Investigation of the patient with suspected allergy

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The term allergy to a member of the general population is viewed as describing any adverse reaction to food, medications or other substance; while to an immunologist, it refers to specific IgE-mediated reactions to allergens. In this article we will focus on the investigation of IgE-mediated reactions.

Medical practitioners are frequently called on to determine if symptoms are due to an allergy. Table 1 lists conditions in which investigations for an allergy may be helpful. Certain conditions, such as asthma and persistent rhinitis, are commonly exacerbated by exposure to allergens, and investigation is useful. On the other hand, the probability of identifying an IgE-mediated precipitating or exacerbating factor for chronic urticaria is very low, and, therefore, investigation with skin prick tests or serum-specific IgE tests is not recommended routinely.

History and examination

The history is vital to allergy diagnosis. It is important to distinguish immediate (type I, IgE-mediated) hypersensitivity from other forms of allergy and from nonallergic reactions, as this will affect decisions about further testing and management. Ascertain the nature and severity of the symptoms, and the time interval between exposure and symptoms. Immediate hypersensitivity is suggested by rapid onset (within minutes to two hours) of symptoms and signs.

In some instances, the history is convincing and clear enough for the diagnosis of immediate hypersensitivity to a certain allergen to be made. However, in many cases confounding factors are present, for example, the ingestion of foods with multiple ingredients, or the administration of local anaesthetic with concomitant exposure to latex gloves. Determine the amount of exposure

IN SUMMARY

- **Investigation for IgE-mediated hypersensitivity usually takes the form of skin prick testing and/or serum-specific IgE testing.**
- **Skin prick testing is the gold standard for detection of allergen-specific IgE; however, testing for serum-specific IgE is more readily available in the primary care setting.**
- **Tests should always be interpreted in the context of a thorough history and physical examination.**
- **False-negative serum-specific IgE tests occur, and a negative serum test should not be used to exclude allergy if the history suggests immediate hypersensitivity.**

Table 1. Likelihood of common conditions having an allergic cause

Condition	Probability of allergic cause*	Differential diagnoses (nonallergic mechanisms)
Acute allergic symptoms (e.g. urticaria, angioedema, bronchospasm)	>80% if possible precipitant is identified on history <20% if no precipitant on history	See below for differentials according to the presenting complaint
Asthma/bronchospasm	~80%[1]	Nonallergic asthma Chronic obstructive pulmonary disease 'Cardiac wheeze': heart failure Endobronchial disease: foreign body, neoplasm, bronchial stenosis Recurrent pulmonary embolism Churg–Strauss syndrome Eosinophilic pneumonia Carcinoid tumours
Persistent or chronic intermittent rhinitis	~80%[2, 3]	Vasomotor rhinitis Irritative–toxic rhinitis (e.g. due to cigarette smoke, ozone, sulphur dioxide, garden sprays, ammonia, wood particles) Postinfectious or recurrent viral infection Pregnancy Rhinitis medicamentosa: overuse of topical vasoconstrictive sprays Nonallergic rhinitis with eosinophilia syndrome (NARES) Vasculitis (e.g. Wegener's granulomatosis) Cocaine abuse
Eczema	In children: up to 35%[4] Adult onset: <5%[5]	Allergic contact dermatitis (delayed hypersensitivity reaction) Irritant contact dermatitis Dyshidrotic eczema Asteatotic eczema due to extremely dry skin Stasis dermatitis due to venous incompetence
Patient-perceived 'food allergy'	<20%	Food intolerance (e.g. lactose intolerance) Pharmacological effects (e.g. tyramine in cheese resulting in migraine) Toxins (e.g. bacterial food poisoning) Non-IgE-mediated hypersensitivity disorders: coeliac disease, food protein-induced entero- or proctocolitis
Adverse reaction to medication	<5%	Pharmacological side effect Toxicity/overdose Idiosyncratic reactions Drug interactions Direct mast cell degranulation (e.g. due to opiates, vancomycin, radiographic contrast media) Cytotoxic (type II), immune complex (type III) or delayed (type IV) hypersensitivity reactions
Angioedema without urticaria	~20%[6]	Hereditary angioedema Acquired C1 inhibitor deficiency ACE inhibitors
Chronic urticaria	<5%	Dermatographism Physical urticaria (e.g. cold-induced, cholinergic, solar) Urticarial vasculitis Association with autoimmune thyroid disease Association with infections Autoantibodies to the IgE receptor

*Probability of identifying an IgE-mediated precipitating or exacerbating factor.

and any exacerbating factors such as exercise, consumption of alcohol and poorly controlled asthma. A thorough history to ascertain previous and subsequent exposure and exposure to cross-reacting substances is valuable.

If the patient presents with 'hives', it is important to confirm the nature of the rash and to assess for dermatographism.

Investigations

Identification of the causative or exacerbating allergen is important in many situations for management of the patient, and in particular, for tailoring immunotherapy.

If the history suggests IgE-mediated mechanisms, initial testing generally involves skin prick testing or serum tests for allergen-specific IgE (Figure). Table 2 shows the availability of specific skin prick and serum tests in Australia.

Subsequent testing by elimination diet or challenge to the substance may be performed, but the latter carries a risk of anaphylaxis and should be performed by an immunologist in a setting where resuscitation equipment is available.

Skin prick testing

Skin prick testing should be performed according to the guidelines established by the Australasian Society for Clinical Immunology and Allergy (ASCIA)[7]; however, there is no accreditation or certification process currently to determine the proficiency of practitioners. Immunologists routinely perform skin prick testing. Other doctors who have an interest in allergy (general practitioners, paediatricians, respiratory physicians, general physicians) may also perform skin prick testing, as may nurses (under medical supervision).

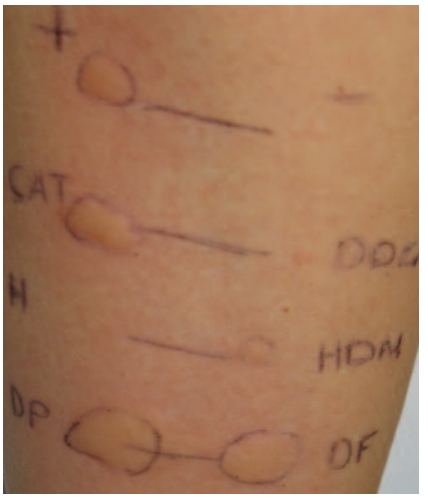


Figure. Skin prick testing. Positive reactions to cat and two types of house dust mite, *Dermatophagoides pteronyssinus* (DP) and *D. farinae* (DF). Negative reactions for dog, horse (H) and house dust mixture (HDM). Interpretation is dependent on valid positive (+) and negative (-) controls.

Table 2. Availability of tests for specific allergens

Allergen	Skin prick test	Serum test ('RAST')*
Food: yeast, egg, gelatin, milk, fruit, grains, meat, nuts, seafood, vegetables	Yes	Yes
Aeroallergens: animal epithelia, dust mites, pollens, moulds	Yes	Yes
Benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxycillin	Yes†	Yes
Cephalosporins	No	For cefaclor only
Anaesthetics	Yes, but limited range	No
Muscle relaxants	Yes	No
Insulin, protamine, chlorhexidine, latex	Yes	Yes
Insect venom: honey bee, paper wasp, yellow jacket	Yes‡	Yes

* 'RAST'= radioallergosorbent test; the commonly used term for serum allergen-specific IgE testing.
† One of the major metabolites of penicillin was previously unavailable for testing, limiting the value of skin tests. Some centres now have access to this and can offer testing.
‡ Skin testing to jack jumper ant venom has been described,[10] but it is not routinely available.

Skin prick testing is performed using a diluted allergen that is pricked into the skin surface. If the patient has IgE specific for that allergen, the IgE will be cross-linked on the mast cell surface, resulting in histamine release and wheal formation. Antihistamines and medications with antihistamine properties should be ceased prior to testing (see Table 3 for the minimal timing of medication cessation prior to testing). In certain circumstances, skin testing is not recommended. Table 4 lists contraindications and precautions for skin prick testing.

A positive control of histamine and a negative control of saline or diluent are essential for correct interpretation of the test. A positive test is generally defined as a wheal with a diameter more than 3 mm larger than the negative control wheal at 15 minutes after the prick.

Intradermal testing may be considered when investigating suspected venom and drug allergy and skin prick tests are negative. Intradermal tests increase the sensitivity of skin testing, but with loss of specificity. Intradermal testing should be performed in a specialist setting.

Allergen-specific IgE testing in serum ('RAST')

There are a number of methods for the detection of allergen-specific IgE in serum. 'RAST' (radioallergosorbent test) is the name for an old method of detecting serum-specific IgE that used radio-labelled conjugates. Although this has now been superseded by enzyme- and fluorescence-based assays, the term 'RAST' is still commonly used for these newer assays.

In general, serum tests are less sensitive than skin tests. This may be because of the low (nanomolar) concentration of specific IgE in serum (which may limit detection), the use of allergen mixtures for testing, and/or the inability to use fresh allergens. Therefore a negative serum-specific IgE test does not exclude significant allergy, especially if the history suggests immediate hypersensitivity. In this situation, skin testing should be performed.

A comparison of the advantages of skin prick testing and 'RAST' is shown in the box on page 56.

Table 3. When to stop medications before skin testing

Medication	When to stop before skin testing
First generation antihistamines (e.g. cyproheptadine, promethazine)	2-4 days
Second generation antihistamines (e.g. cetarizine, loratadine, fexofenadine)	4-10 days
H_2-receptor antagonists (e.g. cimetidine, ranitadine)	Day of testing
Other medications with antihistamine properties (e.g. antidepressants, antimigraine medications, antiemetics, neuroleptics)	Withholding period not established for most; effect varies between individuals
Inhaled and short-term systemic corticosteroids	Generally do not affect skin testing

Interpreting skin prick test and 'RAST' results

It is important to remember the following points when interpreting skin prick or 'RAST' test results.

- Interpret the results in the context of history, examination and allergen exposure.
- A positive result is not necessarily clinically significant. Sensitisation may occur without clinical manifestations. In addition, if there has been no identifiable exposure to the allergen, it is unlikely to be the cause of the patient's symptoms.
- Larger skin test reactions predict a higher likelihood of positive challenge, but do not predict the severity of symptoms.
- Tests may remain positive even after an allergy has clinically resolved.
- False negative skin prick and 'RAST' tests may occur in the six weeks following anaphylaxis.
- A negative serum test does not exclude significant allergy (i.e. there may be false negatives).

Other tests for allergy

The measurement of tryptase is useful for the confirmation of anaphylaxis, and its use has been discussed in another Clinical Investigations article (*Medicine Today* 2006; 7(10): 14-20).[8]

Measuring total serum IgE is generally not helpful as it is not sensitive and does not provide additional information if the history suggests allergy. There are only a few circumstances in which IgE measurement may be useful, such as when allergic bronchopulmonary aspergillosis is suspected and in some rare immunodeficiency syndromes. Peripheral blood eosinophilia is only occasionally detected

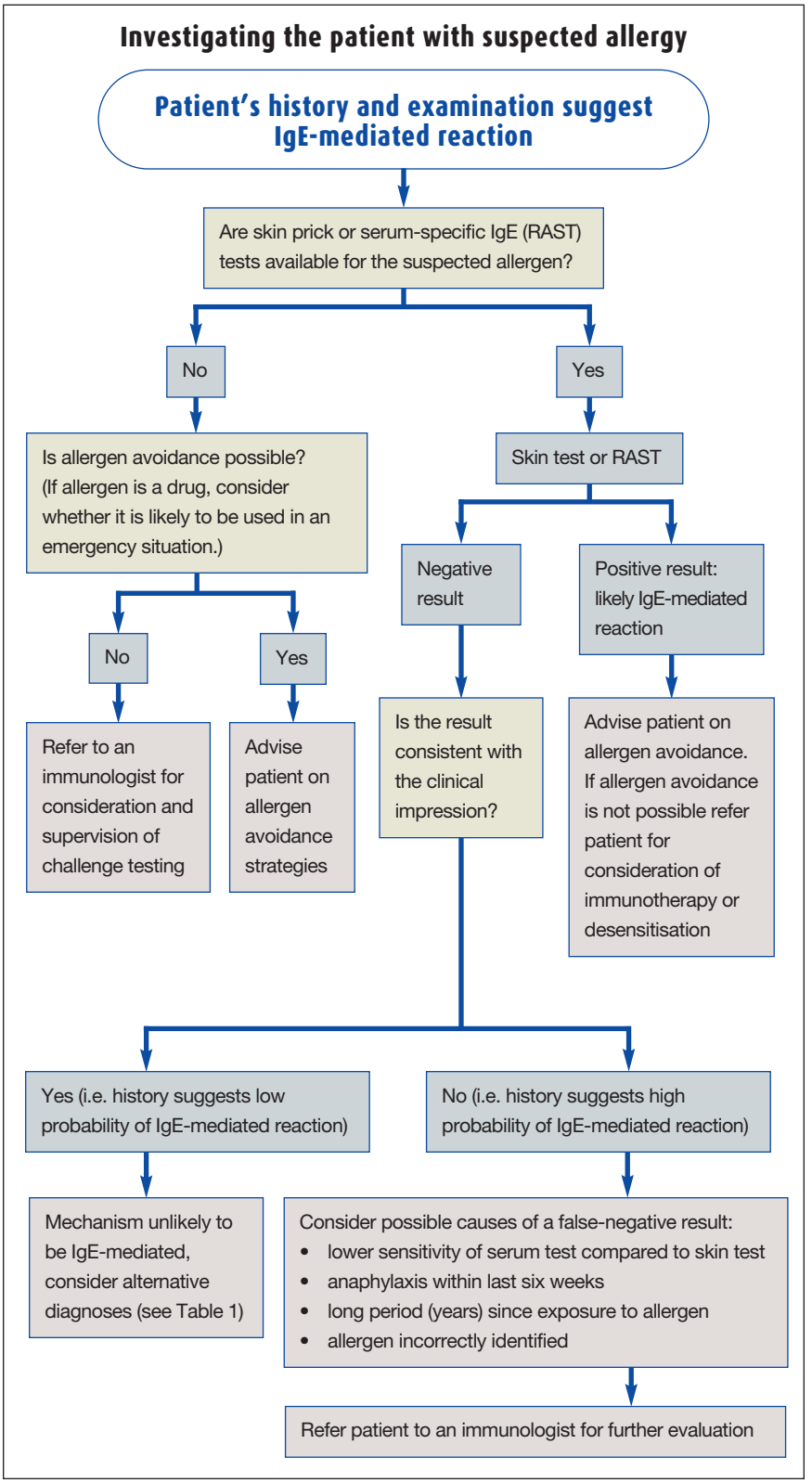
Table 4. Skin prick testing: contraindications and precautions

Contraindications[7]

- Diffuse dermatological conditions
- Severe dermatographism
- Limb affected by lymphoedema
- Poor patient co-operation
- Patient unable to cease interfering medications (see Table 3)
- Inadequate facilities for resuscitation

Precautions

- Persistent severe or unstable asthma
- Pregnancy (small risk of anaphylaxis with hypotension and uterine contractions)
- Babies and infants
- Use of beta blockers (causes difficulty treating anaphylaxis)



in allergic patients, and is not specific for allergy.

A number of tests for allergy are available that lack good evidence to support their use, including sublingual food provocation tests, cytotoxic tests, diagnosis by kinesiology and electrodermal testing.[9] These tests are advocated by some practitioners, but are expensive and have no diagnostic value.

Food allergy

Skin tests for food allergy are more sensitive than serum tests. Therefore a negative skin test is a good way to exclude an IgE-mediated reaction (negative predictive value >95%). Indiscriminate testing should not be undertaken because a positive result does not necessarily imply a causal relationship between the food and the symptoms (specificity <100%).[10]

The size of a wheal on skin testing, or the level of specific IgE can predict the likelihood of an allergic reaction on challenge, but not the reaction severity.[11-13] If there is any doubt, double-blind placebo-controlled oral food challenge is the gold standard for diagnosis, but must be performed under specialist supervision in facilities where resuscitation equipment is readily accessible.[14]

The case scenario on page 56 discusses the investigation of possible nut allergy in a child.

Drug allergy

The diagnosis of drug hypersensitivity can be difficult and the interpretation of tests often requires the expertise of an immunologist. Challenge testing can be performed for most drugs, but the patient should be evaluated first by an immunologist.

Conclusion

The investigation of a patient with suspected IgE-mediated allergy usually entails skin prick testing and/or serum allergen-specific IgE testing, interpreted in the context of the history and physical

Advantages of skin prick testing and 'RAST'*

Advantages of skin prick testing

- Results are available in half an hour.
- It is the gold standard for detection of allergen-specific IgE. In most cases, sensitivity and specificity are better than with 'RAST', if performed correctly.
- Results are visible to the patient and useful for explaining the allergy and improving compliance.
- There is no interference from high total IgE level, as may occur with 'RAST' testing.
- It causes minimal discomfort: only a minor scratch and itch if the test is positive. It may be more acceptable to patients who dislike venepuncture.

Advantages of 'RAST'

- It is widely available to any practitioner.
- It has reasonably good sensitivity.
- Less patient co-operation is required for venepuncture than for skin prick testing.
- It carries no risk of anaphylaxis (risk is <0.03% with skin prick testing, and generally occurs in patients with high risk features such as uncontrolled asthma).
- It is suitable for patients with extensive skin disease.
- It is suitable for patients who cannot stop medications that may interfere with skin testing.

* 'RAST'= radioallergosorbent test; the commonly used term for serum allergen-specific IgE testing.

examination findings (see the flowchart on page 54). Consideration should be given to non-IgE-mediated hypersensitivity reactions and nonimmunological reactions when assessing the patient. Referral to a clinical immunologist should be considered for skin prick testing, interpretation of testing, and consideration of allergen challenge or further management. MT

Case scenario: possible nut allergy

A 3-year-old girl attended a party with her parents. She had eaten a few nuts from a nut mix on the coffee table. A few minutes later she vomited and was taken by her parents to the local medical centre. Was this a clinical manifestation of a nut allergy? What tests would you order to confirm this?

Discussion

An isolated episode of vomiting shortly after ingesting nuts may indicate immediate hypersensitivity. Other symptoms of allergy (e.g. pallor, rash, difficulty breathing, angioedema) should be sought. An exploration of differentials such as viral gastroenteritis and food poisoning should be undertaken. A thorough history of all foods ingested should be taken, including details of the types of nuts in the mixture.

A 3-year-old child is more likely to comply with skin prick testing than with venepuncture for serum tests, but either approach would be reasonable. A wide variety of nuts can be tested for by either method. If sensitisation is not detected on testing, challenge testing may be performed, but the child should be referred to an immunologist for this, due to the small risk of anaphylaxis.

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