Emergency treatment of anaphylaxis: concise clinical guidance

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Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. It is characterised by the rapid development of airway and/or breathing and/or circulation problems. Intramuscular adrenaline is the most important treatment, although, even in healthcare settings, many patients do not receive this intervention contrary to guidelines. The Resuscitation Council UK published an updated guideline in 2021 with some significant changes in recognition, management, observation and follow-up of patients with anaphylaxis. This is a concise version of the updated guideline.

KEYWORDS: anaphylaxis, adrenaline, antihistamine, corticosteroids, resuscitation

DOI: 10.7861/dinmed.2022-0073

Introduction

The Resuscitation Council UK (RCUK) published an updated guideline in 2021 with some significant changes in the recognition, management, observation and follow-up of patients with anaphylaxis. Key updates include a greater emphasis on the use of intramuscular (IM) adrenaline, changes to the role of antihistamines and corticosteroids, the introduction of an algorithm for treating refractory anaphylaxis, and refinement of the duration of observation after anaphylaxis. This is a concise version of the updated guideline.

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. The estimated incidence of anaphylaxis from all causes in Europe is 1.5–7.9 per 100,000 person-years, and 1 in 300 people experience anaphylaxis at some point in their lives. The overall prognosis of anaphylaxis is good, with a case fatality rate of <1% in those presenting to UK hospitals, and the mortality rate in the general population is <1 per million per annum.

There are approximately 20–30 deaths reported each year due to anaphylaxis in the UK, but this may be a significant underestimate; approximately 10 anaphylaxis deaths each year are due to foods, and another 10 due to perioperative anaphylaxis.

The most common triggers are food, drugs and venom. Food is the most common trigger in young people: teenagers and adults up to the age of 30 years appear to be at greatest risk of fatal food-induced reactions. In contrast, the rate of drug-induced anaphylaxis is highest in the elderly, probably due to the combination of comorbidities (such as cardiovascular disease) and polypharmacy (including beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors). The diagnosis is supported if there is exposure to a known trigger, however, in up to 30% of cases, there may be no obvious trigger (‘idiopathic’ or ‘spontaneous’ anaphylaxis). The characteristics of anaphylaxis to the most common causes are shown in Table 1.

Table 1. Causes and characteristics of anaphylaxis

<table>
<thead>
<tr>
<th>Age distribution: anaphylaxis (all severities)</th>
<th>Food</th>
<th>Medication/iatrogenic causes</th>
<th>Insect/venom sting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common in preschool children, less common in older adults</td>
<td>Predominantly older ages</td>
<td>All ages</td>
<td></td>
</tr>
<tr>
<td>Typical presentation</td>
<td>Breathing problems</td>
<td>Circulation problems (breathing problems are less common)</td>
<td>Circulation problems (breathing problems are less common)</td>
</tr>
<tr>
<td>Onset</td>
<td>Less rapid</td>
<td>Rapid</td>
<td></td>
</tr>
<tr>
<td>History of asthma/atopy</td>
<td>Common</td>
<td>Uncommon</td>
<td></td>
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Adapted from the 2021 Resuscitation Council UK guideline, Emergency treatment of anaphylaxis: Guidelines for healthcare providers.
Emergency treatment of anaphylaxis

It is characterised by:
- sudden onset and rapid progression of symptoms
- airway and/or breathing and/or circulation (ABC) problems
- usually, skin and/or mucosal changes (urticaria, flushing or angioedema); these may be subtle or absent in 10%–20% of reactions.

Skin and/or mucosal symptoms alone are not a sign of anaphylaxis. Gastrointestinal symptoms (eg nausea, abdominal pain or vomiting) in the absence of ABC problems do not usually indicate anaphylaxis. Abdominal pain and vomiting can be symptoms of anaphylaxis due to an insect sting or bite. Different phenotypes are associated with different causes of anaphylaxis (Table 1).

Many patients with anaphylaxis are not given the correct treatment because of failure to recognise anaphylaxis. Approximately half of anaphylaxis episodes are not treated with adrenaline, even when they occur in a healthcare setting; at the same time, adrenaline may be given to patients with non-anaphylaxis reactions that present with prominent skin features, such as urticaria or facial swelling.

This updated guideline (Emergency treatment of anaphylaxis: Guidelines for healthcare providers, 2021) supersedes the 2008 RCUK guideline (annotated in 2012 with links to the National Institute for Health and Care Excellence (NICE) guidance). An evidence review was undertaken by the Anaphylaxis Working Group of the RCUK, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks for adoption, adaptation and de novo development of trustworthy recommendations, referred to as GRADE-ADOLOPMENT. A summary of the key recommendations is provided in Box 1.

The importance of appropriate positioning in the treatment of suspected anaphylaxis

Correct posturing is essential in the treatment of anaphylaxis (note the image on the right side of the algorithm in Fig 2). Changes in posture from supine to standing are associated with cardiovascular collapse and death during anaphylaxis, due to a reduction in venous return and consequent reduced myocardial filling and perfusion. It is important to remain flat, with or without legs raised, to maximise venous return. In cases where the symptoms predominantly affect the airway or breathing, the patient may prefer to be semi-recumbent, again with or without the legs raised.

Emphasis on the use of IM adrenaline in the initial treatment of anaphylaxis

IM adrenaline is the first-line treatment for anaphylaxis (Fig 2). There are no randomised trials evaluating adrenaline to treat anaphylaxis, however, extensive observational data exist to support the use of adrenaline, and that delays in administration are associated with more severe outcomes and possibly death. Fatal anaphylaxis is rare but also very unpredictable, so all cases of anaphylaxis should be treated as potentially life-threatening. In approximately 10%–20% of cases of anaphylaxis, skin and/or mucosal changes are common but can be absent in 10%–20% of cases of anaphylaxis.

Correct posturing is essential in the treatment of suspected anaphylaxis: changes in posture from supine to standing are associated with cardiovascular collapse and death.

Intravenous (IV) fluids are an important adjunct in the presence of shock or poor response to an initial dose of adrenaline. Corticosteroids (eg hydrocortisone) are no longer advised for the routine treatment of anaphylaxis, except after initial resuscitation for refractory reactions or ongoing asthma/shock.

A risk-stratified approach is recommended to guide the duration of observation following treatment of anaphylaxis.

**Box 1. Summary recommendations from 2021**

Resuscitation Council UK guideline, *Emergency treatment of anaphylaxis: Guidelines for healthcare providers*

Anaphylaxis is a potentially life-threatening allergic reaction characterised by sudden onset and rapid progression of airway, breathing and circulation (ABC) problems.

Correct posturing is essential in the treatment of suspected anaphylaxis: changes in posture from supine to standing are associated with cardiovascular collapse and death.

Intravenous (IV) fluids are an important adjunct in the presence of shock or poor response to an initial dose of adrenaline.

Corticosteroids (eg hydrocortisone) are no longer advised for the routine treatment of anaphylaxis, except after initial resuscitation for refractory reactions or ongoing asthma/shock.

A risk-stratified approach is recommended to guide the duration of observation following treatment of anaphylaxis.

**Fig 1. Spectrum of severity of anaphylaxis.** Reproduced with permission from Resuscitation Council UK. ABC = airway and/or breathing and/or circulation.
Antihistamines are considered as a third-line intervention and should not be used to treat ABC problems

The role of antihistamines in anaphylaxis is debated, but there is consensus across all guidelines that they are not a first-line treatment. There is no randomised controlled trial (RCT) or quasi-RCT evidence to support the use of antihistamines in the initial treatment of anaphylaxis, and they do not lead to resolution of the respiratory or cardiovascular features of adrenaline, or improve survival. The majority of patients presenting to emergency departments are treated with antihistamines, but only a minority of patients receive adrenaline. A large national prospective registry examined 3,498 cases of anaphylaxis and found that prehospital antihistamine use was associated with a lower rate of administration of more than one adrenaline dose, although this was not the case when less severe cases were excluded. Moreover, use of antihistamines is associated with occurrence of biphasic reactions, possibly due to causing delayed administration of adrenaline.

Although antihistamines are not recommended for the initial treatment of anaphylaxis, there is a role for their use to treat skin symptoms (such as urticaria or angioedema) that may occur as part of anaphylaxis, once ABC features have resolved. Non-sedating antihistamines (for example, cetirizine) are preferred,
Emergency treatment of anaphylaxis

First generation antihistamines (such as chlorphenamine) can cause sedation and, if given rapidly by intravenous bolus, can precipitate hypotension.\(^{39}\)

Corticosteroids (eg hydrocortisone) are no longer advised for the routine emergency treatment of anaphylaxis.\(^{38,40}\) The updated RCUK guideline advises against the routine use of corticosteroids to treat anaphylaxis. There is little evidence that corticosteroids help shorten protracted symptoms or prevent biphasic reactions.\(^{38,40}\) Moreover, there are emerging data to suggest that the routine use of steroids is associated with an increase in morbidity even after correcting for reaction severity.\(^{36,41}\) A large prospective national registry found that prehospital treatment with corticosteroids was associated with an increase in the rate of hospitalisation and/or intensive care admission.\(^{36}\) While this could be due to steroids being used in preference to appropriate adrenaline administration, the association between steroids and more severe outcomes remained irrespective of whether or not prehospital adrenaline was administered.\(^{36}\)

Like antihistamines, steroids are given far more frequently than adrenaline, again raising concern that they distract from early use of adrenaline.\(^{30–36,42}\) A 2012 Cochrane systematic review concluded that ‘Clinicians should nonetheless be aware of the lack of a strong evidence base for the use of a glucocorticoid for the treatment of anaphylaxis’, and subsequent studies have confirmed the absence of evidence that corticosteroids reduce reaction severity or prevent biphasic reactions.\(^{25,40,42}\)

It is important to note that there are specific scenarios in which corticosteroids may be of benefit: first, anaphylaxis occurring in the context of poorly-controlled asthma; and second, in cases of refractory anaphylaxis (defined as persistence of ABC features despite two appropriate doses of adrenaline). In these cases, the balance of risks and benefits is different and, given the uncertainty in evidence, corticosteroids may be beneficial but should not delay or replace appropriate adrenaline doses when treating anaphylaxis.

### Treatment of refractory anaphylaxis

The 2021 RCUK guideline features a specific algorithm for the treatment of refractory anaphylaxis (Fig 3). There is no established definition of refractory anaphylaxis, so the RCUK has defined it as ‘anaphylaxis requiring ongoing treatment (due to persisting respiratory or cardiovascular symptoms) despite two appropriate
Measurement of mast cell tryptase

Anaphylaxis is a clinical syndrome that can present in a variety of ways. There are several differential diagnoses of anaphylaxis, and measurement of an elevated mast cell tryptase can be very helpful in supporting the diagnosis of anaphylaxis over other alternatives. Tryptase is present in mast cell secretory granules: during anaphylaxis, this is released from the cells and, consequently, there may be a measurable but transient rise in the circulating level. Tryptase measurement is not useful in the initial recognition of anaphylaxis, and measurement must not delay initial treatment and resuscitation.\textsuperscript{52} In view of the transient rise and short half-life, the timing of blood samples is important to demonstrate the rise and fall. A minimum of one sample should be obtained, ideally within 2 hours and no later than 4 hours after onset of symptoms. However, ideally three samples should be taken: the first as soon as feasible (not delaying treatment to take the sample), the second 1–2 hours (but no later than 4 hours) after onset of symptoms and a third at least 24 hours after complete resolution of symptoms. The last of these need not delay discharge, provided follow-up with an allergy clinic is arranged.

Refined guidance regarding duration of observation following anaphylaxis and timing of discharge

Patients who have been treated for suspected anaphylaxis should be observed in a clinical area with facilities for treating life-threatening ABC problems, as some patients experience further symptoms following resolution. This can be either a true biphasic reaction, or due to continued allergen exposure (for example, presence of the allergen in the gut).\textsuperscript{51} In cases of food-induced anaphylaxis, it is advisable for the patient to eat some food at least 1 hour prior to discharge to mitigate against further symptoms (due to allergen absorption in the gut) after leaving hospital.

Biphasic reactions can occur many hours after the initial reaction; published studies report a median of 12 hours (ie 50% of biphasic reactions have occurred by 12 hours after the onset of initial symptoms). The optimal duration of observation is uncertain, and the previous RCUK guideline referred to the NICE 2011 recommendation that patients over 16 years of age be observed for 6–12 hours after onset of initial symptoms, although more recent evidence suggests this may miss over 50% of biphasic reactions in the 5% of patients who experience them.\textsuperscript{26,37,54–56} Fatalities due to biphasic reactions are rare.\textsuperscript{37} Risk factors for biphasic reactions include:

- more severe initial presentation of anaphylaxis
- initial reaction requiring more than one dose of adrenaline
- delay in adrenaline administration (>30–60 minutes from onset)
- previous biphasic reaction.

Consistent with the available evidence and other guidelines, the RCUK guideline recommends a risk-stratified approach to the length of observation after anaphylaxis (Table 2).\textsuperscript{1,25,54} All patients should be reviewed by a senior clinician and be discharged with advice on the symptoms of anaphylaxis and what to do if anaphylaxis occurs, be provided with two adrenaline autoinjectors or have provision of replacements if they have been used, be given a demonstration of how to use the autoinjectors, and be given a written emergency treatment or action plan. All
patients presenting to hospital with anaphylaxis should be referred to a specialist allergy service to investigate the cause and to help prepare the patient to manage future episodes.

Conclusion

The use of adrenaline in the initial treatment of anaphylaxis is universally accepted and has not changed in the updated RCUK guideline. However, the new guideline further emphasises the importance of positioning in the treatment of anaphylaxis, and the need to avoid interventions that might delay adequate and appropriate adrenaline administration. Antihistamines can be used as a third-line treatment to reduce skin involvement, but only after successful treatment of ABC features. Corticosteroids are not helpful and emerging evidence suggests that they might worsen outcomes when used routinely for anaphylaxis; their use is, therefore, limited to the treatment of anaphylaxis in the context of poorly-controlled asthma and refractory anaphylaxis. There is a new treatment algorithm for refractory anaphylaxis, providing an easy reference for settings where this may occur. Finally, there is more nuanced advice regarding observation following anaphylaxis, which takes into account risk factors and circumstances where delayed or recurrent symptoms may be experienced.

Acknowledgements

We are grateful to the following individuals for providing internal review to the updated RCUK anaphylaxis guideline and the updated recommendations. Sophie Farooque, Adam Fox, Graham Roberts and Hazel Gowland (patient advocate); and on behalf of Resuscitation Council UK: Charles Deakin, Joe Fawke, David Gabbott, Matt Griffiths, Andrew Lockey, Ian Maconochie, Jerry Nolan, Gavin Perkins and Sophie Skellett.

Working group membership: Dr Jasmeet Soar, co-chair; Dr Paul J Turner, co-chair; Dr Amy Dodd; Ms Sue Hampshire; Dr Anna Hughes; Dr Nicholas Sargent; and Dr Andrew F Whyte. For affiliations and wider consultation panel membership refer to the full guideline.

Conflicts of interest

Andrew F Whyte is the former chair of the Adult Allergy Group of the British Society for Allergy and Clinical Immunology.

Jasmeet Soar is the co-chair of the Anaphylaxis Working Group of the Resuscitation Council UK; editor of Resuscitation and receives payment from the publisher Elsevier; co-chair of the European Resuscitation Council Advanced Life Support (ALS) Science and Education Committee; and chair of the International Liaison Committee on Resuscitation ALS Task Force.

Paul J Turner is the co-chair of the Anaphylaxis Working Group of the Resuscitation Council UK; former chair of the Paediatric Allergy Group of the British Society for Allergy and Clinical Immunology; chair of the World Allergy Organization Anaphylaxis Committee; supported by a UK Medical Research Council Clinician Scientist award (reference MR/K010468/1) and grants from UK Medical Research Council, National Institute for Health and Care Research / Imperial Biomedical Research Centre, UK Food Standards Agency, End Allergies Together and Jon Moulton Charity Trust; personal fees and nonfinancial support from Aimmune Therapeutics, DBV Technologies and Allergenis; and personal fees and other fees from International Life Sciences Institute Europe and UK Food Standards Agency.

References


Table 2. Duration of observation following anaphylaxis; reproduced with permission from the 2021 Resuscitation Council UK guideline, Emergency treatment of anaphylaxis: Guidelines for healthcare providers

<table>
<thead>
<tr>
<th>Consider fast-track discharge (after 2 hours observation from resolution of anaphylaxis) if all or the following:</th>
<th>A minimum of 6 hours observation after resolution of symptoms recommended if:</th>
<th>Observation for at least 12 hours following resolution of symptoms if any one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good response (within 10–15 minutes) to a single dose of adrenaline given within 30 minutes of onset of reaction. and Complete resolution of symptoms. and The patient already has unused adrenaline auto-injectors (AAI) and has been trained how to use them. and There is adequate supervision following discharge.</td>
<td>Two doses of IM adrenaline needed to treat reaction or Previous biphasic reaction.</td>
<td>Severe reaction requiring &gt;2 doses of adrenaline. or Patient has severe asthma or reaction involved severe respiratory compromise. or Possibility of continuing absorption of allergen eg slow-release medicines. or Patient presents late at night or may not be able to respond to any deterioration. or Patients in areas where access to emergency care is difficult.</td>
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</tbody>
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In all cases, discharge must comply with National Institute for Health and Care Excellence clinical guidance CG134. It may be reasonable for some patients to be discharged after 2 hours, eg following a supervised allergy challenge in a specialist allergy setting. IM = intramuscular.
References


48 Alviani C, Burrell S, Macleod A et al. Anaphylaxis refractory to intramuscular adrenaline during in-hospital food challenges: A case...


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