE

SPT	Specific IgE
<ul style="list-style-type: none">• Inexpensive	<ul style="list-style-type: none">• Not affected by concurrent drugs, e.g. antihistamines
<ul style="list-style-type: none">• Immediate results	<ul style="list-style-type: none">• Not influenced by skin disease
<ul style="list-style-type: none">• Educational value	<ul style="list-style-type: none">• Completely safe
<ul style="list-style-type: none">• Generally more sensitive	<ul style="list-style-type: none">• Tests for wider range of possible allergens

Table III. Diagnostic tests of unproven value

- Neutralisation provocation (Miller) tests (based on multiple skin tests; environmental allergens include smoke, petrol, tobacco, etc.)
- Leukocytotoxic tests
- Hair analysis
- Vega testing (a 'black box' electrical test). The test is based on the addition of food extracts to a chamber contained within an electrical circuit completed by the patient
- Applied kinesiology (based on muscle weakness)
- Auricular cardiac reflex testing (based on pulse rate)
- ALCAT
- IgG measurements

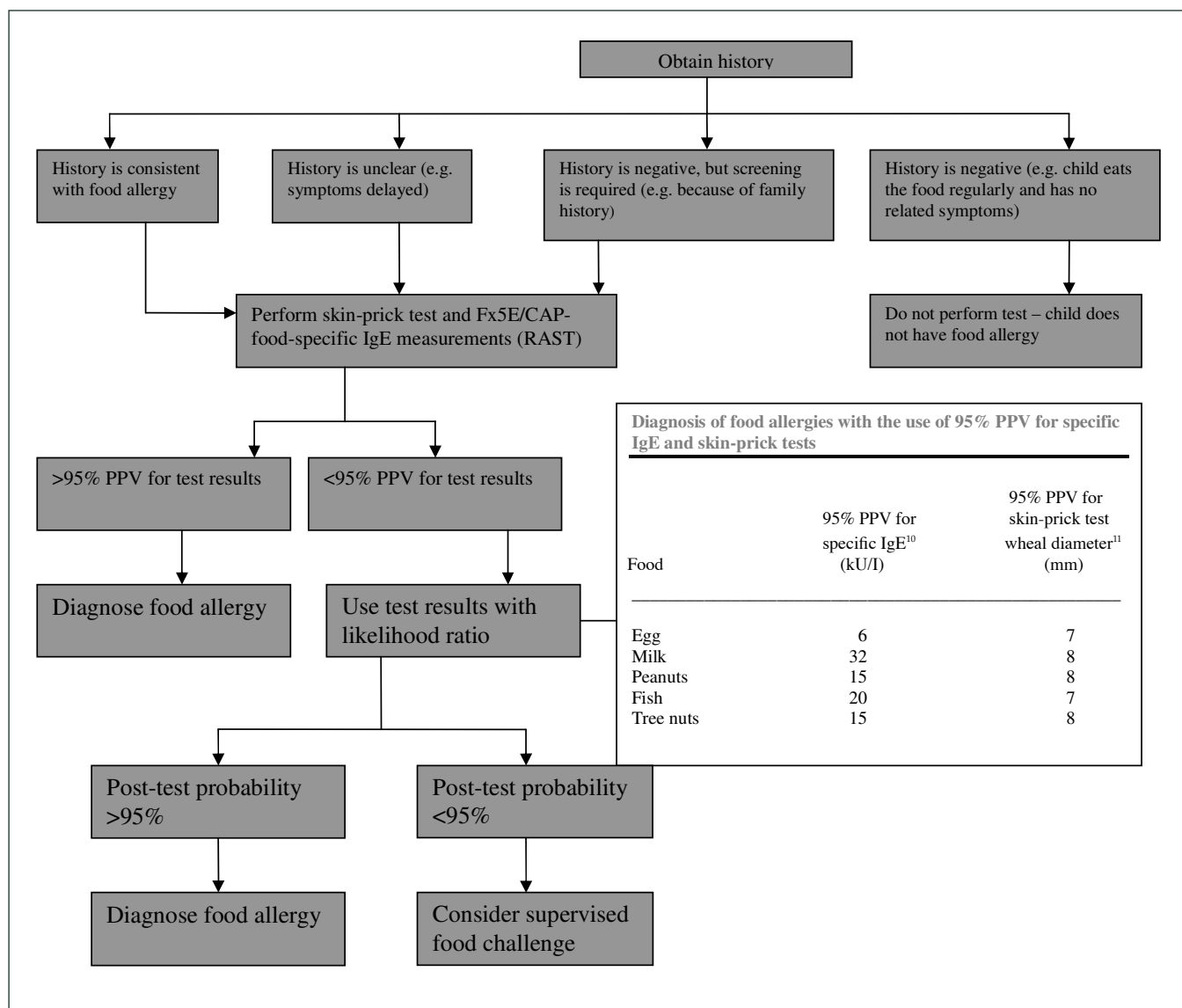


Fig. 1. Diagnostic algorithm for food allergy (adapted from Lack¹⁹). This treatment algorithm can be used for any food allergy if the test result is associated with a positive predictive value (PPV) of >95% and if the likelihood ratio is known for a given test result. A double-blind, placebo-controlled food challenge should not be performed if the patient has a history of severe anaphylaxis. In the skin-prick test, the mean wheal diameter obtained depends in part on the age of the patient, the extract used, the method of performing the test, and the site on the body where the test is performed. Values for specific types of tree nuts have not been validated.

- Rosen JP, Selcow JE, Mendelson ML, et al. Skin testing with natural foods in patients suspected of having food allergies: is it a necessity? *J Allergy Clin Immunol* 1994; 93: 1068-1070.
- Ortolani C, Ispano M, Pastorello EA, et al. Comparison of results of skin prick test (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989; 83: 683-690.
- Ancona GR, Schumacher IC. The use of raw foods as skin testing material in allergic disorders. *Calif Med* 1950; 73: 473-475.
- Bock SA, Lee W-Y, Remigio L, et al. An appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 1978; 8: 559-564.
- Menardo JL, Bousquet J, Rodiere M, et al. Skin test reactivity in infancy. *J Allergy Clin Immunol* 1985; 75: 646-651.
- Novembre E, Bernardini R, Bertini G, et al. Skin-prick test-induced anaphylaxis. *Allergy* 1995; 50: 511-513.
- Hamilton RG. Human immunoglobulins. In: Leffell MS, Rose N, eds. *Handbook of Human Immunology*. Boca Raton, Fla: CRC Press, 1998.
- Sampson HA. Utility of food-specific IgE concentrations in predicting food allergy. *J Allergy Clin Immunol* 2001; 107: 891-896.
- Sporik R, Hill DJ, Hoskings CS. Specificity of allergen skin testing in predicting positive, open challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; 30(11): 1540-1546.
- Williams PB, Siegel C, Portnoy J. Efficacy of a single diagnostic test for sensitization to common inhalant allergen. *Ann Allergy Asthma Immunol* 2001; 86: 196-202.
- Enander I, Matsson P, Andesson AS, et al. A radioimmunoassay for human serum tryptase released during mast cell activation. *J Allergy Clin Immunol* 1990; 85: 154-159.
- Schwartz LB, Yunginger JW, Miller J, et al. Time course of the appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; 83: 1551-1557.
- Condemni JJ. Unproved diagnostic and therapeutic techniques. In: Metcalfe DD, Sampson HA, Simon RA, eds. *Food Allergy: Adverse Reactions to Foods and Food Additives*. 2nd ed. London: Blackwell Scientific, 1997.
- James JM. Unproven diagnostic and therapeutic techniques. *Curr Allergy Asthma Rep* 2002; 2: 87-91.
- Potter PC, Mullineux J, Weinberg EG, et al. The ALCAT test – inappropriate in testing for food allergy in clinical practice. *S Afr Med J* 1992; 81: 384.
- Potter PC. Allergic evaluation and management of the atopic patient. *SA Family Practice* 2008; 50(5): 10-15.
- Lack G. Food allergy. *N Engl J Med* 2008; 359: 1252-1260.

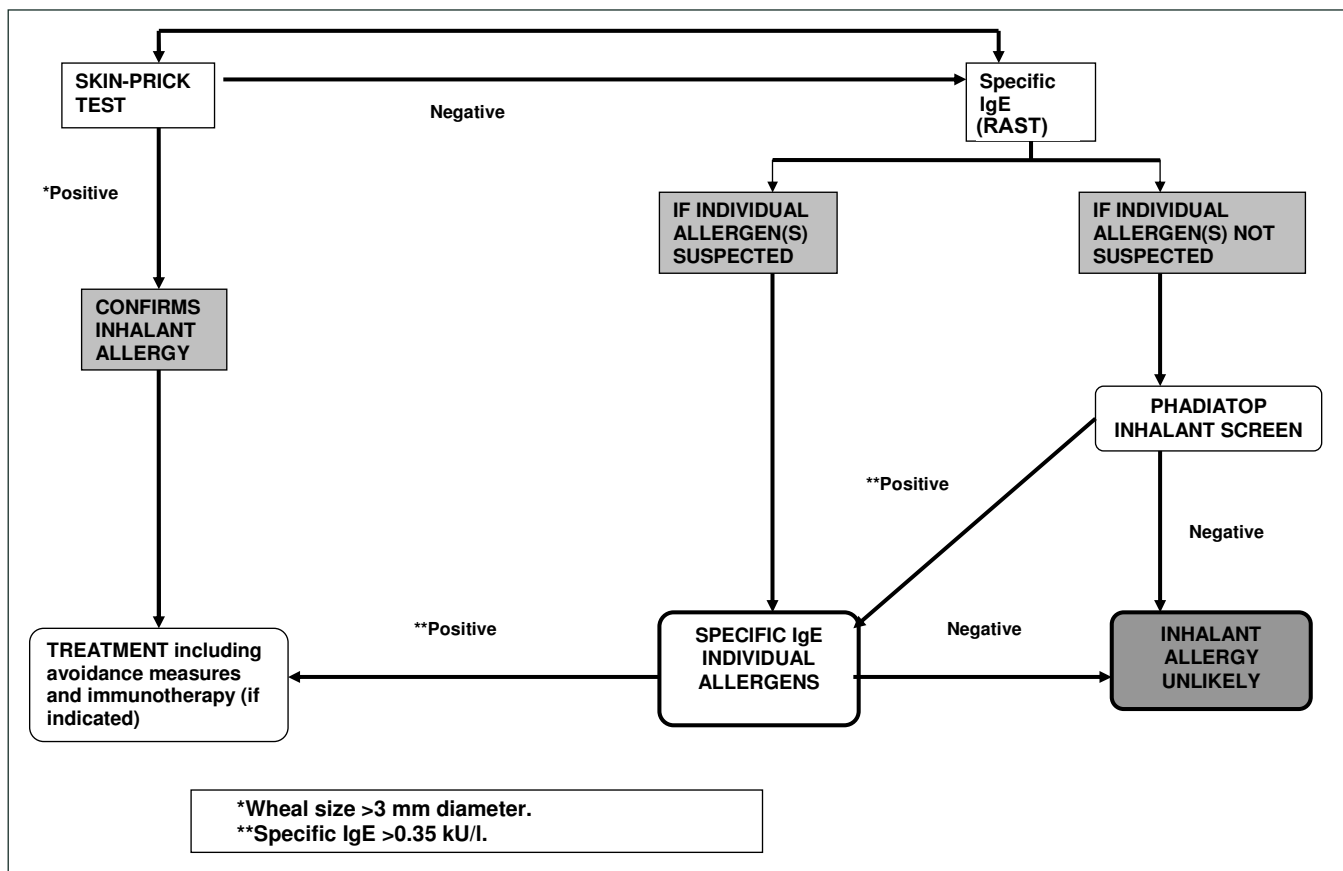


Fig. 2. Diagnostic algorithm for inhalant allergy.