Chapter 2
Anaphylaxis

Rosie Furse

Key Points

1. Anaphylaxis is a generalised reaction. However, its effect on skin and mucosal changes, hypotension and respiratory compromise are noteworthy.
2. The mainstay of treatment is intramuscular epinephrine plus intravenous fluids if hypotensive. All other drug interventions are secondary measures.
3. Detailed history is the key for diagnosis.
4. Serial mast cell tryptase levels will be helpful to the allergy specialist at follow-up.

Introduction

- Anaphylaxis is a severe, potentially life-threatening, generalised, hypersensitivity reaction that is characterised by a rapid onset of airway and/or breathing and/or circulatory problems usually associated with skin or mucosal changes [1]. These occur in response to exposure to a precipitant (e.g. food, insect venom, drugs or exercise) and can be either allergic (IgE mediated) or non-allergic.
- Irrespective of this underlying pathophysiology, the clinical features, investigations and acute treatment are the same, and all of these patients should be given a diagnosis of 'anaphylaxis' or 'suspected anaphylaxis'. Terms such as 'anaphylactoid' or 'severe allergic reaction' are confusing and should be avoided.

R. Furse, MBBS, MRCP, FCEM
Department of Emergency Medicine, Royal United Hospital, Bath BA1 3NG, UK
e-mail: rosie.furse1@nhs.net

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- The incidence of anaphylaxis is as yet not fully defined. This is due to the inconsistency in definition, diagnosis and record-keeping. In 2012, anaphylaxis was retrospectively found to account for 0.1 % and 0.3 %, respectively, of paediatric and adult ICU admissions in the UK [2]. These patients were equally admitted from the ED, from theatres and from other areas of the hospital [3]. The World Allergy Organization (WAO) analysis of international data suggests that the prevalence is increasing worldwide (estimated lifetime prevalence of 0.1–2 %) although it still appears to be more common in the Western world [4, 5]. Fatalities from anaphylaxis remain uncommon [5].
- The diagnosis of anaphylaxis remains a clinical one during the initial presentation, and it is important to consider the main differential diagnoses. It is now recommended that all anaphylaxis patients are referred for outpatient allergy specialist care [2].
- The mainstay of treatment remains the early administration of intramuscular epinephrine. Secondary-level treatments remain non-evidence based, with dosing strategies being extrapolated from other allergy-based diseases.

Pathophysiology

- There are multiple triggers for anaphylaxis, and on occasion it can necessitate two triggers occurring simultaneously (e.g. food and exercise) for the reaction to occur [2, 6].
- Irrespective of the trigger, the body undergoes a widespread release of inflammatory mediators, primarily from mast cells, including histamine, leukotrienes and platelet-activating factor. Mast cells occur in highest concentration in the skin followed by the respiratory tract and then the gastrointestinal system, thus accounting for the distribution of clinical features [7]. They also occur around the coronary vessels and between the myocardial muscle fibres [5].
- The inflammatory mediators cause bronchoconstriction, vasodilatation, increased vascular permeability and weakening of myocardial contractility. They can also cause coronary artery spasm which can mimic an acute coronary syndrome [5].
- Effects occur most rapidly after intravenous administration of a drug, whereas there will be some delay after venom exposure and the potential for an even slower onset after an ingested food allergen [5].
- In children, the majority of reactions are in response to exposure to a food allergen. Most of the children will have a background of atopic disease, and they will present with predominantly respiratory symptoms. Insect venom-related reactions are also more common than in adults [2, 5].
- In adults, reactions to food and drugs are fairly similar in frequency for the first episode and are more common than exposure to insect venom. Atopy is not usually present, and the cardiovascular symptoms and signs become more prominent. In the more elderly population, almost all initial reactions are drug induced [2, 5].

- Amplifying cofactors can either increase the likelihood of a reaction to a trigger (e.g. exercise) or cause the subsequent reaction to be more severe [2]. Alcohol and NSAIDs cause increased gastrointestinal permeability which allows more of the ingested allergen to be absorbed [5, 6]. Intercurrent infections and emotional or physical stress can also amplify the reaction.

IgE Mediated

1. Food triggers
    - In the West, these are most commonly peanuts or other nuts, fish or shellfish, eggs and cow's milk. In the Middle East, sesame seeds are a common allergen, and in Asia chickpeas and rice are prominent [5].
    - There is a significant degree of cross-reactivity, and patients may react to more than one plant-related food. This association also extends to pollens; patients with allergy to grasses or pollens may be at risk of anaphylaxis to plant-based foods [6].
    - Asthma and other atopic diseases are a risk factor for food-based anaphylaxis [6].
2. Drug triggers
    - Antibiotics – This particularly occurs with penicillin-related antibiotics and sulphonamides. These contain haptens which bind to serum proteins and produce IgE antibodies [5]. Unlike the food allergens, past history of atopy does not increase the risk of drug-related anaphylaxis [2]. Reactions are twice as likely to occur after intravenous or intramuscular administration when compared to the oral route [5].
    - Other antimicrobials – antivirals, antihelminthics and TB medications.
    - Muscle relaxants.
    - Antineoplastics/cytotoxics/immunomodulators.
3. Insect venom triggers
    - This includes bees, wasps, yellow jackets, hornets and fire ants. The venom contains enzymes and proteins that provoke an IgE response [6]. Elderly patients or those with very rapid onset of symptoms and/or have minimal or absent skin changes are at increased risk of death [2]. Venom-allergic patients respond well to immunotherapy [2, 5, 6].
4. Other triggers
    - Latex – Note that this is derived from rubber tree sap and has a potential cross-reactivity with stone containing fruits, bananas, kiwis and chestnuts [2, 6].
    - Seminal proteins/human PSA [2].
    - Horse-derived antitoxins (e.g. snake antivenoms) [2]
    - Helminths [2].

Non-IgE Mediated

1. Immune complex – complement mediated
   - This includes reactions to blood products, immunoglobulins and dextrans and occurs due to immune complexes activating complement which leads to mast cell degranulation [6].
2. Non-immunological mast cell activators
   - Radiocontrast media comes into this group (e.g. iodine and other medical dyes) as do narcotics, cold, heat, sunlight and alcohol [5, 6].
3. Modulators of arachidonic acid metabolism
   - This includes aspirin and NSAIDs and is thought to relate to the acetyl group [6].
4. Idiopathic
   - Idiopathic anaphylaxis is a diagnosis of exclusion after careful history taking, skin prick and blood testing plus allergen challenges in certain cases [5]. Tryptase levels help to differentiate these patients from a diagnosis of mastocytosis [5].
5. Exercise
   - This can occur as a single trigger or more commonly as cofactor amplification in conjunction with exposure to a food or pollen trigger [5, 6]. Careful history taking regarding episodes will aid in identification.

Clinical Features

- The World Allergy Organization provides a definition of anaphylaxis based on any one of the three criteria being fulfilled within a timescale of a few minutes to a few hours [5]:
  (a) Acute onset of involvement of the skin/mucosal tissue with respiratory compromise and/or reduced blood pressure (BP).
  (b) Two or more of (i) skin/mucosal changes, (ii) respiratory compromise, (iii) reduced BP and (iv) persistent gastrointestinal symptoms, after exposure to a likely allergen.
  (c) Reduced BP after exposure to a known allergen for that individual patient.
- This definition helps to remind physicians that the presentation of anaphylaxis can vary between patients. This variation may occur between different patients responding to the same or similar allergen or even an individual responding differently each time they have an anaphylactic reaction [5].

- Children are more likely to present with predominantly respiratory symptoms which can mimic an acute asthma exacerbation.
- Adults (and in particular, the elderly) can present primarily with cardiovascular collapse and can mimic other cardiac diseases [2, 3, 5, 6]. Less than 20 % of anaphylaxis episodes will present with mild or no skin or mucosal changes. In these cases, it is usually due to a venom-related allergen and presents primarily with cardiovascular collapse [7].
- Most patients will present with symptoms within the first 5–30 min after exposure to the allergen, but this can be delayed particularly if the allergen has been ingested orally.
- Patients will often report as sense of impending doom or uneasiness prior to symptoms starting [2, 6].
- The speed of onset is quicker with intravenous drug administration, more likely to involve cardiovascular collapse and more likely to result in cardiac arrest and death. In most extreme cases, this can occur over the course of minutes [5] (Table 2.1).

It is important to remember:

- Skin or mucosal changes alone do not constitute anaphylaxis but that anaphylaxis does not have to have skin changes.
- Patients with significant cardiac or respiratory co-morbidity may show a deterioration in this condition during an anaphylactic episode giving a poorer outcome [2, 5, 6].
- Symptom patterns may be altered by prior antihistamine or steroid use.

Table 2.1 Symptoms and signs of anaphylaxis

Skin	Erythema/flushing
	Urticaria/pruritus (itching of palms, soles and perineum is a good indicator of more severe anaphylaxis [8])
	Angioedema – periorbital, lips, tongue
A – Airway	Obstruction secondary to upper airway angioedema
	Stridor/hoarse voice
B – Breathing	Bronchospasm/wheeze
	Hypoxia/cyanosis
	Chest tightness/cough/tachypnoea
C – Circulation	Hypotension/distributive shock
	Arrhythmias/palpitations
	Chest pain/abnormal ECG
D – Disability (neurology)	Irritability/confusion
	Headache
	Dizzy/tunnel vision
E – Enteral, ENT, eyes	Abdominal pain/cramps/diarrhoea
	Dysphagia/nausea and vomiting
	Rhinitis/sneezing
	Conjunctival erythema/tearing
	Metallic taste in the mouth

- Anaphylaxis severity may be worse in patients on concurrent antihypertensives or diuretics [2, 5, 6].
- Infants, pregnant women and the elderly are more vulnerable to the effects of anaphylaxis [2, 5, 6].

History taking and documentation are vitally important. A detailed exploration of the minutes to hours prior to the onset of symptoms may reveal the likely trigger. Even if there are multiple possibilities, this will aid further testing and follow-up and/or correlation with future episodes. It is also important to record the symptoms shown and the speed of onset as well as the response to treatment.

Biphasic Reaction

- Up to 25 % of adult patients (10 % children) will have a biphasic reaction as part of their anaphylaxis episode [5]. This is when further symptoms or signs occur after a symptom-free period [6].
- There are no reliable means of identifying these patients unless they have a prior history of this.
- Severe reactions, predominant hypotension, oral triggers and a background of asthma have all been associated with an increased risk of a biphasic reaction [6].
- The delayed reaction may be milder, similar or, rarely, more severe than the initial symptoms. It will usually occur within the first 4–10 h after the onset of symptoms but has been reported anything up to 72 h from onset [5, 3]. The clinical findings are likely to be attenuated by the earlier administration of epinephrine, antihistamines and glucocorticoids [6].

Differential Diagnosis

Although early treatment of anaphylaxis with intramuscular adrenaline is key, it is also important to consider the possible differential diagnoses. This should be possible with a rapid focussed history and examination considering those most likely for the different age groups (Table 2.2).

The symptoms and signs of surgical emphysema secondary to pneumothorax can mimic the angioedema and breathlessness of anaphylaxis. Hereditary angioedema is usually of a slower onset than anaphylaxis with an average of 3.7 h of angioedema before breathlessness occurs [2].

Mastocytosis is an uncommon condition, which can have two forms: cutaneous or systemic. The systemic version can increase the risk and severity of anaphylaxis episodes particularly from insect venom triggers and to a lesser extent, drugs [2]. In these patients, their baseline tryptase levels will be high which differentiates them from simple anaphylaxis where the levels return to normal.

Table 2.2 Differential diagnoses

Massive surgical emphysema secondary to pneumothorax
Hereditary angioedema (C1 esterase inhibitor deficiency)
Cold urticaria
Cholinergic urticaria
Acute asthma
Pulmonary embolism or amniotic embolism
Choking secondary to foreign body
Acute coronary syndrome
Anxiety attack
Phaeochromocytoma or carcinoid
Scombroid
Red man syndrome secondary to vancomycin
Mastocytosis

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- Red man syndrome secondary to vancomycin
- Mastocytosis

Investigations

- There are currently no biomarkers or laboratory tests than can resolutely confirm or refute the diagnosis and no biomarker that increases in concentration irrespective of trigger [2].
- Tryptase levels
  - These are now recommended for patients presenting with anaphylaxis, but this only needs to be done for one episode [3].
  - When present, the degree of rise in tryptase does correlate with severity of the symptoms, but a rise may not be found in all patients [2].
  - Food-based triggers and patients presenting without hypotension seem to have the lowest incidence of tryptase rise, and as such normal levels do not exclude the diagnosis [5, 7, 3].

  - The levels rise rapidly after the onset of symptoms and remain elevated for 4–6 h. Serial blood tests are recommended as soon as possible after the onset of symptoms, at 1–2 h after (but within 4 h of onset) and then again at baseline (at least 24 h after the episode) [3]. The baseline level should be normal.
  - Tryptase levels are not recommended in children under 16 unless the trigger is likely to be insect venom, drug administration or idiopathic [3].
- Skin prick tests and allergen-specific serum IgE levels can be performed by the allergy specialist after 3–4 weeks to avoid false-positive results.
- Challenge or provocation tests can be performed but should be done with caution in a facility that has the resources to manage any subsequent anaphylaxis [2].

Treatment

- There is no high-quality evidence to support any of the treatments currently used for acute anaphylaxis.
- However, extrapolation from other allergic and atopic disease management plus observational-level evidence in anaphylaxis had led to fairly standardised treatment recommendations [5, 9].
- General measures
  - Ensure removal of the trigger. This includes stopping any drug or contrast or removing an insect sting.
  - If hypotension is a significant symptom, then the patient should be laid flat (or in the left tilt if pregnant). If respiratory symptoms predominate, then the patient may be more comfortable sitting up.
  - Manage in a high-care facility with full cardiac and respiratory monitoring including prompt intravenous access.
  - If airway compromise is present or threatened, early involvement of an anaesthetist is recommended as the airway can deteriorate rapidly and can become difficult to intubate.
  - If the patient progresses to cardiorespiratory arrest, the resuscitation efforts should be carried out in accordance with international advanced life support recommendations [9].
- Specific measures
  - Epinephrine:

    This forms the mainstay treatment of anaphylaxis and has the strongest evidence base of all the interventions [5].

    The earlier it is given, the better and quicker the response appears to be [2, 9]. This is likely due to inhibition of inflammatory mediator release, thus attenuating the severity of the episode [2, 9].

Current recommended doses are shown in the algorithm in Appendix 2.1, but if the only epinephrine available is the patient's own auto-injector pen, then this should be used.
Doses can be repeated every 5–15 min as needed and should be administered in the anterolateral aspect of the middle third of the thigh [9].
Epinephrine works on alpha and beta adrenoceptors to reverse the vasodilatation, bronchospasm and urticaria as well as provide inotropic and chronotropic benefits [5].
Side effects include pallor, tremor, anxiety, palpitations and headaches.
Adverse events can include hypertensive crisis, cerebrovascular events or cardiac failure.
In refractory cases, epinephrine can be given intravenously, but this should be done only by those experienced in its use.
Alternative vasopressors can also be considered for those with refractory hypotension.

– Antihistamines:

Their primary role is to reduce the symptoms from skin and mucosal changes. Both H_1 and H_2 receptor blockers have been used [2, 5, 7].

– Glucocorticoids:

These work by switching off the production of pro-inflammatory proteins.
Their role is to attenuate any protracted symptoms and may help prevent a biphasic response in susceptible individuals [2, 5].

– Intravenous fluids:

Current recommendations suggest crystalloids given as 20 ml/kg boluses for children and 500–1,000 ml boluses for adults [9].
The evidence for this is extrapolated from studies of other conditions. So management should be tailored to the individual patient's needs [5].

– Others:

Salbutamol nebulisers can be used in those with significant or refractory respiratory symptoms.
Glucagon can be used in patients on B-blockers to allow the epinephrine to be able to work on the B-receptors especially in those with significant hypotension [9].

Observation Period

- Patients should be monitored for a minimum of 6 h after resolution of symptoms. This observation period may need to be longer depending on the presence of any of the following high-risk features [9]:

- Extremes of age
- Significant co-morbidity
- Severe reaction with slow onset
- Severe asthma
- Likely continued absorption
- History of significant biphasic reaction
- Evening or night presentation
- Difficulty accessing emergency care

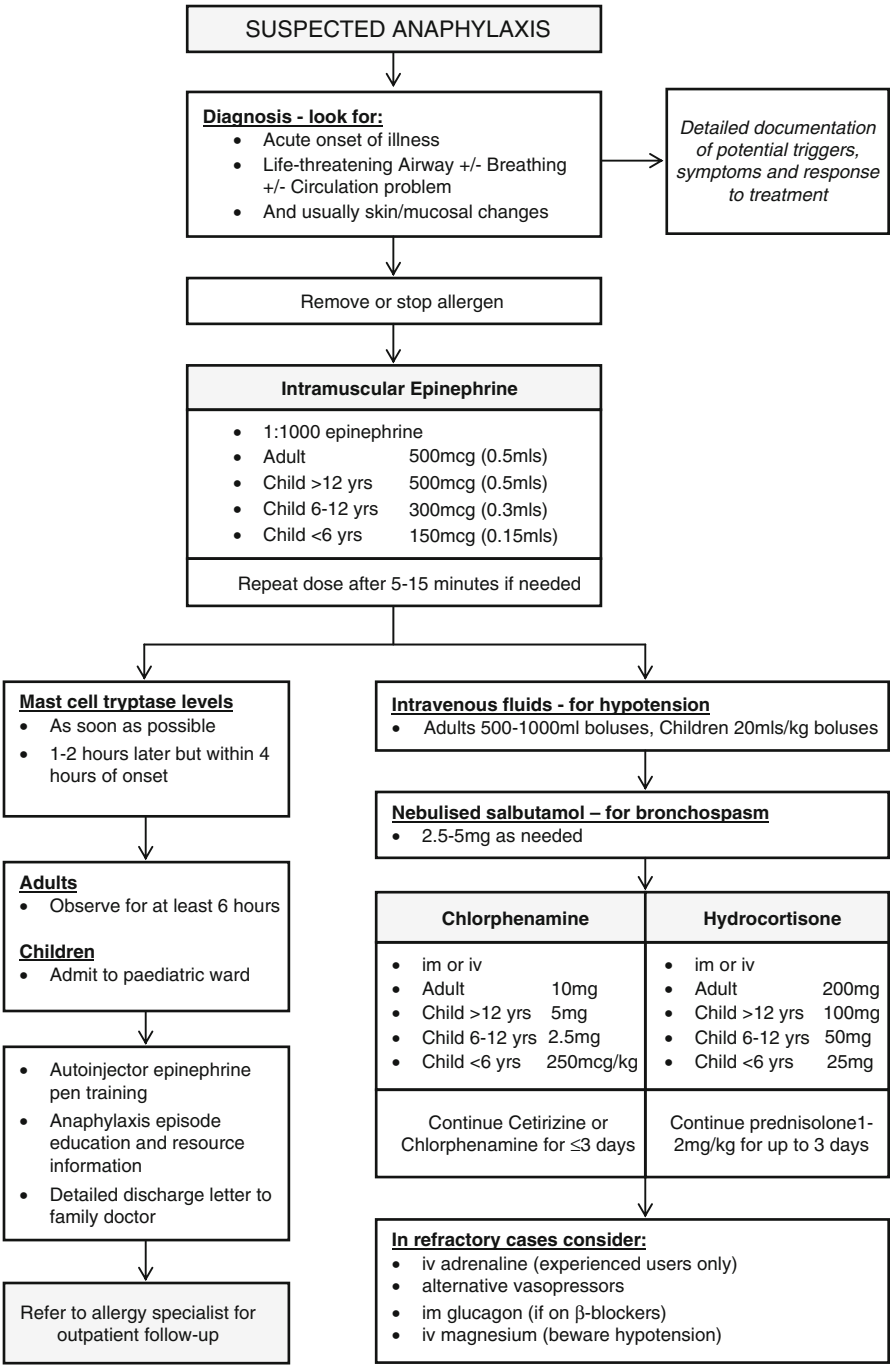
Prognosis and Prevention

The following points should be considered relevant to the patient's prognosis:

1. There is some evidence that children with anaphylaxis at an early age can develop tolerance to the trigger as they get older. This may take years however and primarily relates to food-based triggers [2].
2. Teenagers have the highest morbidity associated with anaphylaxis due to increased exposure to potential triggers and greater risk-taking behaviour [5].
3. Information, both verbal and written, given at the time of the episode and then repeated at health-care follow-up visits is vital in terms of trigger avoidance and anaphylaxis episode management. There are now multiple support organisations and internet-based resources available [2].
4. Epinephrine auto-injector devices should be given to all patients with anaphylaxis unless the trigger is easily avoided (e.g. medication or contrast). If these devices are unavailable, then a simple ampoule and careful instructions regarding its preparation and administration can be used [2].
5. Ongoing education and training surrounding auto-injector device use is vital. Unfamiliarity with the device and anxiety over its use are commonly reported reasons for non-administration of epinephrine [3].
6. Patients should be encouraged to wear medic-alert bracelets or carry alert wallet cards [6, 9].
7. Referral to an allergy specialist can aid specific trigger identification and consideration of further immunological treatments [3, 9]:

    - Subcutaneous venom immunotherapy – This can protect up to 90 % of adults and 98 % of children from further anaphylaxis due to insect venom [2, 5, 6].
    - Desensitisation – This can be via the oral or the sublingual route and is used primarily for food-based triggers and occasionally for drug-induced anaphylaxis if the specific drug cannot be avoided in an individual. The initial treatment takes months, and the effect is only maintained by regular exposure to the trigger, and permanent tolerance has not yet been proven [6]

Appendix 2.1: Suspected Anaphylaxis Algorithm



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