Anaphylaxis: current state of knowledge for the modern physician
Krzysztof Rutkowski, Shelley Dua, Shuaib Nasser

ABSTRACT
Anaphylaxis is a severe, potentially fatal, hypersensitivity reaction of rapid onset. It may trigger life-threatening cardiopulmonary compromise, often with skin and mucosal changes such as urticaria and angioedema. The prevalence of anaphylaxis is increasing and the number of cases of fatal anaphylaxis appears to be rising. Food, insect stings, and drugs are the most common triggers. Novel triggers are increasingly seen and include delayed anaphylaxis to red meat, food-dependent exercise-induced reactions and anaphylaxis to monoclonal antibodies. Anaphylaxis is usually IgE mediated, but other mechanisms also play a role for example direct mast cells activation. Differential diagnosis is discussed including asthma, syncope and shock; excessive endogenous histamine, food related syndromes, and some rare diagnoses. Intramuscular epinephrine is first line treatment. The role of other drugs is reviewed. Timed and serial serum tryptase measurements help to confirm the diagnosis. Long-term management is necessary to minimise the risk of recurrence and includes identification of the trigger(s), management of risk factors, education on avoidance and a formalised treatment plan with an epinephrine auto-injector if appropriate. Every patient who has experienced anaphylaxis should be referred to an allergy clinic for appropriate management. This is endorsed by many national guidelines (eg, UK NICE). Anaphylaxis is often misdiagnosed or miscoded as, for example, asthma or food allergy. Most doctors will encounter a patient with anaphylaxis in their career and should to be familiar with the clinical features, management and mechanisms of this potentially fatal condition.

DEFINITION
Historically, the definition of anaphylaxis has been an area of contention because it is a condition with a variety of underlying mechanisms presenting with a spectrum of clinical features. However, the current consensus is that anaphylaxis is a severe hypersensitivity reaction of rapid onset that, if left untreated, may cause death. There is usually a swift progression of skin changes and development of life threatening airway, respiratory or cardiovascular compromise, or any combination of these three features.

EPIDEMIOLOGY
Prevalence rates reported in the literature vary, and population based estimates are not always reliable due to misdiagnosis, underreporting, and incorrect clinical coding. However, most reports suggest lifetime prevalence rates within the range of 0.5—2%. The prevalence has been increasing for reasons that are not yet clear. A UK study illustrated a sevenfold increase in the number of hospital admissions for anaphylaxis over a period of 15 years (1990—2005). In younger age groups the prevalence of food induced anaphylaxis has increased disproportionately. An Australian study detected a fivefold increase in hospital admissions for food mediated anaphylaxis over a 10 year period in children aged 0—4 years. Additionally, the number of cases of fatal anaphylaxis is believed to be rising. In the UK 20 deaths per year from anaphylaxis are reported, although this may underestimate the true rate.

CLINICAL FEATURES
Anaphylaxis presents with a range of clinical symptoms of varying severity, many of which can present in other conditions associated with severe systemic compromise. The diagnosis is therefore made by the typical pattern of clinical features with rapid progression of symptoms, often with a history of a preceding trigger. However, the clinical presentation varies considerably depending on individual hypersensitivity, the dose and route of trigger delivery, as well as individual traits such as the presence of asthma. The diagnosis of anaphylaxis should be made if a patient develops an acute illness (within minutes of exposure to the trigger) with rapidly progressing skin changes, and life threatening airway and/or breathing and/or cardiovascular compromise. Anaphylaxis frequently produces signs and symptoms within 5—30 min after exposure to a trigger, although sometimes symptoms may not develop for several hours (figure 1).

INTRODUCTION
Anaphylaxis is an acute systemic allergic reaction which may be life threatening. The incidence of anaphylaxis is increasing. Most doctors will encounter a medical emergency due to anaphylaxis at some point in their careers. Early recognition of the signs and symptoms along with prompt initiation of acute treatment is crucial. However, once the acute reaction has resolved, clinical management should focus on preventing further similar episodes. We aim to provide doctors with a better understanding of the condition by discussing the aetiology and mechanisms of anaphylaxis. In addition, we review the current recommendations for its acute and long term management, including recently published guidelines.
Cutaneous manifestations are most common, affecting over 90% of reported cases. These features include flushing, pruritus, urticaria, and angioedema. Other clinical features of anaphylaxis include bronchospasm, laryngeal oedema, hypotension, and cardiac arrhythmias. Some patients also describe gastrointestinal symptoms of nausea, diarrhoea, and abdominal pain. An overwhelming feeling of ‘impending doom’ is common. In severe anaphylaxis rapid cardiovascular compromise and shock can occur without preceding cutaneous features. For example, in intraoperative anaphylaxis, cardiovascular compromise may be the only presenting sign. Special attention should be paid to infants who may be unable to describe their symptoms. However, some presenting features such as flushing, hoarseness after a crying spell, and vomiting after feeding may be evident in healthy infants, leading to misdiagnosis.

### Anaphylaxis and the heart

Anaphylaxis may be complicated by myocardial ischaemia and arrhythmias even without underlying cardiac pathology and in the absence of epinephrine administration. Tachycardia is the norm in anaphylaxis. However, when volume depletion exceeds 20–50%, tachycardia may be followed by bradycardia (two phase physiological response to hypovolaemia). Therefore, heart rate does not always differentiate between anaphylaxis and vasovagal reaction. Moreover, bradycardia may occur in response to the drug taken or may be associated with a conduction defect. Vasodilatation during anaphylaxis impairs venous filling, leading to empty vena cava syndrome if the patient suddenly assumes an upright position. Pulseless electrical activity ensues, followed by myocardial ischaemia and subsequently epinephrine-unresponsive shock due to lack of circulatory volume.

### Fatal anaphylaxis

Fatalities are rare and estimated to occur in <2% cases. Predisposing factors for fatal anaphylaxis include coexistent asthma and in particular poorly controlled asthma. This is especially relevant in the context of food allergy such as peanut and tree nut allergy. A delay in administration of epinephrine is an important risk factor for death and is seen in 80–87% of fatal cases.

### CAUSES OF ANAPHYLAXIS

There are a wide variety of triggers for anaphylaxis and their frequency varies according to age. In children, food is the most common cause whereas drugs are more common in adults.

### Food

Nuts are frequently associated with food mediated anaphylaxis, with peanut being the most common cause in the USA.

Table 1: Mechanism of anaphylaxis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Trigger</th>
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<tbody>
<tr>
<td>IgE mediated</td>
<td>Food (eg, nuts, milk, shellfish), insect venom, β-lactams, NMBA (eg, suxamethonium), latex, occupational allergens (wheat flour in bakers), semen, aeroallergens</td>
</tr>
<tr>
<td>Non-IgE immune mediated</td>
<td>IgM or IgG mediated cytotoxicity, immune complexes, leukotrienes, activation of complement, kallikrein-kinin and coagulation cascade</td>
</tr>
<tr>
<td>Direct, non-immune mediated</td>
<td>Exercise, cold, drugs (vancomycin, opioids)</td>
</tr>
</tbody>
</table>

These reactions have a tendency to be more severe and can occur with the first recognised exposure. Moreover, nuts are often hidden in foods and accidental exposure is sometimes difficult to avoid. Geographic variation affects which foods predominate as causes of anaphylaxis. Buckwheat and rice are more common causes in parts of Asia and sesame in parts of the Middle East.

### Insect stings

Insects of the order Hymenoptera can cause anaphylaxis, namely bees (honey bees, bumble bees), vespid (yellow jackets, hornets, wasps), and stinging ants. Systemic allergic reactions to insect stings are reported by up to 5% of adults and up to 1% of children. The onset of anaphylaxis following insect stings can be rapid.

### Drugs

The most common classes of drugs triggering anaphylaxis include antibiotics, usually β-lactam antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). Biological agents increasingly are identified as causes of anaphylaxis, resulting from their growing in use in clinical practice. The estimated rate of anaphylaxis and immunoglobulin E (IgE) mediated reaction to infliximab, for example, is 2–5%. For accurate diagnosis of anaphylaxis following drug administration a thorough history is vital, including the exact timing of when the agent was administered, the interval to the reaction, medications that

<table>
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<th>Table 2: Major mediators of anaphylaxis</th>
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<tbody>
<tr>
<td><strong>Mediators / cells</strong></td>
</tr>
<tr>
<td>Histamine (via H1–H4 histaminergic receptors)</td>
</tr>
<tr>
<td>Tryptase</td>
</tr>
<tr>
<td>Platelet activating factor (PAF)</td>
</tr>
<tr>
<td>Eosinophils</td>
</tr>
</tbody>
</table>

Figure 1: Timing of fatal anaphylaxis in relation to different triggers. IV, intravenous. Adapted from Pumphrey.
the patient had received previously, and the response to therapy.30

Anaphylaxis at the time of anaesthesia
The reported incidence of anaesthetic induced anaphylaxis varies between 1 in 4000 and 1 in 25000. The mortality rate has been suggested as 4%.31 32 Neuromuscular blocking agents are the most common triggers.33 The diagnosis of anaphylaxis during anaesthesia poses challenges. Patients are unable to report symptoms and the first signs are often profound hypotension or difficulty in inhaling the lungs. Additional diagnostic problems occur due to the concomitant administration of several anaesthetic agents, antibiotics and intravenous fluids such as gelofusine. Other potential agents such as chlorhexidine, patent blue and latex should also be considered.

Exercise induced anaphylaxis
In some patients exercise alone can trigger anaphylaxis. Many patients, however, require one or more co-factors to be present in order to develop symptoms. Food dependent, exercise induced anaphylactic reactions are becoming more prominent.34 Foods most commonly implicated include wheat, shellfish, tomatoes, peanuts, and corn. They are usually ingested 4–6 h before exercise.35 Other reports suggest that the combination of any solid food and exercise may trigger a reaction.36 NSAID, alcohol, menstruation or seasonal pollen exposure in pollen sensitised individuals have also been implicated as co-triggers.36–38 Typically, exposure to the trigger precedes the exercise which then provokes symptoms of anaphylaxis. Changes in plasma pH and osmolality redistribution of splanchnic blood flow, increased tissue transglutaminase (tTG) activity, increased gastrointestinal permeability, and facilitated epitope recognition/allergen binding may all be responsible for food dependent, exercise induced anaphylaxis, but they warrant further studies.34 36 37

Idiopathic anaphylaxis
Rarely, a trigger cannot be identified and therefore by exclusion a diagnosis of idiopathic anaphylaxis can be considered. However, in the rapidly moving field of allergy with the emergence of new diagnostic tests and increasing knowledge of allergenic mechanisms, triggers can be identified in patients previously considered to have an idiopathic label. A recent example is the delayed anaphylaxis to red meat caused by the galactose-α 1,3-galactose allergenic epitope.12 35 39 Furthermore, a baseline serum tryptase concentration should be measured as soon as possible after any associated exercise, exposure to heat or cold, or co-existent medications consumed in the 6 h preceding the event. In addition, serial samples improve the sensitivity and specificity of the test.41 In addition, a baseline level should be taken city of the test.41 In addition, a baseline level should be taken 2 h after the onset of anaphylaxis, and elevated evidence of mast cell activation. Serum tryptase concentrations peak at 1–2 h after the onset of anaphylaxis, and elevated values can persist for several hours. It is recommended that serum tryptase should be measured as soon as possible after emergency treatment has started, and ideally a second timed sample taken at 1–2 h and no later than 4 h after the onset of symptoms.40 Serial samples improve the sensitivity and specificity of the test.41 In addition, a baseline level should be taken at 24 h, or when the patient attends a specialist clinic for follow-up. Although the positive predictive value is excellent, not all anaphylactic reactions are accompanied by a rise in symptoms.40

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Intramuscular epinephrine (0.01 mg/kg of 1:1000)</td>
<td>Adult: 0.5 ml &gt;12 years: 0.5 ml (0.3 ml if small or pre-pubertal) &gt;6–12 years: 0.3 ml &gt;6 years: 0.15 ml</td>
<td>Repeat every 5–15 min</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Highest possible concentration 0.9% NaCl Hartmann’s solution</td>
<td>6–8 l/min (WAO)</td>
</tr>
<tr>
<td>Intravenous fluids (intra-osseous route possible)</td>
<td>Correct hypovolaemia (NaCl remains in intravascular space longer than glucose and contains no lactate) 1–2 litres usually needed in first 5 min (adult); children 30 mg/kg in the first hour Anaphylaxis to colloid described</td>
<td></td>
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</table>

DIAGNOSIS AND INVESTIGATION OF ANAPHYLAXIS
It is sometimes difficult to establish whether anaphylaxis has actually occurred.

The diagnosis relies on the patient’s recollection and adequate accident and emergency (A&E), ambulance or primary care documentation. A meticulous history is essential. Physicians should aim to ascertain a list of all foods and medications consumed in the 6 h preceding the event. In addition, details regarding the time of the episode, the setting in which it occurred, and the treatment required should be sought. A history of potential cofactors is relevant, including any associated exercise, exposure to heat or cold, or co-existent infections.

Serum tryptase
It is useful when diagnosing anaphylaxis to look for objective evidence of mast cell activation. Serum tryptase concentrations peak at 1–2 h after the onset of anaphylaxis, and elevated values can persist for several hours. It is recommended that serum tryptase should be measured as soon as possible after emergency treatment has started, and ideally a second timed sample taken at 1–2 h and no later than 4 h after the onset of symptoms.40 Serial samples improve the sensitivity and specificity of the test.41 In addition, a baseline level should be taken at 24 h, or when the patient attends a specialist clinic for follow-up. Although the positive predictive value is excellent, not all anaphylactic reactions are accompanied by a rise in symptoms.
serum tryptase, particularly in food mediated anaphylaxis and sometimes in normotensive patients. Elevated values of mast cell tryptase postmortem may also be used to establish anaphylaxis as a cause of death. However, there have been reports of postmortem elevations in serum tryptase in some non-anaphylactic deaths. Therefore, high tryptase concentrations suggest anaphylaxis, but must be used in conjunction with the clinical history supplemented by the circumstances of the death.

Measurement of plasma histamine has been suggested in the literature as a possible investigation in the diagnosis of an anaphylactic reaction. Plasma histamine values begin to rise 5–10 min after the onset of symptoms and remain elevated for 30–60 min. However, histamine has a short half-life, peaking at 5 min, and is therefore not useful in patients presenting more than an hour after the onset of a reaction. Moreover, plasma histamine is not stable during routine handling and the sample requires careful treatment. Therefore, an assay of plasma histamine is not routinely available.

Elevated total tryptase concentrations are also found in conditions other than mastocytosis and anaphylaxis—for example, in acute myelocytic leukaemia, myelodysplastic syndromes, and end stage renal disease with endogenous stem cell factor elevation. For this reason other ways of measuring mast cell degranulation are being examined. The measurement of mast cell carboxypeptidase has shown particular promise as a possible investigation in the diagnosis of an anaphylactic reaction.

PATHOGENESIS OF ANAPHYLAXIS

The majority of cases of anaphylaxis are IgE mediated, but other mechanisms have been described (table 1) and the clinical presentation can be identical. Therefore the distinction between anaphylactic (IgE mediated) and anaphylactoid (non-IgE) reactions is not possible and should be abandoned as it leads to a dangerous assumption that anaphylactoid reactions are always less severe.

In IgE mediated anaphylaxis allergen/antigen-stimulated B lymphocytes produce specific IgE which binds to high affinity IgE receptors (FcεRI) on mast cells and basophils. Re-exposure to the allergen leads to cross-linking of receptor bound IgE, triggering cell activation and release of preformed (histamine, tryptase, heparin, chymase) and newly synthesised mediators (leukotrienes, prostaglandins, platelet activating factor PAF, cytokines IL-6, tumour necrosis factor α (TNFα)) (table 2).

The lungs and the heart are the main shock organs of anaphylaxis, due to vasodilatation caused by reduced venous return and hypovolaemia resulting from fluid extravasation (up to 5% of the intravascular fluid may leak out within 10 min).

DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

Differential diagnosis of anaphylaxis encompasses a wide range of conditions. Some of them are common (acute asthma, syncope, panic attack) but less common causes should also be considered (table 3).
Box 1 Role of allergy specialist in management of anaphylaxis

Role of allergy specialist
1. Detailed history and elucidation of triggers and co-factors (eg, food dependent, exercise induced anaphylaxis)
2. Skin tests, blood tests including relevant specific IgE
3. Graded challenge and/or provocation if unclear or to identify alternative medication, for example, non-steroidal anti-inflammatory drug, antibiotic
4. Individualised avoidance plan
5. Written emergency treatment plan
6. Optimisation of asthma treatment
7. Immunotherapy (eg, for insect venom, etc)
8. Desensitisation to a drug if immediately required and no alternative available
9. Education (verbal, written; online resources)
10. Regular follow-up of patients with ‘idiopathic anaphylaxis’

The age and sex of the patient often provides the clue: aspiration of a nut is more likely in a small child; amniotic fluid embolism during labour and a myocardial infarction in a middle aged man.

MANAGEMENT OF ANAPHYLAXIS

Acute
1. Discontinue exposure to potential trigger (stop intravenous (IV) drug/remove insect stinger, etc).
2. Follow the ABCDE rule (Airway, Breathing, Circulation, Disability, Exposure).
3. Simultaneously with step 2, administer intramuscular (IM) epinephrine. Lie patient down with legs elevated (to correct hypovolaemia/avoid empty vena cava) or place in a position of comfort (if vomiting or short of breath). While doing this, summon help, administer oxygen, and obtain access to give IV fluids. Start cardiopulmonary resuscitation (CPR) if needed. Epinephrine is the first line treatment of anaphylaxis and the only one with proven lifesaving properties. Epinephrine vasoconstricts, decreases mediator release and mucosal oedema (via 1-adrenergic receptor); relieves bronchoconstriction (1- and 2-adrenergic receptor), and exerts positive inotropic and chronotropic effect (2-adrenergic receptor).

There are no randomised controlled trials, but a large body of evidence supports prompt use of epinephrine in anaphylaxis. It should be injected intramuscularly in the mid-anterolateral thigh (vastus lateralis) which leads to a better absorption than IM or subcutaneous (SC) injection into the deltoid. Refer to table 4 for dosing.

Some drugs interact with epinephrine—for example, ß-blockers (including eye drops) may reduce the efficacy of epinephrine and the unopposed stimulation of ß receptors may trigger bradycardia, hypertension, and bronchoconstriction. Glucagon and fluid resuscitation are recommended in the management of anaphylaxis in ß-blocked patients. Linezolid, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants increase the risk of arrhythmias and hypertension in response to epinephrine.

Key references

Current research questions
- How common is anaphylaxis, what are the triggers, and is anaphylaxis on the increase?
- New specific and sensitive markers of anaphylaxis—especially when tryptase is negative.
- What are the likely causes of idiopathic anaphylaxis?
- Newly discovered allergens—what proportion of idiopathic anaphylaxis can they explain?
- What is the role of second line drugs in the acute management of anaphylaxis—for example, do corticosteroids prevent the late phase response?

Main messages
- Refer all patients who experience anaphylaxis to an allergy clinic for further investigation and management.
- Explain allergen avoidance, educate the patient and relatives, and provide a written emergency treatment plan including epinephrine auto-injector.
- Serial tryptase measurements are useful in the diagnosis of anaphylaxis.
Other commonly used drugs in the acute management of anaphylaxis should be considered second line, and their administration must never delay treatment with epinephrine (table 5).

4. Measure serum tryptase (see: serum tryptase) and record timing of sample in relation to onset of symptoms.

5. Patients with uncomplicated anaphylaxis can be discharged after 4–6 h. Some should be observed for 24 h or more (severe reaction; history of severe asthma and biphasic reaction; likely ongoing absorption of allergen; presenting late evening/night; vulnerable patients; patients residing in remote areas) (table 6).

Biphasic anaphylaxis has been reported to occur in up to 20% adults with symptoms recurring within 1–72 h (usually 8–10 h) after the initial reaction has resolved, despite no further exposure to the trigger. An experienced clinician should be involved in the decision to discharge the patient as there are no definite predictors of biphasic anaphylaxis. Clear instructions to return to hospital if symptoms recur should be provided, and a 1–3 day course of oral steroids may prevent the delayed recurrence of symptoms.1 2 12 60 63 64


7. Role of allergy specialist (box 1).

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. What is the most common cause of anaphylaxis in children?
A. Radio-contrast media
B. Stinging insect venom
C. Antibiotics
D. Non-steroidal anti-inflammatory drug (NSAID)
E. Food

2. Which drug should be avoided in patients with a history of recurrent anaphylaxis who require an epinephrine auto-injector?
A. Diltilazem
B. Candesartan
C. Propranolol
D. Metoclopramide
E. Domperidone

3. What is the incidence of biphasic anaphylaxis?
A. 25–35%
B. 15%
C. 1–20%
D. 40–60%
E. 100%

4. The most common agents triggering anaphylaxis at the time of general anaesthesia are:
A. Neuromuscular blocking agents (NMBA)
B. Opiates
C. Intravenous fluids (Gelofusin, Hartmann’s)
D. Iodine preparation
E. Chlorhexidine

5. Following the onset of anaphylaxis, when do serum tryptase concentrations peak?
A. 0–10 min
B. 1–2 h
C. 3–4 h
D. 20–50 min
E. 4–5 h

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Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES


ANSWERS

1. A (f); B (f); C (f); D (f); E (f)
2. A (f); B (f); C (f); D (f); E (f)
3. A (f); B (f); C (f); D (f); E (f)
4. A (f); B (f); C (f); D (f); E (f)
5. A (f); B (f); C (f); D (f); E (f)