Anaphylaxis
Recognition and management

Background
Anaphylaxis is a rapid onset, multisystem hypersensitivity reaction. The diagnosis is usually straightforward, but may be difficult when skin signs are absent.

Objective
This article describes the recognition, assessment and evidence based management of anaphylaxis in the general practice setting.

Discussion
Published guidelines on the management of anaphylaxis are broadly consistent and emphasise the early use of intramuscular adrenaline, supine position, airway support and intravenous fluid resuscitation. Intravenous bolus doses of adrenaline should be avoided unless cardiac arrest occurs. Steroids and antihistamines have no proven role and are not recommended as first line management. As protracted or biphasic reactions can occur, patients should be observed in the emergency department setting for at least 6 hours after an acute event. Follow up aims to provide accurate identification of likely cause(s) to help prevent further exposure, immunotherapy if available and an action plan and adrenaline auto-injector where further accidental exposures are likely.

Keywords
anaphylaxis; emergencies; hypersensitivity

Anaphylaxis is a rapid onset, multisystem hypersensitivity reaction that may be caused by both immunological and nonimmunological mechanisms. Most reactions are immunoglobulin (IgE) mediated.

Anaphylaxis admissions in Australia more than doubled between 1995 and 2005 to over 10:100 000 population. It is unclear how much this reflects changes in administrative practices versus a true increase in disease load. During the same time period, anaphylaxis deaths remained uncommon and stable overall at ~0.64 deaths per million people per year, however medicine induced anaphylaxis deaths increased in the order of 300%. Case fatality rates were approximately 1:1000 for food anaphylaxis (commonest in children) and 1:100 for medicine and insect venom anaphylaxis (mostly in adults). Age is a major risk factor for death, with most deaths occurring in adults aged over 35 years. In children and adolescents, fatal and near-fatal anaphylaxis appears to be strongly associated with the combination of known food allergy and asthma.

Causes of anaphylaxis
Anaphylaxis in Australia is most commonly caused by:
- **Medicines**: medicines account for 57% of anaphylaxis deaths, most commonly antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), opiates and anaesthetics
- **Insect venom**: venom from the stings of bees, wasps and ants accounts for 18% of anaphylaxis deaths. However, this is highly dependent on geographical location, for example, insects cause 30% of cases of anaphylaxis deaths in Tasmania, mainly from the jack jumper ant
- **Food**: 6% of anaphylaxis deaths are caused by food. Most food anaphylaxis is caused by peanuts, tree nuts, hen’s eggs, cow’s milk, wheat, shellfish, fish and seeds; these are dependent on dietary exposure. Anaphylaxis caused by food is the commonest cause of deaths in children and young adults, with fatalities primarily occurring in the 15–30 years age group.

Summation anaphylaxis is a relatively new concept whereby a cofactor(s) may be required for a reaction. The best defined example is food-dependent exercise induced anaphylaxis. Many cases of exercise induced anaphylaxis can be related to a food allergen ingested before the reaction. Concurrent ingestion of aspirin or NSAIDs may be a further contributor in some cases.
**Pathophysiology**

Anaphylaxis results from the cascade of many anaphylactic mediators causing:

- vasodilation
- fluid extravasation
- smooth muscle contraction
- increased mucosal secretions.

The fact that multiple mediators are responsible explains the need for physiological antagonism with adrenaline and fluid resuscitation rather than antagonism of individual mediators. Death occurs from hypoxaemia, due to upper airway angioedema, bronchospasm and mucus plugging, and/or shock resulting from massive vasodilation, fluid shift into the extravascular space and depressed myocardial function. Importantly, while tachycardia in response to hypotension is considered a characteristic feature, sudden bradycardia and cardiovascular collapse may sometimes occur before any skin features become apparent. This is an important feature to recognise in order to avoid making an initial misdiagnosis of a panic attack or vasovagal reaction in cases where dyspnœa, nausea, anxiety and bradycardia may precede collapse.

While the pathophysiology of anaphylaxis is dramatic, a large proportion of reactions may recover with minimal or no treatment due to the body’s ability to compensate. This may explain the higher risk of death in older patients, where compensatory mechanisms may not be as robust and where comorbidities are more likely. Sting challenge studies have documented these compensatory mechanisms; most patients will respond, albeit slowly, without adrenaline. Avoiding an upright position, which further reduces venous return and may precipitate cardiac arrest, may be one of the most important treatments. Shock is more common in iatrogenic and venom reactions. In patients who die, the median time to respiratory or cardiac arrest is 30 minutes for foods, 15 minutes for venom and 5 minutes for iatrogenic reactions.

**Recognition of anaphylaxis**

Typical reactions with skin manifestations (urticaria) plus cardiovascular or respiratory involvement are easily diagnosed. However, some reactions are atypical and recognised only when the diagnosis is considered because of the context. A sudden onset of symptoms affecting two or more organ systems or just hypotension on its own, even without skin involvement, should trigger consideration of the diagnosis in the right context, i.e. recent exposure to a potential allergen or stimulant. Hypotension may be absolute (systolic <90 mmHg) or relative – defined as a greater than 30% drop from baseline/normal for that patient.

Anaphylaxis must be considered as a possible cause in any case of acute respiratory distress, bronchospasm, hypotension and/or cardiac arrest. Some real-life examples of difficult to diagnose anaphylaxis are provided in Table 1. A common theme in these examples is the subtlety or absence of skin features. Some other pointers to consider are:

- unless a clear alternate diagnosis is present, life-threatening symptoms affecting two or more organ systems or just hypotension on its own, even without skin involvement, should trigger consideration of the diagnosis in the right context, i.e. recent exposure to a potential allergen or stimulant. Hypotension may be absolute (systolic <90 mmHg) or relative – defined as a greater than 30% drop from baseline/normal for that patient.

**Table 1. Real-life examples of difficult to diagnose anaphylaxis**

<table>
<thead>
<tr>
<th>Example</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A woman, 21 years of age, presents to the emergency department two nights in a row with sudden exacerbations of ‘asthma’ while at a nightclub. The second episode is severe and settles only after repeated nebulisers overnight. Careful history reveals that each episode has been preceded by drinking a specific liqueur, as well as dancing. She is referred for an allergy assessment.</td>
<td></td>
</tr>
<tr>
<td>A man, 50 years of age, collapses in the garden. He has altered consciousness but no skin signs. He is propped upright and then has a generalised seizure before being laid flat again. He is hypotensive on arrival of the ambulance and gradually recovers without specific treatment. He is provisionally diagnosed with epilepsy but is also enrolled in a clinical study involving serial mast cell tryptase measurements on stored blood samples and bee venom specific IgE. The results suggested a diagnosis of bee sting anaphylaxis with a seizure induced by profound hypotension. He was given an EpiPen® and later venom immunotherapy.</td>
<td></td>
</tr>
<tr>
<td>A woman, 70 years of age, presents to a tertiary emergency department with severe abdominal pain and hypotension. She is prepared for an urgent laparotomy for a suspected ruptured abdominal aortic aneurysm but one of the doctors notices that, although she does not have any typical skin features of anaphylaxis, her skin is not as cool and clammy as one would expect for a ruptured aneurysm. Further history reveals that she had a single amoxicillin tablet 30 minutes before the pain began. She responds to an adrenaline infusion and avoids surgery.</td>
<td></td>
</tr>
<tr>
<td>A woman, 30 years of age, collapses and vomits after a jack jumper ant sting. She recovers spontaneously and is noted to be bradycardic and to have an ‘anxious disposition’. In the absence of any other features she is diagnosed as having had an anxiety or ‘vasovagal’ attack. However, she also volunteers to participate in a randomised controlled trial of venom immunotherapy. As part of this trial, she has an insect sting challenge and suffers severe anaphylaxis with a marked rise in mast cell tryptase*</td>
<td></td>
</tr>
<tr>
<td>A man, 80 years of age, presents with urosepsis. After being given intravenous antibiotic his systolic BP falls from 180 to 100 mmHg. This is interpreted as a sign of worsening sepsis and he is given another broader spectrum antibiotic. His BP falls below 90 mmHg and an inotrope infusion (but not adrenaline) is started. His BP gradually improves over many hours but he suffers a stroke as a result of the prolonged hypotension. Further investigation reveals known allergy to the class of antibiotics administered.</td>
<td></td>
</tr>
</tbody>
</table>

* During this trial it was noted that bradycardia, sometimes severe, is a consistent feature of sting anaphylaxis.
hypotension should be treated as anaphylaxis. Severe asthma that does not respond to standard therapy may also be due to anaphylaxis. Paroxysmal onset should trigger a search for allergic precipitants, as should the presence of skin flushing which may be subtle and noticed only by relatives.

- while rashes and angioedema may be associated with anaphylaxis, they may also be caused by other conditions such as postviral and idiopathic urticaria, angiotensin converting enzyme inhibitor (ACEI) induced angioedema and C1 esterase inhibitor deficiency (hereditary/acquired). Distinguishing features are historical (prior/other illnesses, lack of clear precipitant, longer time from onset to presentation) and the absence of more severe features such as significant breathlessness, wheeze or hypotension. Scombroid fish poisoning presents with erythema/urticaria and diarrhoea.
- anxiety/panic attacks present with breathlessness, a normal blood pressure (BP) and without urticaria. Syncope will have rapid and full recovery with lying flat. While bradycardia may occasionally cause syncope, patients do not become bradycardic as a result of a syncopal episode. Conversely, bradycardia may occur in anaphylaxis.
- patients with comorbidities can present with heart failure and pulmonary oedema secondary to anaphylaxis. Dealing with these uncommon cases is difficult and urgent liaison with an emergency/critical care specialist is recommended.

### Acute management

The initial steps for acute management are listed in Table 2. Medical practitioners who are likely to treat walk-in emergencies should familiarise themselves with the recently updated Australian Prescriber Anaphylaxis Wallchart (see Resources). This chart includes guidelines on how to administer an adrenaline infusion and doses for selective vasoconstrictors and glucagon for the rare cases that do not respond to initial treatment. A laminated copy should be attached to the practice emergency trolley. Equipment and medicines must be checked regularly.

Measuring systolic BP is an essential part of both the assessment and management of anaphylaxis. This can be done quickly with a simple cuff using the point at which the radial or brachial pulse disappears/reappears and then the cuff can be used as a tourniquet (keeping it inflated just below systolic pressure) to insert an intravenous (IV) line. Not only will this give an indication of initial reaction severity (which is important for follow up) but repeating the measurement later will guide the administration of further adrenaline; a high BP means adrenaline toxicity and no more should be given (Table 2).

*Table 3* presents case examples of errors in the management of anaphylaxis, including cases from the authors’ experience and a series from the medical literature. These cases illustrate the dangers inherent in giving large doses of adrenaline intravenously and using a parenteral antihistamine as first line management.

### Cases that do not respond to initial treatment

Occasionally patients with profound hypotension respond poorly to initial treatment. Animal models and clinical reports suggest that this indicates that absorption from the intramuscular (IM) route may be compromised and an IV infusion of adrenaline may be required. If this fails, a selective vasoconstrctor such as metaraminol or vasopressin may be useful. Severe reversible cardiac depression has also been

<table>
<thead>
<tr>
<th>Table 2. Initial management of anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Stop exposure to allergen (if possible), assess severity and treat</strong></td>
</tr>
<tr>
<td>- Call for assistance</td>
</tr>
<tr>
<td>- Give adrenaline 1:1000 at a dose of 0.01 mg/kg IM in the lateral thigh (maximum 0.5 mg)</td>
</tr>
<tr>
<td>- Lie patient flat unless this causes increased respiratory distress, in which case the patient may prefer to sit up. However, return to supine position if there is any deterioration in conscious state</td>
</tr>
<tr>
<td>- Document a simple systolic BP by palpation (radial/brachial pulse) and then deflate the cuff to just below systolic pressure as a tourniquet and gain IV access. Start monitoring (ECG, oxygen saturations, 5 minute noninvasive BP) and give oxygen, if available</td>
</tr>
</tbody>
</table>

If the patient is hypotensive:
- give IV N/saline bolus 20 mL/kg stat
- gain additional wide bore IV access (14G or 16G in adults) and prepare to give additional fluid and/or adrenaline infusion if the patient does not respond to initial management

<table>
<thead>
<tr>
<th><strong>2. If there is inadequate response, an immediate life-threatening situation or deterioration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Repeat IM adrenaline injection every 3–5 minutes as needed or start an IV adrenaline infusion as per hospital guidelines/protocol. Monitor BP closely. Nausea, vomiting, shaking, tachycardia or arrhythmias in the setting of normal or raised BP is likely to represent adrenaline toxicity rather than worsening anaphylaxis</td>
</tr>
</tbody>
</table>

If the patient is hypotensive:
- further N/saline fluid boluses (up to 50 mL/kg) may be required in the first 20 minutes
- in the hospital setting, consider adding a selective vasoconstrctor such as metaraminol

<table>
<thead>
<tr>
<th><strong>3. Disposition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- All patients should be transferred by ambulance to an emergency department with monitoring and resuscitation capability for a minimum 4–6 hours observation</td>
</tr>
</tbody>
</table>
Table 3. Case examples of errors in the management of anaphylaxis

A patient with breathlessness is given 1 mg of adrenaline before the arrival of an ambulance. There is no clear record as to how it was given and no BP was taken to gauge reaction severity. The ambulance staff report the injection was given intravenously. The patient experiences severe hypertension and has a subarachnoid haemorrhage. No underlying aneurysm is found. In retrospect, she has a history of anxiety/panic attacks, and this may have been the cause of her original problem.

A patient is admitted to a small hospital with mild generalised symptoms following a jack jumper ant sting. A medicines chart is written: ‘1 mg adrenaline IV, prn for anaphylaxis’. Her symptoms get a little worse, and she is given adrenaline. She has a ventricular tachycardia arrest and myocardial infarction. She survives and is referred for venom immunotherapy having been told ‘the ant nearly killed her’.

A young woman, 36 weeks pregnant, is stung by a bull ant and collapses with a borderline low BP. Her GP does not give adrenaline because of a fear it may harm the pregnancy and instead gives antihistamine (Phenergan) by IV injection. This injection triggers the immediate onset of profound hypotension. Luckily, she recovers with no negative sequelae for herself or her child.

Pumphrey12 reported several cases in which death occurred from pulmonary oedema precipitated by large doses of IV adrenaline. These included two children with only mild reactions before treatment.

Any patient who is treated for anaphylaxis at home, in the community (with an adrenaline auto-injector) or in general practice should then be sent to an emergency department for post acute treatment observation. Current opinion is that a reasonable minimum length of observation after symptom resolution is 4–6 hours after the last dose of adrenaline. However, longer periods of observation (ie. overnight admission) should be considered for more severe/refractory cases and those with significant comorbidities.

**Postacute care**

Referral to a clinical immunologist or allergist can assist with investigation and implementation of a comprehensive management plan. The use of subcutaneous immunotherapy with the relevant insect venom(s) is useful for stinging insect allergy18,19 and in special cases of medicine allergy, medicine desensitisation can also be employed if there is no alternative class of drug that can be used. Patients who experience an initial attack that is severe or refractory to treatment and those with comorbidities may benefit the most from referral.

**Identifying trigger(s) of anaphylaxis**

Accurate allergen identification enables avoidance and guides appropriate management. A careful history is essential, including recent medicine use, food intake and exercise. This history is crucial for guiding subsequent skin prick and Ige testing, however the presence of IgE does not confirm a diagnosis of anaphylaxis, and likewise a negative result cannot fully exclude a cause. Furthermore, allergen terminology and potential cross-reactivity can be complex. Therefore, we recommend that these tests be initiated and analysed only with the help of a qualified clinical immunologist/allergist.

At some point when the offending allergen has been confirmed, it may be appropriate to provide a Medic Alert bracelet as well as ensuring that alerts have been entered in the patient’s medical record. This is particularly important for medicine allergies — patients may need emergency medical care and may be unable to communicate their allergies and might inadvertently be given a medicine to which they are allergic.

Note that there is no scientific validity for cytotoxic or Vega testing, hair analysis and kinesiology, and their use should be strongly discouraged.20

**Anaphylaxis management plans**

An anaphylaxis management plan should ideally be delivered in written and verbal form and centre on education on allergen avoidance, symptom recognition and emergency management of anaphylaxis. Prescription of an adrenaline autoinjector is recommended if there is an ongoing risk of accidental exposure, but proper education of the patient and caregivers is vital and this also needs to be repeated at every opportunity. Resources for healthcare professionals and patients, including prescribing guidelines and examples of written management plans, are freely available (see Resources).
Regular follow up: ‘Doc I just need a repeat for my Epipen’

In most cases a request such as this should prompt a longer consultation, as it provides an important opportunity to ensure that:

- the precipitating allergen has been identified; sometimes further reactions have occurred since the last visit, and a careful history may reveal additional clues
- the patient is clear on how to avoid the allergen. Would they benefit from a Medic Alert bracelet, if this has not already been provided?
- the patient and/or caregivers understand their action plan and how to use their adrenaline autoinjector
- important comorbidities (asthma, chronic obstructive pulmonary disease [COPD], cardiovascular disease) are optimally controlled. Remember to check for any symptoms on exertion. For example, for a patient who has problems with their asthma (or angina) walking up a hill, another episode of anaphylaxis could be catastrophic.

Resources

- Online anaphylaxis education programs for health professionals and parents and teachers are available at the Australasian Society for Clinical Immunology and Allergy: www.allergy.org.au/about-ascia/about-ascia-e-training
- Australian Prescriber Anaphylaxis Wallchart: www.australianprescriber.com/magazine/34/4/artid/1210
- Resources for healthcare professionals and patients, including prescribing guidelines and examples of written management plans: www.allergy.org.au/health-professionals/anaphylaxis-resources.

Authors

Shelley J Kirkbright MBBS, FACEM, is Research Fellow in Emergency Medicine, Royal Perth Hospital, Perth, Western Australia
Simon GA Brown, MBBS, PhD, FACEM, is an emergency physician, Royal Perth Hospital and Professor in Emergency Medicine, University of Western Australia, Perth, Western Australia. simon.brown@uwa.edu.au.

Conflict of interest: none declared.

References