Anaphylaxis and its Treatment

Introduction
Anaphylaxis a severe, life-threatening, generalised or systemic hypersensitivity reaction which is likely when both of the following criteria are met:

- Sudden onset and rapid progression of symptoms.
- Life-threatening airway and/or breathing and/or circulation problems.

Skin and/or mucosal changes (flushing, urticaria, angio-oedema) can also occur, but are absent in a significant proportion of cases.

Its identification and management are based on the Resuscitation Council UK Guidelines. However, it is important in outlining guidelines to emphasise the importance of prompt administration of adrenaline (epinephrine) and resuscitation measures. Use of antihistamines is included in the guidelines but there is a lack of evidence either to support or refute their value in the treatment of anaphylaxis. They are certainly very much secondary in importance and useful to treat cutaneous manifestations of anaphylaxis (especially the pruritus) but without relieving airway symptoms or hypotension. They may indeed complicate management because of the risk of drowsiness with their use. Administration of antihistamines should certainly never delay administration of adrenaline (epinephrine). There is a similar lack of evidence for use of steroids, although they may have value in preventing a biphasic reaction.

Incidence
The number of people who experience severe systemic allergic reactions is increasing. The incidence is about 1-3 reactions per 10,000 population per annum, although anaphylaxis is not always recognised, so certain UK studies may underestimate the incidence.

Aetiology
An anaphylactic reaction occurs when an allergen reacts with specific IgE antibodies on mast cells and basophils (type 1 hypersensitivity reaction), triggering the rapid release of stored histamine and the rapid synthesis of newly formed mediators. These cause capillary leakage, mucosal oedema and ultimately shock and asphyxia. Anaphylactic reactions can vary in severity and rate of progression - they may progress rapidly (over a few minutes) or occasionally in a biphasic manner. Rarely, manifestations may be delayed by a few hours (adding to diagnostic difficulty), or persist for more than 24 hours. Anaphylactoid reactions are not IgE-mediated but cause similar mast cell activation.

A significant number of cases of anaphylaxis are idiopathic. The most common triggers of anaphylaxis are:

Foods
- Peanuts.
- Pulses.
- Tree nuts (eg, brazil nut, almond, hazelnut).
- Fish and shellfish.
- Eggs.
- Milk.
Venom
For example:

- Bee stings.
- Wasp stings.

Drugs
These include:

- Antibiotics.
- Opioids.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Intravenous (IV) contrast media.
- Muscle relaxants.
- Other anaesthetic drugs.

Presentation
There is often (but not always) a history of previous sensitivity to an allergen, or recent history of exposure to a new drug (eg, vaccination). Initially, patients usually develop skin symptoms, including generalised itching, urticaria and erythema, rhinitis, conjunctivitis and angio-oedema.

Signs that the airway is becoming involved include itching of the palate or external auditory meatus, dyspnoea, laryngeal oedema (stridor) and wheezing (bronchospasm). General symptoms include palpitations and tachycardia (as opposed to bradycardia in a simple vasovagal episode at immunisation time), nausea, vomiting and abdominal pain, feeling faint - with a sense of impending doom; and, ultimately, collapse and loss of consciousness.[3]

Airway swelling, stridor, breathing difficulty, wheeze, cyanosis, hypotension, tachycardia and reduced capillary filling suggest impending severe reaction.[1]

If no history is available in a collapsed patient, use an ABCDE advanced life-support approach (see quick reference algorithm under 'Emergency treatment', below) to recognise and treat an anaphylactic reaction. Treat life-threatening problems as you find them. The basic principles of treatment are the same for all age groups.

Differential diagnosis[1]

Life-threatening conditions
- Sometimes an anaphylactic reaction can present with symptoms and signs that are very similar to life-threatening asthma - this is most common in children.
- A low blood pressure (BP) - or normal in children - with a petechial or purpuric rash can be a sign of septic shock.
- Seek help early if there are any doubts about the diagnosis and treatment.

Non-life-threatening conditions
These usually respond to simple measures:

- Faint (vasovagal episode).
- Panic attack.
- Breath-holding episode in a child.
- Idiopathic (non-allergic) urticaria or angio-oedema.
Emergency treatment[1]

Treatment in an emergency means following without delay a systematic assessment and treatment plan.

Quick reference anaphylaxis algorithm

- **Rapid assessment:**
  - **Airway:** look for and relieve airway obstruction; call for help early if there are signs of obstruction. Remove any traces of allergen remaining (e.g., nut fragments caught in teeth, with a mouthwash; bee stings without compressing any attached venom sacs).
  - **Breathing:** look for and treat bronchospasm and signs of respiratory distress.
  - **Circulation:** colour, pulse and BP.
  - **Disability:** assess whether responding or unconscious.
  - **Exposure:** assess skin with adequate exposure, but avoid excess heat loss.

- **Consider anaphylaxis** when there is compatible history of rapid-onset severe allergic-type reaction with respiratory difficulty and/or hypotension, especially if there are skin changes present.
- **Give high-flow oxygen** - using a mask with an oxygen reservoir (greater than 10 litres min⁻¹ to prevent reservoir collapse).
- **Lay the patient flat:**
  - Raise the legs (with care, as this may worsen any breathing problems).
  - In pregnant patients, use a left lateral tilt of at least 15° (to avoid caval compression).

- **Adrenaline (epinephrine)** intramuscularly (IM) in the anterolateral aspect of the middle third of the thigh (safe, easy, effective):
  - Adult IM dose 0.5 mg IM (= 500 micrograms = 0.5 mL of 1:1000) adrenaline (epinephrine).
  - Child IM dose (the equivalent volume of 1:1000 adrenaline (epinephrine) is shown in brackets):
    - >12 years: 500 micrograms IM (0.5 mL), ie the same as the adult dose.
    - 300 micrograms (0.3 mL) if the child is small or prepubertal.
    - >6-12 years: 300 micrograms IM (0.3 mL).
    - <6 years: 150 micrograms IM (0.15 mL).

IM adrenaline (epinephrine) should be repeated after 5 minutes if there is no clinical improvement. Patients requiring repeated IM doses may benefit from IV adrenaline (epinephrine). In these circumstances, expert help is required as soon as possible.

- **NB:** IV adrenaline (epinephrine) should only be administered by those with the necessary training and experience - such as anaesthetists, intensivists and emergency department physicians. It can be administered as a bolus dose or as an infusion. Patients requiring repeat bolus dosing should commence an infusion of adrenaline (epinephrine).
- **NB:** half doses of adrenaline (epinephrine) may be safer for patients on amitriptyline, imipramine, monoamine-oxidase inhibitor (MAOI) or beta-blocker.

- **When skills and equipment are available:**
  - Establish airway (in anaphylaxis, airway obstruction from tissue swelling is difficult to overcome and early expert intubation is often needed).
  - IV fluid challenge:
    - Insert one or more large-bore IV cannulae (enable the highest flow).
    - Use intraosseous access (if trained to do so) in children when IV access is difficult.
• Give a rapid fluid challenge:
  - Adults - 500 mL of warmed crystalloid solution (e.g., Hartmann's or 0.9% saline) in 5-10 minutes if the patient is normotensive or 1 L if the patient is hypotensive.
  - Use smaller volumes (e.g., 250 mL) for adult patients with known cardiac failure and use closer monitoring (listen to the chest for crepitations after each bolus).
  - The use of invasive monitoring (e.g., central venous pressure (CVP)) can help to assess fluid resuscitation.
  - For children - give 20 mL/kg of warmed crystalloid.

• Chlorphenamine (after initial resuscitation). Dose depends on age:
  - >12 years and adults: 10 mg IM or IV slowly.
  - >6-12 years: 5 mg IM or IV slowly.
  - >6 months-6 years: 2.5 mg IM or IV slowly.
  - <6 months: 250 micrograms/kg IM or IV slowly.

• Hydrocortisone (after initial resuscitation). Dose depends on age:
  - >12 years and adults: 200 mg IM or IV slowly.
  - >6-12 years: 100 mg IM or IV slowly.
  - >6 months-6 years: 50 mg IM or IV slowly.
  - <6 months: 25 mg IM or IV slowly.

• Continuing respiratory deterioration requires further treatment with a bronchodilator, such as salbutamol (inhaled or IV), ipratropium (inhaled), aminophylline (IV) or magnesium sulfate (IV - unlicensed indication). Magnesium is a vasodilator and can compound hypotension and shock. For doses, refer to the British National Formulary (BNF).

• Monitor:
  - Pulse oximetry
  - ECG
  - BP

Monitoring
• All critically ill patients should be given oxygen.
• Maintain the PaO\textsubscript{2} as close to normal as possible (approximately 13 kPa or 100 mm Hg).
• When/if a pulse oximeter is available:
  - Titrate the oxygen to maintain an oxygen saturation of 94-98%.
  - In the sickest patients this is not always possible so you may have to accept a lower value, i.e., above 8 kPa (60 mm Hg), or 90-92% oxygen saturation on a pulse oximeter.

• A normal SpO\textsubscript{2} on oxygen does not necessarily mean ventilation is adequate (because the pulse oximeter detects oxygenation and not hypercapnia). The patient may be breathing inadequately (with a high PaCO\textsubscript{2}).
• Use bag-mask ventilation while calling urgently for expert help. In an anaphylactic reaction, upper airway obstruction or bronchospasm can make bag mask ventilation difficult or impossible.
• Consider early tracheal intubation (if equipment and expertise are available). If the patient is intubated, give high-concentration oxygen with a self-inflating bag. Occasionally emergency tracheotomy is required.

Blood pressure - reassess the pulse rate and BP regularly (every 5 minutes).
Aim for:

• In adults, normal BP (or a systolic BP greater than 100 mm Hg).
• In children:
  - 0-1 month: minimum 50-60 mm Hg.
  - >1-12 months: minimum 70 mm Hg.
  - >1-10 years: 70+ (age in years x 2) mm Hg.
  - >10 years: minimum 90 mm Hg.

• If the patient does not improve, repeat the fluid challenge.
If there are symptoms and signs of cardiac failure (shortness of breath, increased heart rate, raised JVP, a third heart sound, and inspiratory crackles in the lungs on auscultation):
  - Decrease or stop the fluid infusion.
  - Seek expert help (inotropes or vasopressors may be needed).

**Further investigation**

Serum mast-cell tryptase can be measured in cases of anaphylaxis, particularly to clarify diagnosis where ambiguity exists. Tryptase is the preferred marker for demonstrating mast-cell degranulation (histamine elevation, for example, is very transient).

Levels of serum tryptase, which is a mast-cell specific protease, peak at one hour after an anaphylactic reaction, remaining elevated for approximately six hours. Elevated serum tryptase levels imply either massive mast-cell degranulation, as occurs in anaphylaxis, or a condition such as mastocytosis. However, not every case of anaphylaxis causes a rise in tryptase - both the sensitivity and specificity are around 95%. Guidance from the National Institute for Health and Care Excellence (NICE) advises measurement of mast-cell tryptase:

- As soon as possible after emergency treatment for anaphylaxis.
- 1-2 hours after onset of first symptoms of anaphylaxis (and no later than 4 hours).

A further sample can be taken after 24 hours or at follow-up in an allergy clinic. This establishes an individual's baseline level. In children (under the age of 16), mast-cell tryptase should only be measured in cases thought to be either idiopathic, venom-induced or drug-related.

**Observation**

- Observe patients for a period of 6-12 hours from the onset of symptoms, depending on their response to emergency treatment.[5] If symptoms are controlled swiftly and easily, a shorter period of observation may be appropriate. Here it is necessary to ensure a safe discharge to the care of an adult, with advice on what to do in the event of further difficulties (ie biphasic reaction).[5]
- Children under 16 with anaphylaxis should be admitted under the care of a paediatric team, rather than just receiving emergency treatment in the emergency department.[5] However, in practice, many emergency departments do have specific paediatric facilities and observation units. Often swifter discharge can be effected safely.

**Follow-up**

When time allows:

**Immediate**

- Take a full history from the patient (relatives, friends, and other staff). This should include documenting all symptoms in full, so as to confirm diagnosis. In particular, record the time of onset of the reaction and the circumstances immediately before the onset of symptoms.[6]
- Review the patient's notes and charts. Study both absolute and trends of values relating to vital signs.
- Check that important routine medications are prescribed and being given.
- Review the results of laboratory or radiological investigations.
- Consider what level of care is required by the patient - eg, transport to hospital if in the community.
- In the patient's notes, make complete entries of your findings, assessment and treatment. Record the patient's response to therapy.
- Consider definitive treatment of the patient's underlying condition.

**In the long term**

- Refer to an allergist or allergy clinic to try to identify the allergen, so that it can be avoided in future.
- Organise self-use of pre-loaded pen injections for future attacks (eg, EpiPen®; containing 0.3 mL of 1 in 1000 strength (that is, 300 micrograms) for adults; and for children 0.3 mL of 1 in 2000 (150 micrograms)). This again may be best done in allergy clinics. It is important that the technique for using these auto-injectors should be demonstrated and taught.[1]
• Give a written self-management plan, information about anaphylaxis and biphasic reactions, and
details of the possible signs and symptoms of a severe allergic reaction.\(^5\)
• Encourage the patient to wear a medical emergency identification bracelet or similar.

Further reading & references

- **Anaphylaxis; NICE Quality Standard, March 2016**
- 4. British National Formulary; NICE Evidence Services (UK access only)
- 5. **Anaphylaxis; NICE Clinical Guideline (December 2011)**

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