# Investigating a patient with anaphylaxis

**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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Anaphylaxis is best defined as an acute or rapidly evolving, systemic or multi-organ, life threatening reaction resulting from the release of preformed and newly synthesised bioactive mediators, predominately from mast cells and basophils. These mediators include histamine, leukotrienes, prostaglandins and proteases which have pleomorphic activities including (and most importantly) vasodilation with an increase in vascular permeability, and bronchospasm.

The term anaphylaxis does not necessarily imply an underlying type 1 IgE mediated allergic aetiology; a number of mechanisms can lead to the final pathway of mast cell and basophil mediator release. Some authors use the term 'anaphylactic' to characterise an IgE mediated reaction triggered by allergens and 'anaphylactoid' to imply a non-IgE mediated aetiology, such as excess leukotriene production, plasma complement activation or direct mast cell degranulation. More recent nomenclature uses the terminology 'allergic' and 'nonallergic' anaphylaxis for IgE mediated and non-IgE mediated reactions, respectively.[1]

## Clinical features

When anaphylaxis occurs secondary to allergen exposure or to a defined nonallergic trigger (e.g. IV contrast), the onset of symptoms is rapid – usually within 15 to 30 minutes, and sometimes within 5 to 10 minutes.

The key clinical features of anaphylaxis and their frequencies are summarised in Table 1. Patients may present with any one or any combination of these features.

**IN SUMMARY**

- **Anaphylaxis is an acute or rapidly evolving, systemic or multi-organ, life threatening reaction resulting from the release of mediators predominantly from mast cells and basophils.**
- **For most patients presenting with anaphylaxis, a confident diagnosis should be possible from the history and examination.**
- **If there is doubt about the diagnosis, the plasma tryptase level should be measured. Plasma tryptase is specific for anaphylaxis.**
- **In determining the cause of anaphylaxis, skin prick testing is the standard method for detection of specific IgE, and is simple, quick and highly sensitive.**
- **Serological testing for specific IgE is preferable to skin prick testing in selected cases – e.g. in patients with extensive skin disease, in those who are taking antihistamines or in those who are at risk of anaphylaxis.**
- **Provocation testing is the most definitive method of determining the cause of allergic or nonallergic anaphylaxis but is associated with significant risk.**

**Table 1. Clinical features of anaphylaxis**

| Feature | Frequency (%) |
|---|---|
| Urticaria and/or angioedema | 90 |
| Upper airway obstruction | 60 |
| Bronchospasm | 33 |
| Hypotension | 30 |
| Syncope | 25 |
| Gastrointestinal symptoms | 20 |
| Flushing | 15 |
| Rhinoconjunctivitis | 15 |

## Epidemiology

Anaphylaxis is usually considered to be quite rare, although some studies have indicated that the true incidence is probably far greater than realised, with up to 1% of the population affected at some time.[2] Among Australian preschool and school children, recent data indicate that 0.6% have had at least one episode of anaphylaxis.[3] Furthermore (and as with other atopic disorders, including rhinoconjunctivitis and eczema), the incidence of food allergy and consequently the incidence of anaphylaxis are increasing. In any major acute hospital, at least one or two patients would be expected to present with anaphylaxis each week.[4]

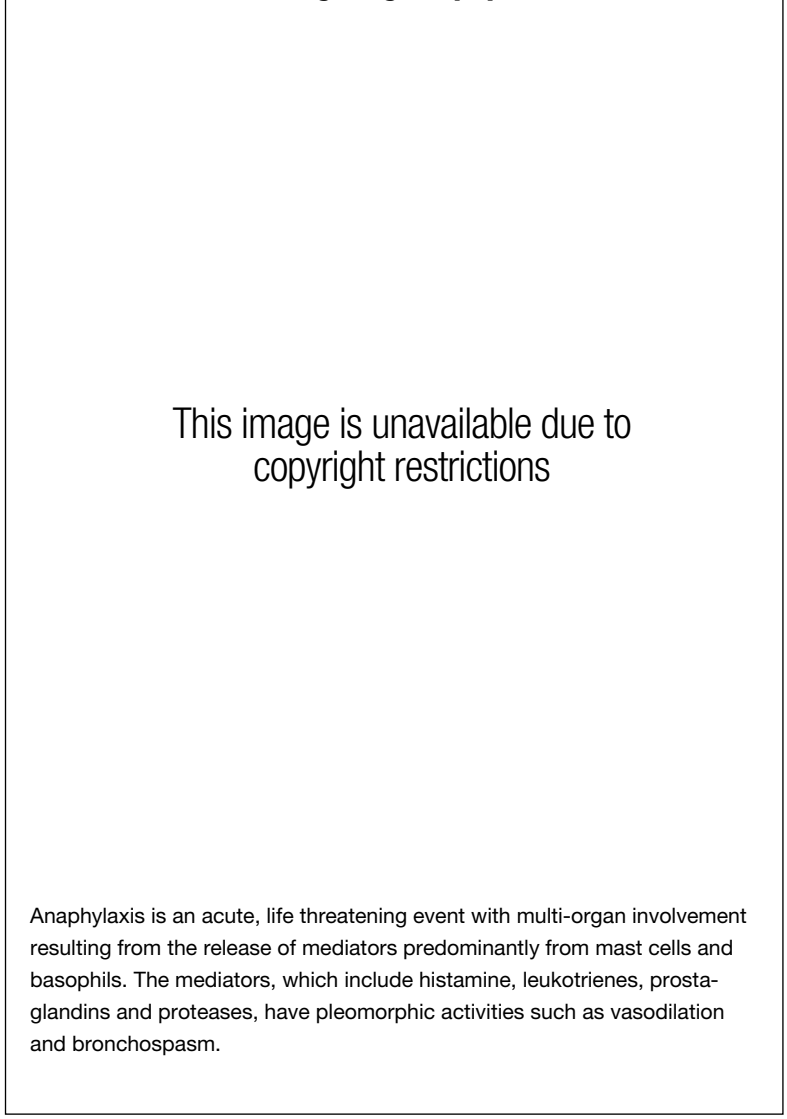
## Aetiology

The aetiology of anaphylaxis varies from study to study depending on a number of factors, including the age of the population studied and, more particularly, the site at which data were gathered. The incidence in general practice would be different from that seen in an emergency department, which would again be different from that seen in a tertiary referral centre.

In a recent large study undertaken in the emergency department of a Melbourne teaching hospital, where both adults and children are treated, a single likely cause was identified in 88% of patients presenting with anaphylaxis.[4] Table 2 lists the common aetiologies recorded in this study. In 12% of patients, no aetiology could be determined, despite a detailed history having been taken and investigations, including skin and blood tests, performed. These patients were labelled as having idiopathic anaphylaxis.

Frequently implicated foods in the aetiology of anaphylaxis include peanuts and tree nuts (cashew, almond, brazil and hazel nuts), egg, milk, seafood, wheat, soy and fruits. Allergy to fruit is being increasingly recognised. Fruits implicated include stone fruits (pears, peaches, plums, etc), kiwi fruit, banana, avocado and apple. It is now also recognised that fruit allergy often coexists with seasonal pollen-induced rhinoconjunctivitis, and patients should be asked about this in their history.

**Investigating anaphylaxis**




Anaphylaxis is an acute, life threatening event with multi-organ involvement resulting from the release of mediators predominantly from mast cells and basophils. The mediators, which include histamine, leukotrienes, prostaglandins and proteases, have pleomorphic activities such as vasodilation and bronchospasm.

**Table 2. Causes of anaphylaxis in emergency department presentations*[4]**

| Cause | Percentage of cases |
|---|---|
| Medication, excluding IV contrast | 39 |
| Food | 28 |
| Idiopathic | 12 |
| IV contrast | 8 |
| Bee sting | 7 |
| Latex | 6 |

* In patients with anaphylaxis presenting to Western Hospital, Melbourne.[4]

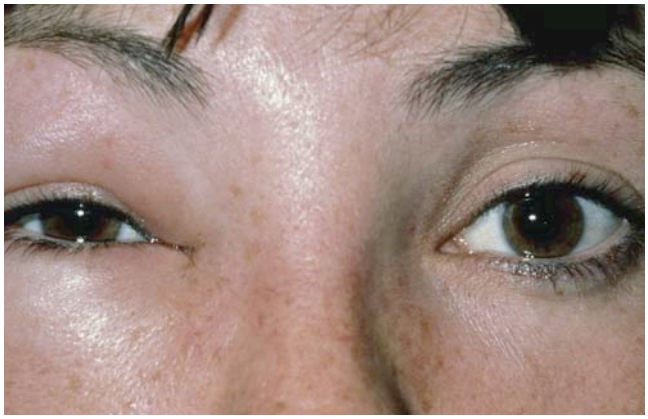


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Figure 1. Oedema around the eye due to a bee sting.

Medications that should be considered as causes of anaphylaxis include penicillins, cephalosporins and other β-lactam antibiotics; sulfonamides; macrolides; aspirin and other NSAIDs; opiates; complementary medicines; desensitisation extracts; and anaesthetic agents.

Apart from bees, other stinging insects that need to be considered as causes of anaphylaxis include European wasps, paper wasps and jumper ants (Figure 1). Jumper ants (*Myrmecia pilosula*) are common in Tasmania, rural Victoria, southern New South Wales and the Adelaide Hills and are a major cause of anaphylaxis in these areas.

Many studies reveal a higher incidence of idiopathic anaphylaxis than the 12% cited in the Australian study above.[5] Idiopathic anaphylaxis tends to be more common in older subjects and hence would be under-represented in studies of or including children. Patients with idiopathic anaphylaxis often have a history of previous anaphylactic episodes and frequently have or have had recurrent urticaria and/or angioedema.

**Table 3. Differential diagnosis of anaphylaxis: conditions to consider**

- Urticaria and angioedema
- Hereditary angioedema (and other causes of C1 esterase deficiency)
- Vasovagal attack
- Acute severe asthma
- Shock from any other cause
- Medical syndromes – e.g. mastocytosis, carcinoid syndrome and phaeochromocytoma
- Functional disorders – e.g. laryngospasm, globus hystericus

## Diagnosis

The diagnosis of anaphylaxis includes both the diagnosis of the acute event and the determination of any specific aetiology.

### Differential diagnosis of the acute anaphylactic event

For most patients presenting with probable anaphylaxis, a confident diagnosis should be possible from the history and examination. The history should be that of an acute life threatening event with multi-organ involvement, usually including both urticaria and angioedema. In the rare cases in which urticaria and/or angioedema is absent, a higher level of suspicion is needed. Anaphylaxis should certainly be considered among the differential diagnoses in patients presenting with circulatory collapse, acute severe asthma or acute gastrointestinal symptoms. Important differentials for anaphylaxis are listed in Table 3.

It is important that urticaria alone is not confused with anaphylaxis as the former is neither life threatening nor associated with multi-organ involvement. As such, urgent treatment with medications such as adrenaline (see the box on page 17) is not required. The presence of isolated angioedema (from whatever cause) is also insufficient to confirm a diagnosis of anaphylaxis as it is not systemic, although it may be life threatening and urgent treatment may be necessary. A common differential of anaphylaxis is that of a patient presenting with urticaria and moderate or severe angioedema. The diagnosis here can sometimes merge with that of anaphylaxis, especially if upper airway involvement and potential obstruction is present.

Asthma can also be acute and life threatening and affected patients may require urgent treatment, but it is not systemic and a separate list of causes needs to be considered for this condition.

Generally, causes of shock other than anaphylaxis, such as cardiac failure or blood loss, should be evident from their own specific clinical features, and they are not usually associated with multi-organ involvement. An important diagnostic clue is that in shock from anaphylaxis, the patient's periphery is typically vasodilated, being erythematous and warm, whereas in most other causes of shock, the patient is peripherally 'shutdown', with pale and cool (clammy) skin.

Although the diagnosis of anaphylaxis is usually apparent from the patient's history and examination, there are cases in which uncertainty remains. If there is doubt, the plasma tryptase level should be determined. Tryptase is released from mast cells and is specific for anaphylaxis; generally it is not elevated in patients in other similar clinical situations, including those with acute asthma, urticaria and/or angioedema, or shock from other causes. Clearly the determination will not help in making the immediate diagnosis, but the information obtained from the test will be extremely helpful in the patient's subsequent management.

Sensitivity of mast cell tryptase determination varies between centres, lying somewhere between 55 and 90%.[6] Thus a positive finding is much more helpful in making a diagnosis of anaphylaxis than a negative finding is in excluding the diagnosis. The tryptase level is said to be elevated in the circulation from 30 minutes to 24 hours after the episode, but is optimal somewhere between one and four hours. Care is required in the handling of the blood sample, which should be kept on ice, with serum collected as soon as possible. The specimen should then be frozen until it is assayed. It important that the laboratory is contacted as soon as possible, preferably before venepuncture.

## Immediate management of patients with anaphylaxis

- Cease administration of causative agent (if relevant).
- Place patient in a recumbent position and elevate his or her feet if tolerated.
- Administer oxygen, if available, at a high flow rate.
- Inject intramuscular adrenaline (Adrenaline Injection, Epipen) into the outer thigh:
  - for adults: 0.3 to 0.75 mg, depending on body weight
  - for children: 0.01 mg/kg to a maximum of 0.5 mg
  - dose can be repeated every 5 to 15 minutes, depending on response.
- Establish a wide bore venous access and infuse crystalloid rapidly.
- Administer antihistamines and corticosteroids and continue this treatment for 3 to 5 days.
- Admit the patient to hospital and monitor for at least 8 hours, and preferably 24 hours.

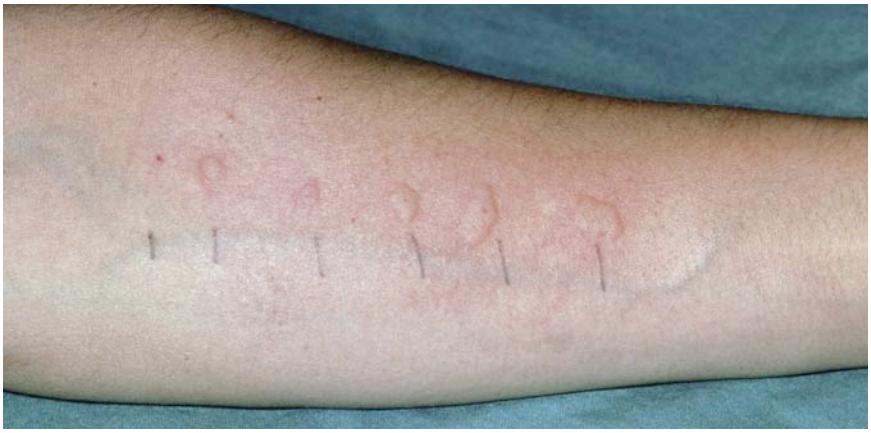

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Figure 2. Skin prick testing is the standard method for detecting specific IgE bound to cutaneous mast cells. It is simple, quick and highly sensitive.

## Clinical diagnosis of a specific aetiology

As with the initial diagnosis of anaphylaxis, the history is absolutely critical in the elicitation of any specific cause. Often the cause is clearly evident, especially if it is an IgE mediated reaction, including those to medications (e.g. penicillin) or foods (e.g. peanut and other nuts, fish, eggs or milk). In these cases, the reaction typically starts within 15 or 30 minutes of exposure to the allergen. In most cases of anaphylaxis due to a true food allergy, the patient has no doubt regarding the causative food.

Reactions to foods can be either a specific IgE mediated true food allergy or due to intolerance, the latter often to food additives and chemicals. IgE mediated reactions generally occur very soon after exposure and are often severe, whereas reactions to food chemicals are often delayed and generally less severe with anaphylaxis occurring only rarely. Typical symptoms from food intolerances include abdominal bloating, irritability and headache, urticaria and, sometimes, angioedema. Although rare, anaphylaxis to food chemicals can occur in some very reactive individuals. Whereas patients with true food allergy are typically highly atopic and often have other allergic disorders such as asthma, rhinoconjunctivitis or eczema, those patients with food additive or chemical intolerance are usually nonatopic and do not have an increased risk of the above allergic conditions.

Reactions to latex are important to recognise as they can be life threatening and the exposure may not be recognised. Moreover, the development of anaphylaxis may be delayed, sometimes not occurring until 30 minutes or more after the exposure.[7] As with true food allergies, latex reactivity is also IgE mediated and tends to occur in individuals with other atopic disorders. Most typically, reactions occur to powdered latex products, such as gloves, and usually follow a period of latex-induced contact urticaria. Nevertheless, reactions can occur seemingly 'out of the blue', and patients should be questioned on their contact with all latex products, including balloons, condoms, catheters and other medical devices.

Exercise-induced anaphylaxis is being recognised more frequently and particularly affects young adults.[8] Sometimes the anaphylaxis occurs with exercise alone, but more often it occurs when patients have ingested a potentially allergenic food at around the same time as exercising. Most often, the food intake has been within the preceding two hours of the exercise, and the exercise is typically quite vigorous. The reaction to the food is usually IgE mediated. Foods that have been implicated include vegetables (especially celery) and fruits, shellfish, wheat and nuts.

## Investigating the cause of anaphylaxis

Three different forms of investigation for a specific cause of anaphylaxis are available:

- skin prick testing (Figure 2)
- serological testing for specific IgE, including radioallergosorbent test (RAST) and enzyme-linked immunoassay (ELISA)
- provocation testing, most often an oral challenge.

As there are difficulties and uncertainties associated with all of these forms of investigation, it is preferable for testing to be organised by an allergist or immunologist, or by a physician or medical practitioner with a special interest in allergic disease.

## Skin prick testing

Skin prick testing is the standard method for detection of specific IgE; it detects IgE bound to cutaneous mast cells. It can be used to detect allergen-specific IgE to many different candidate foods, some medications, a limited number of insect stings and latex. The test is simple and quick and, because most of the specific IgE in the body is bound to the mast cells, it is highly sensitive. Although the test is extremely safe, the risk of systemic absorption remains, and anaphylaxis during skin prick testing has been very occasionally reported in highly sensitised individuals. In particular, testing for latex and peanut allergy has been regarded as having some risk in very allergic patients. Because of this possibility, testing should only be performed under the supervision of a trained clinician with resuscitation equipment immediately available.

Testing for food allergies is best used to confirm or refute the diagnosis of an underlying allergy to one or just a few

specific foods. Testing of a large number of foods, each with a low clinical probability of reactivity, is fraught with problems. False-positive results, in which skin test reactivity to one or more foods occurs in the complete absence of any clinical reactivity, is seen reasonably often in highly allergic individuals. This can lead to great difficulty in interpretation, and result in unnecessary dietary modification.

False-negative results are also a possibility as testing is generally undertaken using commercial extracts of foods that may not contain the relevant allergen and, furthermore, the allergen may have been denatured or altered during the extraction procedures. This applies particularly to fruits, but in all cases in which there is a suspicion of a false-negative result, skin testing should be repeated using the fresh food itself.

Well-validated skin tests are available only to a few medications, specifically β-lactam antibiotics and anaesthetic agents. It must also be borne in mind that a number of drug reactions, including those to aspirin and other NSAIDs and opiates, are not usually IgE mediated and, consequently, skin testing would not be helpful. In such cases, serological tests would also be negative and, if confirmation or exclusion of a particular agent was regarded as essential, a medication challenge might need to be considered.

### Immunoassays for specific IgE

Although serum tests for specific IgE are still performed by the RAST in some laboratories, they are now more often undertaken by ELISA. Results are usually presented in a semiquantitative fashion, with a score of 0 indicating no reactivity and 4, 5 or 6 indicating an increasingly higher concentration of specific IgE. Because only nanogram amounts of IgE are present in the circulation (most IgE being bound to mast cells, as noted previously) the sensitivities of *in vitro* methods are much less than that of skin prick testing and low-level reactivity may not be detected. Moreover, many laboratories batch allergens together to increase the number that can be tested, and this further reduces the sensitivity and increases the difficulty in determining individual allergen reactivity.

Despite these disadvantages, there are certain situations in which serological testing is preferable to skin prick testing. Such situations include patients:

- with extensive skin disease such as eczema
- who are taking antihistamines, which can lead to false-negative skin prick test findings

- in whom there is a risk of anaphylaxis.

Another important indication for serological test is for patients in whom there is an unexpectedly negative skin prick testing result. In this case, a RAST or equivalent can confirm or provide new information regarding potential allergen sensitivity.

### Provocation testing

In some clinical situations, despite the availability of the above diagnostic tests, doubt may still remain about the aetiology of the anaphylactic event. In these cases provocation testing to food, medication or, sometimes, exercise is appropriate.

Oral food challenge may be considered in patients in whom testing for specific IgE has shown reactivity to a number of possible foods or to no foods. This must be done under the supervision of a trained specialist in allergy in a monitored environment where resuscitation facilities are immediately available. Very small quantities of well-defined foods are used in the oral challenges.

As mentioned previously, skin prick test or serological testing can have limited applicability in the investigation of certain medications as a cause of anaphylaxis. When the clinical diagnosis is not certain and a more definitive diagnosis is required, medication challenges can be undertaken, again in very controlled circumstances.

## Conclusion

Anaphylaxis is a very serious and relatively common diagnosis. There are several well-defined causes, but in a significant percentage of patients no cause is found. The most important step in eliciting a possible aetiology is careful history taking; investigations such as skin prick testing and serological testing are only occasionally helpful and can be misleading. Provocation testing is the most definitive method of determining the cause but is associated with a significant risk and false-negatives can occur. MT

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**DECLARATION OF INTEREST: None.**