Anaphylaxis: the acute episode and beyond

F Estelle R Simons,1 Aziz Sheikh2

Anaphylaxis is an alarming medical emergency,1-3 not only for the patient or care giver, but also sometimes for the healthcare professionals involved. Although it is thought of as uncommon, the lifetime prevalence is estimated at 0.05-2%,4,5 and the rate of occurrence is increasing. Hospital admissions, although uncommon, are also increasing, as are admissions to critical care units.6,7 Many anaphylaxis episodes now occur in community settings.8 Accurate community based population estimates are difficult to obtain because of underdiagnosis, under-reporting, and miscoding, as well as use of different anaphylaxis definitions and different methods of case ascertainment in the populations studied.9 Although death from anaphylaxis seems to be uncommon, it is under-reported.9

In this article, we draw on evidence from randomised controlled trials, quasi-experimental and other observational studies, and systematic reviews. We also reference key evidence based international and national anaphylaxis guidelines and their updates.1,2,10-11

How is anaphylaxis defined?
The widely used definition of anaphylaxis—“a serious allergic reaction that is rapid in onset and may cause death”—is accompanied by clinical criteria for diagnosis,1 which have been validated for use in clinical and research contexts (fig 1, bmj.com).1,3,11-13 In emergency departments, this definition has high sensitivity (97%) and high negative predictive value (98%), with lower specificity (82%) and positive predictive value (67%), as anticipated in a multisystem disease.1,12 Hypotension and shock are not prerequisites for making the diagnosis of anaphylaxis. Death occurs as often after respiratory arrest as it does after shock or cardiac arrest.1,4

What are the mechanisms, triggers, and patient risk factors for anaphylaxis?
The clinical features of anaphylaxis result from sudden release of histamine, tryptase, leukotrienes, prostaglandins, platelet activating factor, and many other inflammatory mediators into the systemic circulation. Typically, this

SUMMARY POINTS
Diagnosis is based on clinical presentation—sudden onset of characteristic symptoms in more than one body system, minutes to hours after exposure to a likely or known allergen
Factors associated with increased risk of severe or fatal anaphylaxis include asthma, cardiovascular disease, mastocytosis, and drugs such as β blockers
When anaphylaxis occurs, promptly call for help, inject adrenaline intramuscularly, and place the patient on the back or in a semi-reclining position with lower extremities raised
During the episode, if needed, give high flow supplemental oxygen, establish intravenous access to provide high volume fluids, and perform cardiopulmonary resuscitation
Provide at risk patients with adrenaline autoinjectors, personalised anaphylaxis emergency action plans, and medical identification
Confirm the specific trigger so that it can be avoided or allergen specific immune modulation—such as venom immunotherapy to prevent anaphylaxis from insect stings—can be carried out

 SOURCES AND SELECTION CRITERIA
We based this review on Medline and other searches for publications relevant to human anaphylaxis, including Cochrane reviews and other systematic reviews, randomised controlled trials, and quasi-experimental and other observational studies. We also used World Allergy Organization guidelines for the assessment and management of anaphylaxis and UK Resuscitation Council guidelines for emergency treatment of anaphylactic reactions (both of which were not commercially sponsored).

Box 1 | Mechanisms and triggers of anaphylaxis

<table>
<thead>
<tr>
<th>Mechanism Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune mechanism</td>
<td>IgE dependent*</td>
</tr>
<tr>
<td>IgG mediated</td>
<td>Infliximab, high molecular weight dextran (rare)</td>
</tr>
<tr>
<td>Immune aggregates</td>
<td>Intravenous immunoglobulin (rare)</td>
</tr>
<tr>
<td>Other immune mechanisms</td>
<td>IgE independent*</td>
</tr>
<tr>
<td>Drug</td>
<td>Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Other physical factors</td>
<td>Exercise, usually with a cofactor such as a food or drug</td>
</tr>
<tr>
<td>Other physical factors</td>
<td>For example, cold air or cold water</td>
</tr>
<tr>
<td>Drug</td>
<td>Opioids such as codeine or morphine</td>
</tr>
<tr>
<td>Other factors</td>
<td>Seminal fluid (rare)</td>
</tr>
<tr>
<td>Other factors</td>
<td>Idiopathic anaphylaxis*</td>
</tr>
</tbody>
</table>

No trigger can be identified

*Examples of mechanisms and triggers are given; the number of triggers is infinite.
†Different classes of drugs induce anaphylaxis through different mechanisms.
‡Consider the possibility of an uncommon or novel trigger (such as galactose-α-1,3-galactose, the carbohydrate moiety in red meat; saliva injected by biting insects; or topically applied allergens such as chlorhexidine) or a concurrent diagnosis of mastocytosis.

occurs through an immune mechanism involving interaction between an allergen and allergen specific IgE bound to high affinity IgE receptors on mast cells and basophils. However, IgE independent immune mechanisms and direct degranulation of mast cells are sometimes responsible, and other episodes, especially in adults, are idiopathic (box 1).1

Patient risk factors for anaphylaxis include vulnerability owing to age or physiological state (box 2).1,11-18 Some diseases such as asthma and cardiovascular disease, and some drugs such as β adrenergic blockers and angiotensin converting enzyme inhibitors also increase the risk of severe or fatal anaphylaxis episodes (box 2).1,11,14,16-20

Cofactors that can amplify or augment acute anaphylactic episodes have been identified (box 2).8,11,21,22 Doctors and
Box 2 | Patient risk factors for anaphylaxis

Age related factors
Infants: anaphylaxis can be hard to recognise, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk taking behaviours such as failure to avoid known triggers and to carry an adrenaline autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs

Concomitant diseases
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Mastocytosis
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse

Drugs
β adrenergic blockers†
Angiotensin converting enzyme (ACE) inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient’s ability to recognise triggers and symptoms

Cofactors that amplify anaphylaxis
Exercise: anaphylaxis associated with exercise may be food dependent or food independent; non-steroidal anti-inflammatory drugs and other listed cofactors may also be relevant
Acute infection such as an upper respiratory tract infection
Fever
Emotional stress
Disruption of routine—for example, travel and jet lag
Premenstrual status in women and girls

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings
†Patients taking β adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis.
In addition, those taking β adrenergic blockers may not respond optimally to adrenaline treatment and may need glucagon, a polypeptide with non-catecholamine dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Box 3 | Symptoms and signs of anaphylaxis

During an anaphylaxis episode, symptoms and signs can range from few to many. A comprehensive list is provided to aid in prompt recognition and to indicate the possibility of rapid progression to multiorgan system involvement.

Skin, subcutaneous tissue, and mucosa
Generalised flushing, itching, urticaria (hives), angio-oedema, morbilliform rash, pilor erection
Periorbital itching, erythema, oedema, conjunctival erythema, tearing
Itching or swelling (or both) of lips, tongue, palate, uvula, external auditory canals
Itching of the genitalia, palms, soles

Respiratory
Nasal itching, congestion, rhinorrhea, sneezing
Throat itching, tightness, dysphonia, hoarseness, dry staccato cough, stridor
Lower airways: cough, increased respiratory rate, shortness of breath, chest tightness, wheezing
Cyanosis
Respiratory arrest

Gastrointestinal
Abdominal pain, dysphagia, nausea, vomiting (stringy mucus), diarrhoea

Cardiovascular system
Chest pain (myocardial ischaemia)*
Tachycardia, bradycardia (less common), other dysrhythmias, palpitations
Hypotension, feeling faint, incontinence, shock
Cardiac arrest

Central nervous system
Feeling of impending doom, uneasiness, headache (pre-adrenaline), altered mental status or confusion owing to hypoxia, dizziness or tunnel vision owing to hypotension, loss of consciousness

Other
Metallic taste in the mouth

*This can occur in patients with coronary artery disease and (owing to vasospasm) in those with normal coronary arteries.

To some extent, symptoms and signs depend on age and physiological state. As examples, infants and young children who cannot describe their symptoms typically develop sudden behavioural changes and become anxious, frightened, or cliny. Children sometimes use terms such as “burning” or “tingly” to mean itching, and those with upper airway involvement sometimes scratch at their throat or gag. Pregnant women can experience intense itching of the genitalia, abdominal cramps, back pain, signs of fetal distress, and preterm labour. Skin symptoms and signs are reported in 80-90% of patients. In their absence, anaphylaxis can be difficult to recognise. Upper and lower respiratory tract symptoms and signs occur in up to 70% of those experiencing anaphylaxis and cardiovascular symptoms and signs in about 45%. Gastrointestinal symptoms occur in about 45% and central nervous system symptoms and signs in about 15%.

The patterns of target organ involvement vary between patients, and in the same patient from one episode to another (fig 1, bmj.com). Symptoms and signs therefore differ from one patient to another and from one episode to another in the same patient in terms of type, number of organ systems affected, time of onset in relation to exposure to the inciting agent, and duration.

Anaphylaxis can range in severity from transient and unrecognised or undiagnosed episodes, to respiratory arrest,
shock, cardiac arrest, and death within minutes. At the onset of an episode, it can be difficult or impossible to predict the rate of progression, the ultimate severity, or the likelihood of death. In a UK registry study of anaphylaxis related deaths, median times to cardiac or respiratory arrest were five minutes in iatrogenic anaphylaxis, 15 minutes in insect sting anaphylaxis, and 30 minutes in food anaphylaxis. Some patients develop biphasic or multiphasic anaphylaxis, in which symptoms resolve, then reappear hours later despite no further exposure to the trigger. Protracted anaphylaxis, in which uninterrupted symptoms recur for days despite treatment, is uncommon.

More than 40 differential diagnoses exist, including episodes of acute asthma, acute generalised urticaria, or acute angio-oedema, acute anxiety or panic attacks, and syncope (box 4, bmj.com).

What investigations should be considered?
Measurement of mast cell tryptase concentration—the most widely used laboratory test—is not universally available, takes hours to perform, is not available on an emergency basis, and is not helpful for confirming the clinical diagnosis of anaphylaxis in the initial minutes or hours after symptom onset. Treatment must therefore not be delayed to obtain a blood sample for tryptase measurement.

Total tryptase concentrations measured in serum during anaphylaxis episode can, however, sometimes be helpful later to confirm the diagnosis, especially in patients with drug or insect sting induced anaphylaxis and those with hypotension. Tryptase concentrations are seldom raised in patients with anaphylaxis triggered by food, or in those whose blood pressure remains normal during the anaphylactic episode. Several factors may explain this: localised mast cell degranulation—for example, in the upper airway—with less tryptase entering the circulation than after generalised degranulation; involvement of respiratory epithelial mast cells rather than perivascular and cardiac mast cells that contain more tryptase; greater distance of respiratory epithelial mast cells than perivascular mast cells from the circulation; and involvement of basophils, which release minimal tryptase. A serum tryptase concentration within the reference range of 1-11.4 ng/mL does not refute the clinical diagnosis of anaphylaxis, and an increased concentration is not specific for anaphylaxis.

Tryptase has a short elimination half life. Serial measurements are reported to improve test specificity and are ideally obtained 15-180 minutes after symptom onset, one to two hours later, and after resolution of the episode. A raised baseline value suggests the diagnosis of mastocytosis rather than anaphylaxis.

How should an acute episode of anaphylaxis initially be treated?
Figure 2 outlines a systematic approach to the basic initial management of anaphylaxis that emphasises the primary role of adrenaline. In healthcare settings, it is important to prepare for this medical emergency by using an anaphylaxis assessment and management protocol based on current national or international guidelines. This protocol should be displayed in locations where all healthcare professionals and staff can access it and rehearse it.

At the time of diagnosis, exposure to the trigger should be halted if possible—for example, by discontinuing an intravenously administered diagnostic or therapeutic agent. The patient’s circulation, airway, breathing, mental status, skin, and body weight (mass) should be assessed.

Simultaneously and promptly, call for help—from emergency medical services in a community setting or a resuscitation team in a hospital or other healthcare setting. In an adult, inject adrenaline 0.3 mg (0.3 mL) by the intramuscular route in the mid-outter thigh to a maximum of 0.5 mg (0.5 mL) of a 1 mg/mL (1:1000) solution; in a prepubertal child, inject adrenaline 0.15 mg (0.15 mL) to a maximum of 0.3 mg (0.3 mL). Adrenaline is classified as an essential drug by the World Health Organization and is available worldwide in a 1 mL ampoule (1 mg/mL), even in most low resource areas.

As soon as the symptoms of anaphylaxis are recognised, the injection should be given by anyone trained or authorised to administer it. In healthcare settings, it is typically ordered or given by a doctor. However, in many immunisation clinics, infusion clinics, and allergen immunotherapy clinics, nurses are preauthorized to do this. In community settings, adrenaline is often self injected through an autoinjector by the patient or injected by the parent, teacher, or other person responsible for the child. Delay in administration is associated with greater likelihood of biphasic and protracted anaphylaxis, and of death. In a UK series, only 14% of the patients who died from anaphylaxis received adrenaline before respiratory or cardiac arrest.

The adrenaline injection can be repeated after five to 15 minutes, if needed. When the initial injection is given promptly after symptoms are recognised, patients seldom require more than two or three injections. Compared with the intravenous route, the intramuscular route has the advantages of rapid initial access and a considerably wider margin of safety.

For ethical and practical reasons, no randomised controlled trials of adrenaline have been conducted during anaphylaxis. The recommendation for intramuscular injection of adrenaline is based on consistent clinical evidence sup-
Initial treatment of anaphylaxis

1. Have a written emergency protocol for recognition and treatment of anaphylaxis and rehearse it regularly.
2. Remove exposure to the trigger if possible—for example, discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.
3. Assess patient’s circulation, airway, breathing, mental status, skin, and body weight (mass).
4. Promptly and simultaneously perform steps 4, 5, and 6.
5. Call for help: resuscitation team (hospital) or emergency medical services (community) if available.
6. Inject adrenaline (epinephrine) intramuscularly in midouter thigh, 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mg (adult) or 0.3 mg (child); record time of dose and repeat it in 5-15 minutes, if needed.
7. Place patient on back or in a position of comfort if there is respiratory distress and/or vomiting; elevate lower extremities; deaths can occur within seconds if patient stands or sits suddenly.
8. When indicated, give high flow supplemental oxygen by face mask.
9. Establish intravenous access using needles or catheters with wide bore cannulas (14-16 gauge). When indicated, give 1-2 L of 0.9% (isotonic) saline rapidly (for example, 5-10 mL/kg in first 5-10 minutes to an adult; 10 mL/kg to a child).
10. When indicated, at any time, perform cardiopulmonary resuscitation with continuous chest compressions and rescue breathing.

In addition,

- Monitor (continuously, if possible) patient’s blood pressure, cardiac rate and function, respiratory status, and oxygenation.
- Assess patient’s circulation, airway, breathing, mental status, skin, and body weight (mass).
- Rapidly (for example, 5-10 mL/kg in first 5-10 minutes to an adult; 10 mL/kg to a child).
- Give 1-2 L of 0.9% (isotonic) saline rapidly.
- Cardiopulmonary resuscitation.
- Continuous chest compressions.
- Rescue breathing.

What additional treatment might be indicated for an acute episode of anaphylaxis?

At any time during the episode, when indicated, additional important steps include giving high flow supplemental oxygen and maintaining the airway, establishing intravenous access and administering high volumes of fluid, and initiating cardiopulmonary resuscitation with chest compressions before starting rescue breathing. As soon as possible, start continuous monitoring of blood pressure, heart rate and function, respiratory rate, and oxygenation using pulse oximetry to titrate oxygen therapy (fig 2).

Do not delay prompt intramuscular injection of adrenaline—the first line drug—by taking time to draw up and give a second line drug such as an H1 antihistamine or a glucocorticoid. H1 antihistamines relieve skin and nasal symptoms and glucocorticoids might prevent biphasic or protracted symptoms, but these drugs fail to prevent release of the inflammatory mediators that escalate the response; fail to relieve life threatening upper or lower airway obstruction, hypotension, or shock; and fail to prevent death.

Promptly transfer patients who are refractory to initial treatment of anaphylaxis to the care of specialists in emergency medicine, critical care medicine, or anaesthesiology. Such specialists and their teams are trained, experienced, and equipped to provide skilled management of the airway and mechanical ventilation, and to manage shock by administering adrenaline or other vasopressors through an infusion pump. The absence of established dosing regimens for intravenous vasopressors necessitates frequent dose titrations based on continuous monitoring of vital signs, cardiac function, and oxygenation.

After treatment and resolution of anaphylaxis, keep patients under observation in a healthcare facility for at least four to six hours. Observe those who have experienced respiratory or circulatory compromise for eight to 10 hours, or even longer.

How should patients be equipped for self treatment of anaphylaxis in the community?

Tell patients that they have experienced a potentially life threatening medical emergency. If possible, they should be discharged with an adrenaline autoinjector, or at a minimum, a prescription for one, and taught why, when, and how to inject adrenaline (box 5, bmj.com). They should also be equipped with a personalised emergency action plan that lists common anaphylaxis symptoms to help them recognise a recurrence and reminds them to inject adrenaline promptly using an autoinjector and seek prompt medical help. Such plans typically also list patients’ confirmed

*anaphylaxis guidelines*
anaphylaxis trigger(s), their relevant comorbidities (such as asthma or cardiovascular disease), and relevant concurrent drugs. In addition, patients should wear medical identification (bracelet or card) that states their diagnosis of anaphylaxis, its causes, and any relevant diseases or drugs.

Beyond the acute episode: how should anaphylaxis be investigated?
The natural course of anaphylaxis is one of recurrent acute episodes, unless the patient’s specific triggers are identified and consistently avoided. Appropriate investigation and follow-up after recovery from an episode may protect against recurrences. Confirm triggers suggested by a meticulous history of previous episodes by measuring allergen specific IgE in serum or by performing allergen skin tests (or both), because self identification of food, drug, and stinging insect triggers by patients may be non-specific or incorrect and prevention of recurrence must be trigger specific. Avoid testing with large numbers of allergens because sensitisation to allergens is common even without a history of symptoms or signs after exposure to the specific allergen. Skin tests are optimally performed about four weeks after the acute episode, rather than immediately after, when test results may be falsely negative. Patients with a convincing history of anaphylaxis who have negative skin tests within a few weeks after an episode should be retreated later.

Some patients will need additional investigations to rule out other diseases in the differential diagnosis. Patients with idiopathic anaphylaxis need additional tests to investigate any unusual or novel triggers and to rule out mastocytosis. Other patients might need additional tests to distinguish asymptomatic sensitisation to an allergen, such as a food or venom, from risk of subsequent clinical reaction to this allergen. Allergen component tests, such as microassay based immunoassays, might help to distinguish patients who are sensitised to an allergen and at increased risk of anaphylaxis after exposure to the allergen from those who are sensitised but clinically tolerant (remain asymptomatic after exposure to the allergen).

Most doctors will want their patients with anaphylaxis to be investigated by a qualified allergy specialist, although ready access to such specialists and to basic tests for sensitisation to allergens is a problem in many parts of the world. In the United Kingdom, an evidence and consensus based national care pathway has been designed to improve assessment and management of infants, children, and young people who have experienced anaphylaxis.

How can recurrences of acute anaphylaxis be prevented?
Personalised written instructions about avoidance of confirmed relevant trigger(s) and safe alternatives should be provided for patients at risk, who should also be directed to reliable, up to date information resources. In healthcare settings, flag medical records with “anaphylaxis” and list relevant triggers.

For anaphylaxis to foods, strict avoidance of the relevant foods, even in trace amounts, is currently the only recommended approach for prevention of recurrence. Long term avoidance of food triggers can be stressful because of the threat of hidden crossreactive or cross contaminating allergens. New immune modulation strategies to achieve clinical and immunological tolerance to implicated foods and prevent recurrences of food triggered anaphylaxis are within reach, as demonstrated in randomised controlled trials, although they are not yet recommended for clinical implementation because of high adverse event rates.

For anaphylaxis to a drug, prevention of recurrence involves substitution of a safe effective non-crossreacting agent, preferably from a different pharmacological class. If such an agent is not available, desensitisation to the implicated agent is indicated to induce temporary clinical tolerance for one uninterrupted course of treatment with that agent. Desensitisation to antimicrobials, antifungals, antivirals, chemotherapeutics, monoclonal antibodies, and other agents is carried out in specialised hospital units.

For anaphylaxis to stinging insect venoms, recurrences can be prevented by a three to five year course of subcutaneous immunotherapy with the relevant standardised specific venom(s). This approach, which is based on high quality randomised controlled trials, should be initiated and monitored by an allergist. It leads to clinical and immunological tolerance, and in about 90% of adults and 98% of children, to longlasting protection against recurrence.

For exercise induced anaphylaxis and food dependent exercise induced anaphylaxis, recurrence can be prevented by avoiding relevant co-triggers such as foods, non-steroidal anti-inflammatory drugs, or alcohol and avoiding exercise under adverse environmental conditions (extreme cold or heat, high humidity, or high pollen counts). Patients should not exercise alone and should carry an adrenaline autoinjector and a mobile phone. If an episode occurs despite preventive measures, treatment involves discontinuing exertion immediately on recognition of initial symptoms, calling for help, and self injecting adrenaline promptly.

Pharmacological approaches are commonly used in the prevention of anaphylaxis. As an example, patients at high risk of anaphylaxis from infusion of radiotranst medium during diagnostic procedures, or those with frequent episodes of idiopathic anaphylaxis, are often treated prophylactically with an H1 antihistamine, glucocorticoid, or other drug. Most prophylactic regimens are based on clinical experience rather than on randomised controlled trials.

Do patients with a history of anaphylaxis need long term follow-up?
Patients at risk for anaphylaxis in the community should be monitored regularly—for example, at yearly intervals—by their doctor. Such visits provide the opportunity for personalised education on how to prevent recurrences, recognise anaphylaxis symptoms, and self inject adrenaline correctly. An important aspect of follow-up is to help patients (and carers of at risk children) control asthma or other comorbid disease that potentially increase the risk of severe or fatal anaphylaxis episodes.

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