Resuscitation Council UK

Emergency treatment of anaphylaxis
Guidelines for healthcare providers

Working Group of the Resuscitation Council UK

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5th Floor, Tavistock House North
Tavistock Square
London WC1H 9HR

Tel: 020 7388 4678
Fax: 020 7383 0773
E-mail: enquiries@resus.org.uk
Website: www.resus.org.uk
Registered charity no. 1168914

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Members of the Working Group

Name	Details	Conflict of interest
Dr Paul Turner (Co Chair)	Reader in Paediatric Allergy & Clinical Immunology, National Heart & Lung Institute Imperial College London London, UK E: p.turner@imperial.ac.uk	Chair, Paediatric Allergy Group, British Society for Allergy and Clinical Immunology Chair, World Allergy Organisation Anaphylaxis Committee
Dr Jasmeet Soar (Co Chair)	Consultant in Anaesthetics & Intensive Care Medicine Southmead Hospital Bristol, UK E: jasmeet.soar@nbt.nhs.uk	Executive Committee Member, Resuscitation Council UK
Dr Amy Dodd	Specialty Registrar in Anaesthetics Severn Deanery, UK E: amy.dodd5@nhs.net	No relevant conflict of interest
Sue Hampshire	Director, Clinical & Service Development Resuscitation Council UK London UK E: sue.hampshire@resus.org.uk	No relevant conflict of interest
Dr Anna Hughes	Specialty Registrar in Paediatrics Severn Deanery, UK E: annahughes@nhs.net	No relevant conflict of interest
Dr Nicholas Sargant	Consultant in Paediatric Emergency Medicine & Allergy Bristol Royal Hospital for Children Bristol, UK E: nicholas.sargant@uhbristol.nhs.uk	No relevant conflict of interest
Dr Andrew Whyte	Consultant in Allergy & Immunology Derriford Hospital University Hospitals Plymouth NHS Trust Plymouth UK E: andrew.whyte@nhs.net	Chair of Adult Allergy Group, British Society for Allergy and Clinical Immunology

Members of Consultation Panel:

Charles Deakin	RCUK
Joe Fawke	RCUK
Sophie Farooque	BSACI
Adam T. Fox	BSACI
David Gabbott	RCUK
Hazel Gowland	Patient Advocate
Matt Griffiths	RCUK
Andrew Lockey	RCUK
Ian Maconochie	RCUK
Jerry Nolan	RCUK
Gavin Perkins	RCUK
Graham Roberts	BSACI
Sophie Skellett	RCUK

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Key Recommendations for clinical practice

- Anaphylaxis is a potentially life-threatening allergic reaction.
- Recognise anaphylaxis based on:
  - Sudden onset and rapid progression of symptoms
  - **A**irway and/or **B**reathing and/or **C**irculation problems
  - Skin and/or mucosal changes (flushing, urticaria, angioedema)
  - Exposure to a known allergen for the patient supports the diagnosis.
- Treat life-threatening features, using the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach.
- Give intramuscular (IM) adrenaline early for Airway/Breathing/Circulation problems. Adrenaline is the first-line treatment for anaphylaxis.
  - A single dose of IM adrenaline is well-tolerated and poses minimal risk in the context of an individual having an allergic reaction. If in doubt, give IM adrenaline.
  - Repeat IM adrenaline every 5 minutes if features of anaphylaxis do not resolve.
- Intravenous (IV) adrenaline must only be used in certain specialist settings and only by those skilled and experienced in its use.
  - IV adrenaline infusions form the basis of treatment for refractory anaphylaxis: seek expert help early in patients with anaphylaxis refractory to 2 doses of IM adrenaline.
- Follow the NICE guideline for the assessment and referral of patients suspected to have had anaphylaxis; specifically:
  - All patients should be referred to a specialist allergy clinic.
  - Consider whether to prescribe an adrenaline auto-injector. These are usually indicated in individuals with suspected anaphylaxis to an insect sting or a food which cannot be easily avoided.
  - Individuals prescribed adrenaline auto-injectors must receive training in their use.
- Further research is needed to better identify and manage patients at greatest risk of severe anaphylaxis.
  - Anaphylaxis reactions should be reported at the UK Anaphylaxis Registry (link).
  - Follow guidance for reporting and debriefing of adverse events.

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Summary of changes from previous guideline

This guideline replaces the previous guideline from Resuscitation Council UK: Emergency treatment of anaphylactic reactions - Guidelines for healthcare providers *(originally published January 2008, annotated July 2012 with links to NICE guidance).*[1]

- Intramuscular adrenaline should be given early to treat anaphylaxis.
- Repeat adrenaline every 5 minutes if symptoms of anaphylaxis do not resolve.
- A specific dose of adrenaline is now included for children <6 months of age.
- Increased emphasis on the importance of avoiding sudden changes in posture and maintaining supine/semi-recumbent position during treatment.
- Corticosteroids (e.g. hydrocortisone) are no longer routinely recommended for the emergency treatment of anaphylaxis.
- Antihistamines are considered a third line intervention and are not helpful during emergency treatment.
    - Non-sedating oral antihistamines may be given following stabilisation, in preference to chlorphenamine which can cause sedation and hypotension.
- There are 2 new algorithms:
    - Initial management of anaphylaxis with an emphasis on repeating the dose of adrenaline every 5 minutes.
    - Management of refractory anaphylaxis (defined as anaphylaxis requiring ongoing treatment despite two appropriate doses of IM adrenaline).
- New guidance is offered relating to the duration of observation following anaphylaxis, and timing of discharge.

This updated guideline has been developed according to the GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations (GRADE-ADOLOPMENT).[2] Detailed information can be found online at Resuscitation Council UK website, and links will be included in the text with a red sidebar in the final guidance.

Areas covered by NICE Clinical Guidance CG134 will be highlighted in the text with a pink sidebar in the final guidance, which is a web link to the NICE CG134 guidance web page.

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1. Introduction

1.1 Purpose of this guideline

Anaphylaxis presentations to hospitals in the UK are rising.[3,4] Despite previous guidelines, there remains confusion over the diagnosis, treatment, investigation and follow-up of patients who have anaphylaxis.[5-8]

This guideline replaces the previous guideline from Resuscitation Council UK: Emergency treatment of anaphylactic reactions - Guidelines for healthcare providers (originally published January 2008, annotated July 2012 with links to NICE guidance).[1]

This guideline provides:

- An updated consensus about the recognition and treatment of anaphylaxis in healthcare settings.
- A focus on the treatments that a patient with anaphylaxis should receive, that are relevant to all healthcare providers.
- Recommendations for treatment that are easy to implement, and that will be appropriate for most anaphylaxis reactions.
- New guidance on the treatment of refractory anaphylaxis.

There are no randomised controlled clinical trials in humans providing unequivocal evidence for the optimal treatment of anaphylaxis; such evidence is unlikely to be forthcoming.[9,10] Nonetheless, the evidence-base for specific management strategies has increased and systematic reviews of the limited evidence have been published.

This guideline does not cover every possible scenario involving anaphylaxis; the guidance has been written to be as simple as possible to enable improved teaching, learning and implementation. Improved implementation should reduce harms and deaths from anaphylaxis.

1.2 Scope of this guideline

This guideline is for healthcare providers who are expected to manage anaphylaxis during their usual clinical role (e.g. doctors, nurses, paramedics) working in the hospital or out-of-hospital setting.

There is considerable variation and overlap between the skills and knowledge of different healthcare providers who are expected to treat anaphylaxis. We have therefore deliberately not developed guidelines for specific groups of healthcare providers.

This guideline does not expect individuals to obtain intravenous access in an emergency if this is not part of their usual role. Any extra skills specifically for the treatment of a patient with anaphylaxis should be reasonably easy to learn, remember and implement (e.g., intramuscular (IM) injection of adrenaline).

The Association of Anaesthetists (https://anaesthetists.org/)[11] and the British Society for Allergy and Clinical Immunology (https://www.bsaci.org/)[12] have published specific guidance for the treatment of anaphylaxis associated with anaesthesia. Additional resources relating to the management and investigation of peri-operative anaphylaxis - including referral

pathways - can be found at the National Audit Project on Perioperative Anaphylaxis (NAP6) website.[13]

There is also specific guidance from the UK Departments of Health and Social Care for managing anaphylaxis in schools and other educational settings.[14]

The treatment of a patient having anaphylaxis in any setting is broadly the same for children and adults.[9,10] Minor differences are highlighted.

1.3 Key points

Treatment of anaphylaxis should be based on general life support principles:

- Call for help early.
- Use the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach to recognise and treat problems. Treat the greatest threat to life first.
- Give intramuscular (IM) adrenaline* to treat Airway/Breathing/Circulation problems.
- Initial treatment should not be delayed by a lack of a complete history or definite diagnosis.
- Repeat IM adrenaline every 5 minutes if features of anaphylaxis do not resolve.

Patients having anaphylaxis in any setting should expect the following as a minimum:

- Recognition that they are seriously unwell.
- An early call for help.
- Initial assessment and treatment based on an ABCDE approach.
- Prompt treatment with IM adrenaline*.
- Investigation and follow-up by an allergy specialist.

*Both IM and IV routes are recommended for the treatment of peri-operative anaphylaxis. IV adrenaline should only be used by those with experience in the use and titration of vasopressors in their normal clinical practice, and with cardiac monitoring in place. See Section 5.1.2 for more information.

1.4 Methods

The Executive Committee of Resuscitation Council UK appointed two co-chairs who subsequently formed a working group to identify key areas that require updating, based on review of the previous guideline, new international evidence-based guidelines and a database of frequently asked questions.

The group initially met in February 2020. The updated guideline was developed according to the GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations (GRADE-ADOLOPMENT).2 The EtD tables are available on the Resuscitation Council UK website: https://www.resus.org.uk/sites/default/files/2020-12/EtD.Summary.pdf.
Experts from outside the group were consulted for specific issues.

A draft version of the guideline was made available for comment on the Resuscitation Council UK website (www.resus.org.uk) between xxx and xxx December 2020. The document was accessed xxxx times during this period. The feedback was reviewed at a December working group meeting and the document updated. This guideline was made available on the Resuscitation Council UK website in xxx.

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2. Anaphylaxis

2.1 Definition of anaphylaxis

The World Allergy Organisation (WAO) Anaphylaxis Committee has proposed the following broad definition, [9] which is aligned with the previous RCUK definition: [1]

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death.

Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present.

Anaphylaxis is a clinical diagnosis; a precise definition is not important for the emergency treatment of anaphylaxis.

2.2 Clinical criteria for anaphylaxis

The following clinical criteria have been proposed by the WAO for the diagnosis of anaphylaxis (Table 1):

Anaphylaxis is highly likely when any <u>one</u> of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Hypotension or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens 2. Acute onset of hypotension, bronchospasm† or laryngeal involvement‡ after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Table 1: Clinical criteria for the diagnosis of anaphylaxis[14]
†Bronchospasm can occur due to allergen exposure via inhalation, however such reactions would not normally warrant treatment as anaphylaxis; ‡Laryngeal symptoms include: stridor, vocal changes, painful swallowing (odynophagia).

2.3 Epidemiology

Incidence rate and lifetime prevalence
A recent systematic review undertaken by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy & Anaphylaxis Group estimated the incidence for all-cause anaphylaxis in Europe to be 1.5 to 7.9 per 100,000 person-years.[15] The same data indicated that an estimated 1 in 300 people will experience anaphylaxis at some point in their lives. Notably, these figures are somewhat lower than those reported in the USA, which may reflect differences in diagnostic criteria for anaphylaxis between Europe and North America.

Mortality
The overall prognosis of anaphylaxis is good, with a case fatality rate of under 1% in those presenting to hospitals in the UK,[3] and a mortality rate within the general population of less than 1 per 1,000,000 per annum. [16] The risk of death may be increased in those with pre-existing asthma, particularly if this is poorly controlled or treatment with adrenaline is delayed. [17]

There are approximately 20 deaths reported each year due to anaphylaxis in the UK, although this may be a significant underestimate.[3] Around 10 of these fatalities are related to food-anaphylaxis.

Triggers
Anaphylaxis can be caused by a broad range of triggers, but the most common allergens identified include food, drugs and venom.[3] There are clear age-distributions for both hospitalisations and fatalities, that vary by trigger. **Food is the most common cause of anaphylaxis in young people**. Preschool-aged children have the highest rate of hospitalisation due to food-anaphylaxis, but a disproportionately low rate of fatal outcomes. **The greatest risk from fatal food allergy appears to be in teenagers and adults up to age 30 years.** In contrast, fatal anaphylaxis due to drugs is rare in children, and peaks in the elderly (presumably due to polypharmacy in this age group) (Figure 1).

Hospital Admissions due to anaphylaxis **Fatalities due to anaphylaxis**

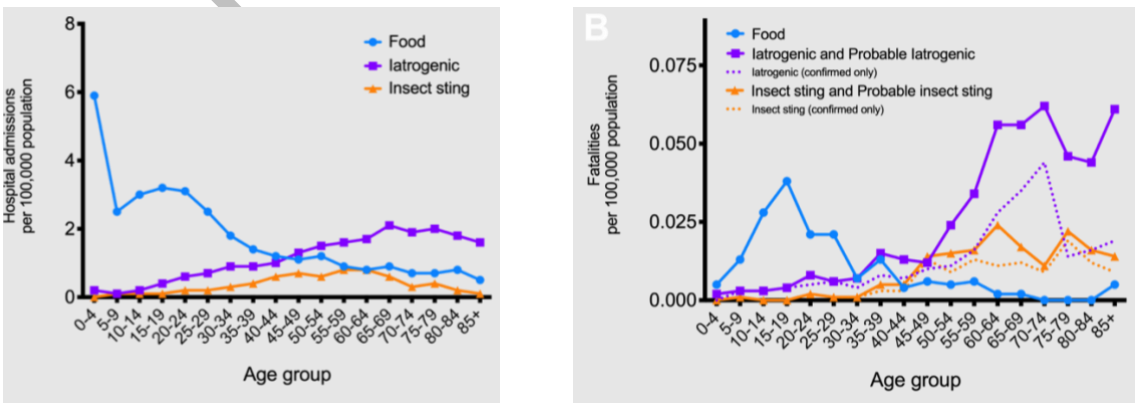

Figure 1: Age distribution for admissions (left) and fatalities (right) in the UK (1992-2012) by triggering agent (food, iatrogenic causes, and insect stings)[3]

Virtually any food or class of drug can be implicated as a cause of anaphylaxis, although the classes of foods and drugs responsible for the majority of reactions are well described (see Table 2). In around one third of cases, the specific food or drug trigger may not be evident.[3]

A significant number of cases of anaphylaxis are termed "idiopathic", either because a trigger cannot be identified or a non-immune mechanism is relevant. Nonetheless, the acute management of these cases is the same.

	Hospital admission due to anaphylaxis	Fatal anaphylaxis
Foods	35% of admissions[4] Commonest triggers: • Peanut • Tree nuts • Cow's milk (children)	19% of deaths[3] Commonest triggers: [4] • Peanut & Tree nuts (50%) • Cow's milk (11% of total, 26% in children)

Medication	17% of admissions[3]
	
	Commonest triggers are antibiotics and chemotherapeutic agents
	
	Commonest triggers in peri-operative setting: [18]
	• Antibiotics (47%)
	  ○ Co-amoxiclav (23%)
	  ○ Teicoplanin (18%)
	• Neuromuscular blocking agents (NMBAs) (33%)
	• Chlorhexidine (9%)
		39% of deaths[3]
		
		Commonest triggers:[19]
		• NMBAs (32%)
		• Antibiotics (27%)
		  ○ Penicillins (11%)
		  ○ Cephalosporins (12%)
		• Contrast media (11%)
		• NSAIDs (6%)

Insect stings	6.5% of admissions[3]	14% of deaths[3]

Table 2. Common causes of anaphylaxis (non-fatal and fatal) in the UK

Risk of recurrence

In an individual with prior anaphylaxis, the risk of another anaphylaxis in the future has been estimated at approximately 1 in 12 per year in the UK context.[20] Two studies undertaken in the USA reported a recurrence rate of 2.6-3.6 per 100 person-years.[21,22] Even in children admitted to paediatric ICU with anaphylaxis, there was a recurrence rate of 1.4 per 100 person-years.[23] These data reinforce the importance of specialist allergy investigation and follow-up after anaphylaxis.

Trends over time

An analysis of UK hospitalisations due to anaphylaxis reported a 174% increase in admissions since 1998, from 4.2 to 11.5 admissions per 100,000 population. [4] Around 30% of these are due to food-induced anaphylaxis. Of note, while hospital admissions have increased irrespective of cause, anaphylaxis fatalities have remained stable over the same time period (Figure 2).

Hospital Admissions due to anaphylaxis **Fatalities**

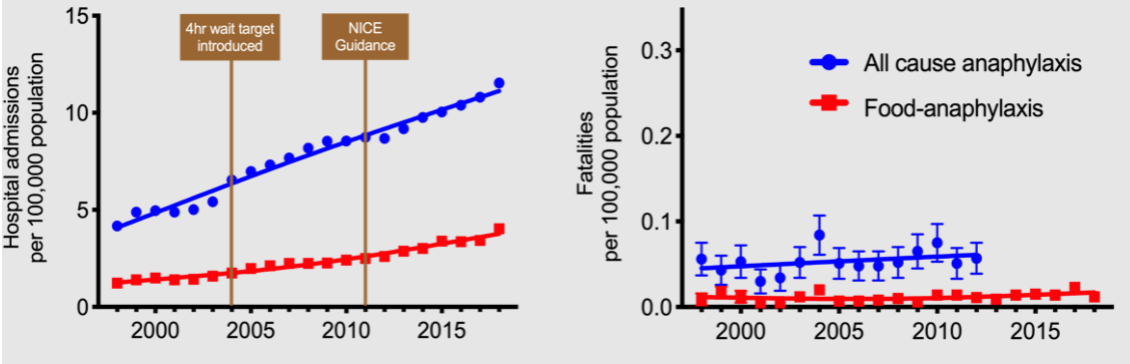

Figure 2: Time trends in UK hospital admissions (left) and fatalities (right) due to anaphylaxis (all cause anaphylaxis and food as the identified trigger), 1998-2018. [4] Vertical bars represent standard error of the mean.

Time course for fatal anaphylaxis

Where anaphylaxis is fatal, death usually occurs very soon after exposure to the trigger. Fatal food reactions typically cause respiratory arrest after ~30 minutes; insect stings cause collapse from shock after 10–15 minutes; and deaths caused by intravenous medication occur most commonly within five minutes. While rare, most cardiorespiratory arrests occur within 2-4 hours from initial allergen exposure (Figure 3). [24]

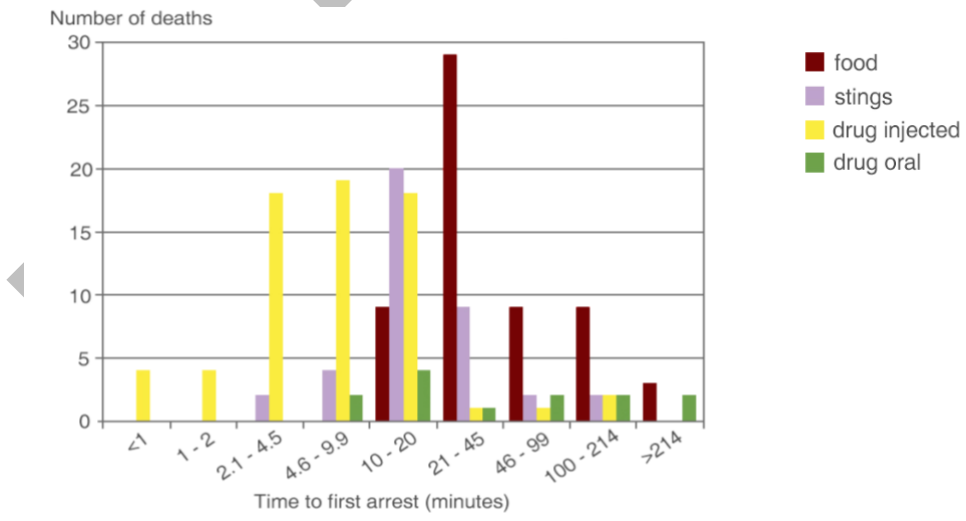

Figure 3: Time to cardiac arrest following exposure to triggering agent [24]

2.4 Pathophysiology of anaphylaxis

In anaphylaxis, the activation of multiple inflammatory pathways causing Airway/Breathing/Circulation problems:

- Tissue oedema and smooth muscle contraction in the airways (causing bronchospasm and wheeze). This is the most common presentation for food-induced anaphylaxis.
- Fluid extravasation (tissue oedema, hypovolemia), and a profound reduction in venous tone.[25-27]
    - If severe, this mix of hypovolemic and distributive shock cannot be overcome by compensatory mechanisms and combine to cause reduced blood flow back to the heart and an empty ventricle.[26]
- Depressed myocardial function has also been reported, which can cause cardiogenic shock as well. Electrocardiographic (ECG) changes have been noted, either due to the release of mediators which can cause arrhythmia or a reduction in coronary perfusion.[27]
- Fluid redistribution into the bowel and smooth muscle contraction (resulting in abdominal and pelvic cramps).[28]

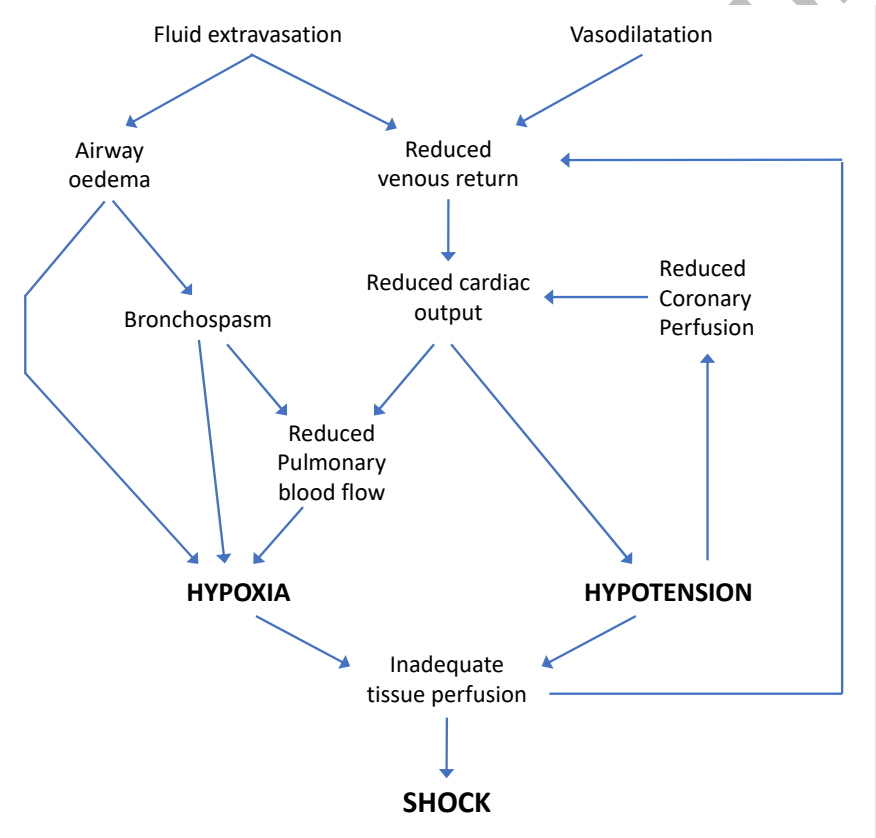

Figure 4: Physiological mechanisms responsible for anaphylactic shock

In a landmark paper, Fisher described 205 patients with peri-operative anaphylaxis, many of whom had central venous monitoring in situ.[29] He reported:

- Low right-filling pressures in all patients without cardiac disease; in 9 of 11 patients with cardiac disease, despite observing elevated pressures, these patients appeared to need volume expansion to achieve a stable blood pressure.

- Increases in haematocrit in 22 patients were indicative of **extravasation of up to 35% of circulating blood volume within 10 minutes of reaction onset**.

These data emphasise the need for aggressive fluid resuscitation in anaphylactic shock.

Changes in posture – from a supine to upright or semi-recumbent (sitting upright) position – have been associated with cardiovascular collapse and fatal outcome during anaphylaxis.[30,31] The change in posture reduces venous return to the heart, this can compromise myocardial perfusion and lead to a further reduction in cardiac output.

Keeping a patient with cardiovascular instability flat or with the legs raised will maximize venous return to the heart and is therefore a key component of the initial response to anaphylaxis (see section 4.3). Pregnant patients should lie on their left side to prevent aortocaval compression, if necessary, with the bed in a head-down position (see Section 4.7).

3. Recognition of anaphylaxis

Anaphylaxis is likely if a patient who is exposed to a trigger (allergen) develops a sudden illness (usually within minutes of exposure) with rapidly progressing skin changes and potentially life-threatening airway and/or breathing and/or circulation problems. The reaction is usually unexpected.

Many patients with anaphylaxis are not given the correct treatment because of failure to recognise anaphylaxis.[6-8,32] Similarly, prominent skin features (including facial swelling and generalised urticaria) may be misdiagnosed as anaphylaxis.[33,34]

A single set of criteria will not identify all anaphylaxis reactions. There is a range of signs and symptoms, none of which are entirely specific for anaphylaxis; however, certain combinations of signs make the diagnosis of anaphylaxis more likely.[35] Follow an ABCDE approach and treat life-threatening problems as they are recognised.[36] Guidelines for the treatment of anaphylaxis must take into account some inevitable diagnostic errors, with an emphasis on the need for safety.

3.1 Anaphylaxis is likely when all of the following 3 criteria are met:

- Sudden onset and rapid progression of symptoms
- Airway and/or Breathing and/or Circulation problems
- Skin and/or mucosal changes (flushing, urticaria, angioedema)

The following supports the diagnosis:

- Exposure to a known allergen for the patient

Remember:

- Skin or mucosal changes alone are not a sign of anaphylaxis
- **Skin and mucosal changes can be subtle or absent in up to 20% of reactions** (some patients can have only bronchospasm or a decrease in blood pressure (i.e., a **C**irculation problem) initially)
- There can also be gastrointestinal symptoms (e.g. vomiting abdominal pain, incontinence). These are more significant where the route of exposure is non-oral e.g. venom sting.

Confusion may arise because some patients have systemic reactions that are not anaphylaxis. Generalised urticaria, angioedema, and rhinitis are not considered to be anaphylaxis because life-threatening features – an **A**irway problem, respiratory difficulty (**B**reathing problem) and hypotension (**C**irculation problem) – are not present. However, **if in doubt, give IM adrenaline and seek senior help**.

3.2 Sudden onset and rapid progression of symptoms

- The patient will often feel and look unwell.
- Most reactions develop quickly over minutes.
- The time of onset of anaphylaxis depends on the trigger. Allergens given by a parenteral route (e.g. intravenous drug, intramuscular injection, insect sting) cause a more rapid onset of symptoms, than reactions due to an ingested food (Figure 3).[24]
- The patient is usually anxious and can experience a "sense of impending doom".[14]

3.3 Airway / Breathing / Circulation problems

Patients can have either an A or B or C problem, or any combination. Use the ABCDE approach to recognise these and treat early.

Airway problems:

- Airway swelling, e.g. throat and tongue swelling (pharyngeal/laryngeal oedema). The patient has difficulty in breathing and/or swallowing and may complain that their throat is closing up.
- Hoarse voice.
- Stridor (a high-pitched inspiratory noise caused by upper airway obstruction).

Breathing problems:

- Shortness of breath – increased respiratory rate.
- Wheeze and/or persistent cough.
- Patient becoming tired with the effort of breathing.
- Confusion caused by hypoxia.
- Cyanosis (mucous membranes appear blue) – this is usually a late sign.
- Respiratory arrest.

Respiratory presentations can vary from anaphylaxis with mild bronchospasm to life-threatening asthma with no other features to suggest anaphylaxis.[37] Anaphylaxis can present primarily as respiratory arrest.[17,19,24] Consider anaphylaxis in a person with sudden onset breathing difficulties, especially if known to be allergic to a food or insect sting.

Circulation problems:

- Signs of shock – pale, clammy.
- Significant increase in heart rate (tachycardia).
- Low blood pressure (hypotension) – feeling faint (dizziness), collapse.
- Decreased conscious level or loss of consciousness.
- Anaphylaxis can cause myocardial ischaemia and electrocardiograph (ECG) changes,[29] even in individuals with normal coronary arteries.[38]
- Cardiac arrest.

Circulation problems (often referred to as anaphylactic shock) can be caused by direct myocardial depression, vasodilation and capillary leak, and loss of fluid from the circulation. Characteristically, this results in a compensatory tachycardia. Bradycardia (a slow pulse) is usually a late feature, often preceding cardiac arrest.[27]

In a study of 21 healthy adults with anaphylaxis to insect venom, an initial tachycardia was followed by a relative bradycardia which occurred with the onset of hypotension.[39] This may have been due to an inability to further compensate for the fall in blood pressure. Both bradycardia and tachycardia have been reported during peri-operative anaphylaxis, although tachycardia is more common.[18,26,27]

The above Airway, Breathing and Circulation problems can all alter the patient's neurological status (**Disability problems**) because of decreased brain perfusion or the effect of local allergic mediators in the CNS. There may be confusion, agitation and loss of consciousness.

Patients can also have gastro-intestinal symptoms (abdominal pain, incontinence, vomiting). These symptoms are more likely to indicate anaphylaxis in the context of reactions due to envenomation or the parenteral administration of medicines.

3.4 Skin and/or mucosal changes

These are assessed as part of the **Exposure** when using the ABCDE approach.

- These are often the first feature of allergic reactions and present in over 80% of anaphylaxis.[35]
- They can be subtle (e.g. patchy erythema) or dramatic (generalised rash).
- They may involve just the skin, the mucosal membranes (e.g. lips), or both.
- There may be urticaria (also called hives, nettle rash, wheals or welts), which can appear anywhere on the body. Wheals may be pale, pink or red, can be different shapes and sizes, and are often surrounded by a red flare. They are usually itchy.
- Angioedema involves swelling of deeper tissues, most commonly in the eyelids and lips, and sometimes the tongue and in the throat.

Although skin changes can be worrying or distressing for patients and those treating them, skin changes without life-threatening airway, breathing or circulation problems are not anaphylaxis. Reassuringly, most patients who present with skin changes caused by an allergic reaction do not go on to develop anaphylaxis.

3.5 Differential diagnosis

- Following an ABCDE approach will help with treating the differential diagnoses.
- In all of the circumstances below, IM adrenaline is unlikely to cause harm and might be clinically useful.

Life-threatening conditions:

- Sometimes anaphylaxis can present with symptoms and signs that are very similar to life-threatening asthma – this is most common in children.
- A low blood pressure (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) – this can occur in the context of non-anaphylaxis allergic reactions.
- Panic attack.
- Breath-holding episode in a child.
- Idiopathic (non-allergic) urticaria or angioedema.

There can be confusion between anaphylaxis and a panic attack. Patients with prior anaphylaxis may be prone to panic attacks if they think they have been re-exposed to the allergen that caused a previous reaction. The sense of impending doom and breathlessness leading to hyperventilation are symptoms that can resemble anaphylaxis. Sometimes, there may be flushing, or blotchy skin associated with anxiety adding to the diagnostic difficulty.

Diagnostic difficulty may also occur with vasovagal attacks after immunisation procedures, but the absence of rash, breathing difficulties, and swelling are useful distinguishing features, as is the slow pulse of a vasovagal attack (whereas anaphylaxis usually occurs with a tachycardia). Fainting will usually respond to lying the patient down and raising the legs.

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4. Initial treatment of anaphylaxis

Use an ABCDE approach to recognise and treat anaphylaxis. Treat life-threatening problems as you find them. The basic principles of treatment are the same for all age groups.

4.1 The specific treatment of anaphylaxis depends on:

1. Location.
2. Training and skills of rescuers.
3. Number of responders.
4. Equipment and drugs available.

Location
Treating a patient with anaphylaxis in the community will not be the same as in an acute hospital. Out of hospital, seek advice by dialling 999 for ambulance support.

Training of rescuers
All clinical staff should be able to call for help and initiate treatment in a patient with anaphylaxis. Public Health Agencies recommends that staff who give immunisations should have annual updates in the treatment of anaphylaxis.[40]

Number of responders
A single responder must always ensure that help is coming. If there are several rescuers, several actions can be undertaken simultaneously.

Equipment and drugs available
Resuscitation equipment and drugs (at the minimum, access to 1mg/ml (1:1000) adrenaline) to help with the rapid resuscitation of a patient with anaphylaxis must be immediately available in all clinical settings. Clinical staff should be familiar with the equipment and drugs they have available and should check them regularly.

All patients who have anaphylaxis must be monitored (pulse oximetry, non-invasive blood pressure, 3-lead ECG) as soon as possible. Monitoring must be supervised by an individual who is skilled at interpreting and responding to any changes.

4.2 Patients with anaphylaxis in any setting should expect the following as a minimum:

1. Recognition that they are seriously unwell.
2. An early call for help.
3. Initial assessment and treatments based on an ABCDE approach.
4. Prompt treatment with intramuscular adrenaline.
5. Investigation and follow-up by an allergy specialist.

4.3 Patient positioning

All patients should be placed in a comfortable position. The following factors should be considered:

- Fatality can occur within minutes if a patient stands, walks or sits up suddenly. Patients must NOT walk or stand during acute reactions. Use caution when transferring patients who have been stabilised.

- Patients with Airway and Breathing problems may prefer to sit up as this will make breathing easier.

- Lying flat with or without leg elevation is helpful for patients with a low blood pressure (Circulation problem).

- Patients who are breathing normally and unconscious should be placed on their side (recovery position). Monitor breathing continuously and prepare to intervene if this changes.

- Pregnant patients should lie on their left side to prevent aortocaval compression.[41] See section 4.7 for further guidance.

4.4 Remove the trigger if possible

- Stop any drug suspected of causing anaphylaxis (e.g. a drug infusion, blood products).
- Remove the stinger after a bee sting. Early removal is more important than the method of removal.[42]
- Attempts to make the patient vomit are NOT recommended.
- Do not delay definitive treatment if removing the trigger is not feasible.

4.5 Cardiorespiratory arrest during anaphylaxis

- Recognise cardiorespiratory arrest has occurred if the person becomes unresponsive or unconscious, and breathing is absent or abnormal.
- Start cardiopulmonary resuscitation (CPR) immediately and follow current guidelines.[36] Good quality CPR with minimal interruption for other interventions improves the chances of survival from cardiac arrest.
- Rescuers should ensure that help is on its way, as early advanced life support is essential.

- Once cardiac arrest has occurred, absorption of adrenaline given by the intramuscular route will not be reliable and attempts to give it may interrupt CPR. Use doses of intravenous/intraosseous (IV/IO) adrenaline recommended in advanced life support guidelines.
- Prolonged resuscitation may be successful (as with hypothermia) – see section 6 on 'Refractory Anaphylaxis'.

4.6 Anaphylaxis algorithm

The key steps for the initial treatment of anaphylaxis are shown in the algorithm (Figure 5) on the next page.

4.7 Anaphylaxis during pregnancy

The medical management of anaphylaxis during pregnancy is similar to the non-pregnant patient. Manoeuvres are required from around 20 weeks gestation (when the uterus is palpable at or above the umbilicus) if the mother has to remain on her back, to reduce compression of the inferior vena cava (IVC) and abdominal aorta by the pregnant uterus.[41]

- Pregnant patients should lie on their left side to prevent aortocaval compression
- If the mother is breathing normally with a cardiac output, then maximal venous return is achieved in the full lateral (recovery) position. She can be then be placed in a head-down position instead of lifting the legs.
- If she is placed supine in order to manage the airway or perform CPR then the uterus must be displaced manually to the left with one or two hands. A tilt can be performed if she is on a firm surface e.g. operating table.
- If anaphylaxis is severe and refractory to treatment, consideration should be given to an early peri-arrest caesarean section.[43]

MANAGEMENT OF ANAPHYLAXIS IN THE VACCINATION SETTING

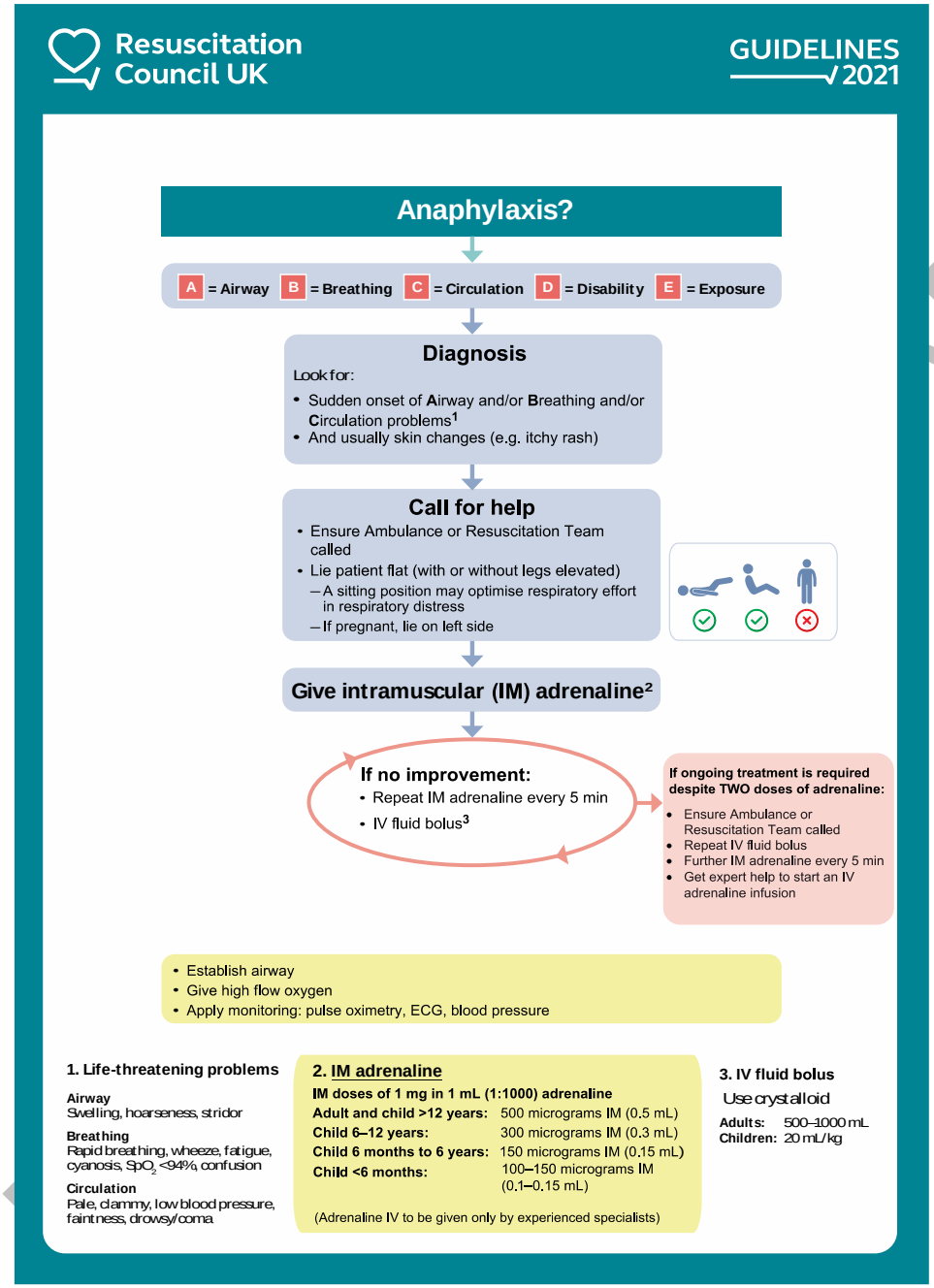

Figure 5. Anaphylaxis algorithm

5. Drugs used in the initial treatment of anaphylaxis

5.1 Adrenaline (Epinephrine)

- Intramuscular adrenaline is the first-line treatment for anaphylaxis (even if intravenous access is available).
- A single dose of IM adrenaline is well-tolerated and poses minimal risk in the context of an individual having an allergic reaction.
- If features of anaphylaxis persist despite 2 doses of IM adrenaline, follow the refractory anaphylaxis algorithm (see section 6) and start an adrenaline infusion with expert support.

Adrenaline is the most important drug for the treatment of anaphylaxis.[9,10] Although there are no randomised controlled trials (RCTs), evidence from observational data, clinical experience and animal models support its use to improve bronchoconstriction and restore adequate tissue oxygenation.

As an alpha-receptor agonist, adrenaline reverses peripheral vasodilation and reduces tissue oedema. Its beta-receptor activity dilates the bronchial airways, increases the force of myocardial contraction, and suppresses histamine and leukotriene release. Adrenaline also acts directly on beta-2 adrenergic receptors on mast cells to inhibit activation,[44-46] so early adrenaline may attenuate the severity of IgE-mediated allergic reactions.

Adrenaline seems to work best when given early after the onset of anaphylaxis symptoms.[47] Delayed administration is associated with protracted reactions, hypotension and fatal outcomes.[48,49] However, adrenaline – particularly via the intravenous route – is not without risk.[50,.51] Adverse effects are extremely rare with correct doses injected by the intramuscular (IM) route.[51] Rarely, complications (e.g. myocardial ischaemia) have been reported, but there is uncertainty about whether these were due to the allergic reaction itself, or the adrenaline used to treat it.

Difficulties can arise if the clinical picture is evolving when the patient is first assessed. Adrenaline should be given to all patients with life-threatening features i.e. evidence of **A**irway / **B**reathing / **C**irculatory involvement. If these features are absent but there are other features of a systemic allergic reaction, the patient needs careful observation and appropriate symptomatic treatment using the ABCDE approach.

Adrenaline must be readily available in clinical areas where anaphylaxis could occur. This includes out-of-hospital settings e.g. where immunisations might be administered.[40]

5.1.1 Intramuscular (IM) adrenaline (give as soon as possible)

- **Intramuscular adrenaline is the first-line treatment for anaphylaxis in all healthcare settings.**

The IM route has several benefits:

- There is a greater margin of safety.
- It does not require intravenous access.
- The IM route is easier to learn.

Attach monitoring (pulse, blood pressure, ECG, pulse oximetry) as soon as possible: this will help assess the patient's response to adrenaline.

The best site for IM injection is the anterolateral aspect of the middle third of the thigh.[52] The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into muscle (See Appendix 2 for guidance regarding needle length and IM injection technique).[4]

The subcutaneous or inhaled routes for adrenaline are not recommended for the treatment of anaphylaxis, because they are less effective.[49,52-54]

Adrenaline IM dose – adults

0.5 mg (500 micrograms) IM = 0.5 mL of 1mg/ml (1:1000) adrenaline

Adrenaline IM dose – children

The scientific basis for the recommended doses is weak. The recommended doses are based on what is considered to be safe and practical to draw up and inject in an emergency.[48]

(The equivalent volume of 1mg/ml adrenaline is shown in brackets)

> 12 years:	500 micrograms IM (0.5 mL) i.e. same as adult dose
	300 micrograms (0.3 mL) if child is small or prepubertal
6 – 12 years:	300 micrograms IM (0.3 mL)
6 months – 6 years:	150 micrograms IM (0.15 mL)
< 6 months:	100-150 micrograms IM (0.1 to 0.15 mL)

Repeat the IM adrenaline dose if there is no improvement in the patient's condition. Further doses should be given at about 5-minute intervals, depending on the patient's response. There is large inter-individual variability in the response to adrenaline.

If anaphylaxis symptoms persist despite 2 doses of adrenaline, follow the algorithm for refractory anaphylaxis (Section 6).

Pallor can occur following adrenaline (due to vasoconstriction). This might be misinterpreted as ongoing cardiovascular compromise or anaphylaxis and can increase the risk of adrenaline overdose. **This is a particular concern in small children, who may remain pale following 2-3 doses of adrenalin**e.[55] A significantly raised blood pressure may be a key indicator of adrenaline overdose.[56]

Measure vital signs (respiratory rate, oxygen saturations, pulse, blood pressure, level of consciousness) **and auscultate for wheeze to monitor the effect of treatment and assess if further doses of adrenaline are required.**

5.1.2 Intravenous (IV) adrenaline (for specialist use only)

The intramuscular (IM) route for adrenaline is the route of choice for the vast majority of healthcare providers. There is a much greater risk of causing harmful side effects when using IV adrenaline due to dilution errors or incorrect dosing.[33,34,50-52] Excessive doses of

adrenaline, particularly by the IV route, can cause tachyarrhythmias, severe hypertension, myocardial infarction and stroke. Fatalities have occurred in the UK due to the inappropriate use of intravenous adrenaline to treat allergic (but non-anaphylaxis) reactions.[34]

Healthcare providers with experience in the use and titration of vasopressors in their normal clinical practice (e.g. anaesthetists, emergency physicians, intensive care doctors) may choose to administer adrenaline by the intravenous route. Both IM and IV routes are recommended in treating perioperative anaphylaxis,[11,13] although **international guidelines recommend IM adrenaline for first-line treatment of anaphylaxis in ALL settings.**

Many healthcare providers will have given IV adrenaline as part of resuscitating a patient in cardiac arrest. **This alone is insufficient experience to use IV adrenaline for the treatment of anaphylaxis.** In patients with a spontaneous circulation, intravenous adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias, and myocardial infarction.

More information about the use of intravenous adrenaline can be found in Section 6 (refractory anaphylaxis).

5.1.3 Nebulised adrenaline

Nebulised adrenaline may be effective as an adjunct to treat upper airways obstruction caused by laryngeal oedema, but only after treatment with IM (or IV) adrenaline and not as an alternative.[10] Recommended doses are 5ml of 1mg/ml (1:1000) adrenaline.

5.1.4 Adrenaline in special populations

Dose-adjustments are no longer recommended in specific patient groups, for example in patients taking tricyclic antidepressants.

5.1.5 Adrenaline auto-injector devices

Auto-injectors are often prescribed to patients at risk of anaphylaxis for self-injection in the community. Depending on the brand, they are available in three doses of adrenaline: 150 micrograms, 300 micrograms and 500 micrograms (0.5mg). Healthcare professionals should be familiar with their use.

In all healthcare settings, giving adrenaline by needle/ampoule/syringe is preferred, since auto-injectors will not deliver an age/weight-appropriate dose in most patients. In addition, concerns have been raised as to whether auto-injectors will deliver an intramuscular dose in some patients.[57] If the only available adrenaline preparation is an auto-injector, then this can be used in the first instance.

Auto-injectors are not recommended in healthcare settings for administration of adrenaline in patients needing more than 1 dose of adrenaline. If further doses of adrenaline are needed, give these by needle/ampoule/syringe.

5.2 Oxygen (give as soon as available)

Initially, give the highest concentration of oxygen possible, using a mask with an oxygen reservoir.

As soon as is feasible, adjust the inspired oxygen concentration to achieve an oxygen saturation of 94-98% (in patients at risk of hypercapnic respiratory failure, consider a target range of 88-92%).[58] If the patient has been intubated, ventilate the lungs with appropriate concentration of oxygen. Use blood gas measurements to guide further oxygen therapy.

5.3 Intravenous Fluids

In the presence of hypotension/shock, or poor response to initial adrenaline:

- Secure intravenous access and give a rapid IV fluid bolus (20 mL/kg in a child or 500-1000 mL in an adult) and monitor the response.
  - > Use non-glucose-containing crystalloids that contain sodium in the range 130–154 mmol/l (e.g. 0.9% sodium chloride, Hartmann's) for initial resuscitation.[59]
- Give further fluids as necessary. A large volume (up to 3-5 litres) may be needed for severe anaphylactic shock. Use a non-glucose-containing crystalloid (e.g. Hartmann's and Plasma-Lyte®) rather than 0.9% sodium chloride to reduce the risk of hyperchloraemia.
- Give fluids via the intraosseous route if intravenous access is delayed.

Ensure IM adrenaline is administered every 5 minutes while attempting to secure intravenous or intraosseous access.

Up to one third of the circulating volume may be lost through extravasation and fluid redistribution during anaphylaxis,[29] causing hypotension and shock.[26,27] Anaphylaxis causes vasodilation, which can mask the presence of poor tissue perfusion which would normally be a presenting sign of circulatory shock. Venous return is reduced in anaphylaxis, even in the absence of apparent cardiovascular compromise.[25]

Colloid solutions are not recommended and are a recognised cause of anaphylaxis. Stop a colloid infusion in any patient presenting with symptoms of anaphylaxis.[60]

5.4 Antihistamines

- **Antihistamines are not recommended for the treatment of acute anaphylaxis.**

The evidence to support the use of antihistamines is weak.[9,10,56,61] They are of no benefit in treating life-threatening symptoms of anaphylaxis, and their administration may delay more appropriate interventions such as further doses of adrenaline.

Antihistamines must not be given preferentially to adrenaline: in the event of ongoing symptoms of anaphylaxis, give further IM adrenaline every 5 minutes and seek expert advice. Anecdotal evidence suggests that adrenaline is very effective in treating cutaneous allergic symptoms.

Antihistamines may be helpful in alleviating cutaneous symptoms but should only be given after the patient has been stabilised. In this context, **use a non-sedating oral antihistamine**, such as cetirizine.[9,56] Recommended doses are shown in Table 3. If the oral route is not possible, chlorphenamine can be given by intravenous or intramuscular injection, but note that H1-antihistamines can cause hypotension when given as an IV bolus.[62]

There is no evidence to support the routine use of an H_2-antihistamine (e.g. ranitidine) to treat anaphylaxis.[9,10]

Age	Dose of oral cetirizine
< 2 years	250 micrograms/kg
2–6 years	2.5–5mg
6–11 years	5–10mg
12+ years	10–20mg
Adults	10–20mg

Table 2. Recommend doses for oral cetirizine for an allergic reaction

5.5 Steroids

- **The routine administration of corticosteroids is NOT recommended.**
- Consider giving steroids after initial resuscitation for refractory reactions or ongoing asthma/shock (conditional recommendation). Steroids must not be given preferentially to adrenaline.

There is no strong evidence that corticosteroids help shorten protracted symptoms or prevent biphasic reactions.[63-66] In asthma, early corticosteroid treatment may be beneficial in adults and children.[67,68] However, for anaphylaxis, early administration of steroids is associated with an increased risk of intensive care admission, even after adjusting for severity of initial presenting symptoms.[64]

Oral corticosteroids may be indicated where an acute asthma exacerbation may have contributed to the severity of anaphylaxis. Steroids should be given via the oral route where possible. Refer to the (c)BNF for appropriate dosing information.

5.6 Other drugs

Bronchodilators
The presenting symptoms and signs of severe anaphylaxis and life-threatening asthma can be the same. Individuals presenting with asthma in the context of possible exposure to a known allergen (and thus anaphylaxis is a differential diagnosis) should receive treatment with intramuscular adrenaline.

In addition to the drugs listed above, consider further inhaled bronchodilator therapy with salbutamol and/or ipratropium. There are no data to support the choice of one bronchodilator above another in the treatment of anaphylaxis.[10]

Further guidance on the management of bronchospasm in severe asthma can be found in the British Thoracic Society – SIGN asthma guidelines (www.brit-thoracic.org.uk).

Resuscitation Council UK

Cardiac drugs

Adrenaline remains the first line vasopressor for the treatment of anaphylaxis. Refer to Section 6 for details of alternative vasopressors and inotropes when initial resuscitation with adrenaline and fluids has not been successful.

6. Refractory Analysis

6.1 Key Points

Refractory anaphylaxis is defined as anaphylaxis requiring ongoing treatment despite two appropriate doses of IM adrenaline

- When treating refractory anaphylaxis, a rapid ABCDE assessment should be undertaken and prioritisation given to treating the greatest threat to life.
- Critical care support should be sought early (in hospital, call for the resuscitation team according to local protocol; dial 999 in the community setting).
    - This algorithm is designed to support staff, rather than replace the expertise of experienced critical care clinicians.
- **Maintenance adrenaline therapy is critical**, using an intravenous adrenaline infusion.
    - Adrenaline therapy should be supported with an initial rapid fluid bolus and maintenance fluid therapy.
    - Intravenous adrenaline infusions are important in the management of all aspects of anaphylaxis and not only cardiovascular shock.
- Prolonged resuscitation and critical care support (hours to days) may be required.
- In settings where it is available, consider extra-corporeal life support techniques.

6.2 Introduction

The majority of anaphylaxis reactions respond to initial treatment with intramuscular adrenaline, although around 10% will require more than 1 dose.[69] This may sometime be due to the use of auto-injectors which cannot deliver an age/weight-appropriate dose in most patients.

Less than 1% of reactions are refractory to initial adrenaline treatment, and intensive care admissions are uncommon.[70]

The working group agreed the following definition:

Refractory anaphylaxis is defined as anaphylaxis requiring ongoing treatment despite two (appropriate) doses of IM adrenaline.

6.3 Pathophysiology of refractory anaphylaxis

Refractory anaphylaxis is poorly studied, however evidence from case series[39,71] and animal models[47,72] of severe anaphylaxis suggest that refractory reactions may be a combination of the following:[26,27]

1. Delayed or insufficient delivery of adrenaline (COMMON)
2. Progression of reaction due to ongoing release of inflammatory mediators (COMMON)
3. Diminished response to further adrenaline administered during reactions (tachyphylaxis) (UNCOMMON)

The management of refractory anaphylaxis should therefore include the following strategies:

1. Patients with refractory anaphylaxis require **critical care support** to ensure effective airway management, tissue oxygenation and circulatory support.

2. **Optimise delivery of adrenaline**: adrenaline is important in the management of all aspects of anaphylaxis and not only cardiovascular shock. A single dose of adrenaline (by any route) is unlikely to be sufficient in severe reactions; refractory reactions should therefore be treated with an adrenaline infusion and fluid therapy to support delivery of adrenaline at a tissue level.

   Data from case series in severe human anaphylaxis[39,71] and animal models[73] suggest that low-dose intravenous adrenaline infusions may be more efficient in the treatment of anaphylaxis compared with other routes of administration and/or intravenous bolus therapy.

3. The response to the adrenaline infusion may sometimes be suboptimal, particularly if cardiovascular shock is fully established. Seek urgent expert advice to guide the use of other vasopressors to treat shock.

   There are no in-human data to recommend a specific vasopressor strategy in anaphylaxis refractory to an adrenaline infusion. Data from animal models of anaphylaxis suggest that adrenaline infusion followed by an alternative vasopressor (e.g. vasopressin) is superior to vasopressin alone in the management of refractory anaphylactic shock.[72,74]

   Follow local protocols for management of refractory shock including the choice of noradrenaline, metaraminol and/or vasopressin.

6.4 Refractory Anaphylaxis algorithm

The key steps for the treatment of refractory anaphylaxis are shown in the algorithm (Figure 6) on the next page.

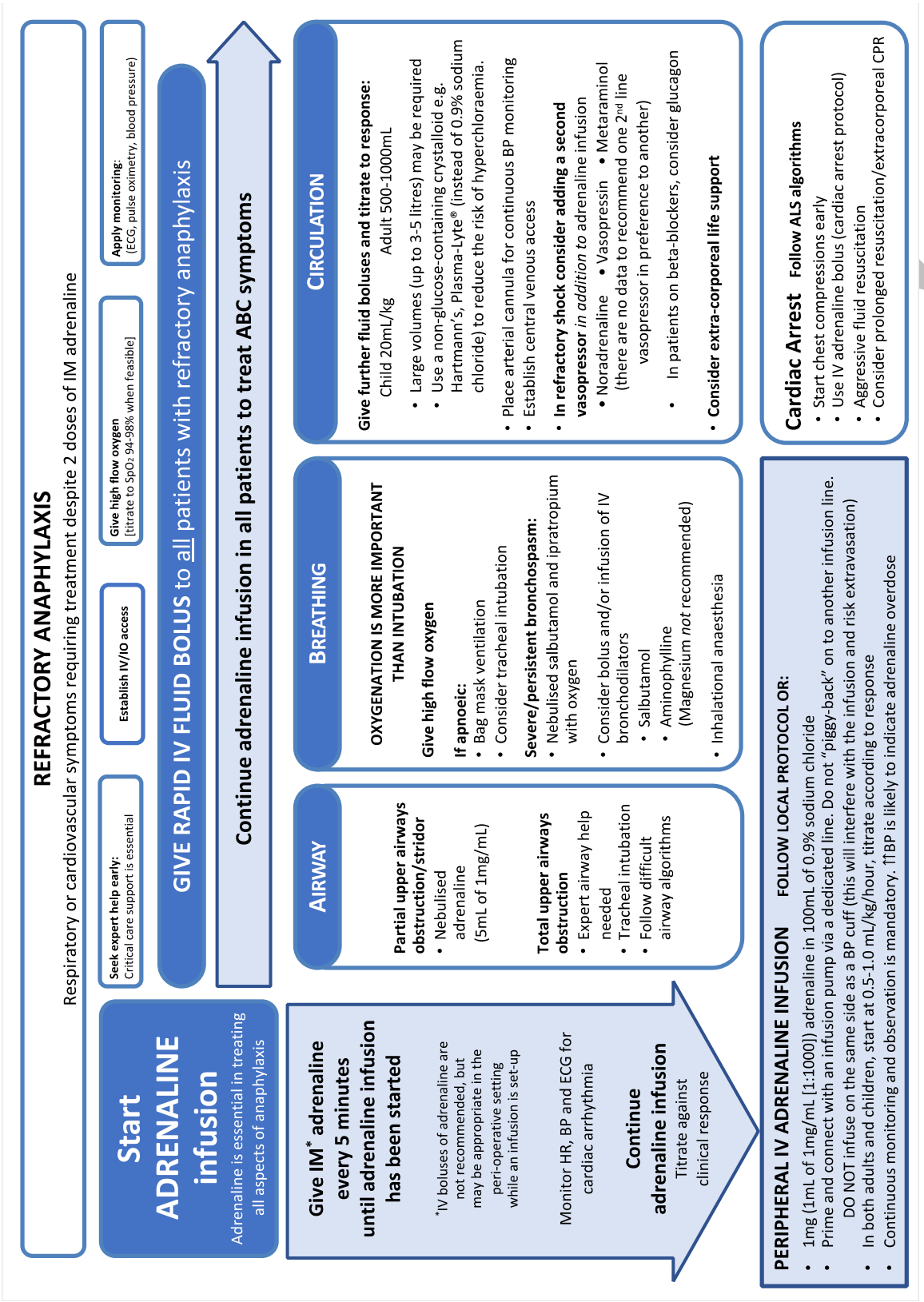

Figure 6. Refractory anaphylaxis algorithm

6.5 Intravenous (IV) adrenaline infusion

Patients who require ongoing treatment for anaphylaxis despite 2 or more doses of adrenaline should be commenced on an adrenaline infusion.

Dilute adrenaline can be infused via a peripheral cannula or intraosseous needle until central venous access is obtained.[39,75] Where a local protocol is not readily available, the protocol[39] below (used in other guidelines[55,76]) can be followed.

Continue to administer IM adrenaline every 5 minutes until the infusion has been started. IV boluses of adrenaline are NOT recommended for refractory anaphylaxis unless the patient is in cardiac arrest but may be used by healthcare providers with experience in the use and titration of vasopressors in their normal clinical practice, while an infusion is set-up.

Monitor for adrenaline side effects: tachycardia, arrhythmia, hypertension. If present, reduce the infusion rate (or stop infusion if severe).

PERIPHERAL IV ADRENALINE INFUSION REGIMEN[39]
FOR INITIAL TREATMENT OF REFRACTORY ANAPHYLAXIS

PREPARATION

- **Continuous monitoring and observation mandatory**:
  - ECG, pulse oximetry, non-invasive BP at least every 5 minutes
- Mix 1 mg (1 mL of 1mg/ml [1:1000]) adrenaline in **100 mL** of 0.9% sodium chloride and connect using an infusion pump via a dedicated line.
  - **Do not "piggy-back" on to another line** unless using an anti-reflux value.
- DO NOT infuse on the same side as a BP cuff, as frequent measurements will interfere with the infusion and risks extravasation injury.

INITIATION AND ADJUSTMENT

- **In children and adults, start at 0.5-1.0 mL/kg/hour** depending on severity:
  - Moderate severity: 0.5ml/kg/hour (~0.1 microgram/kg/minute)
  - Severe (hypotensive or hypoxic): 1ml/kg/hour
- **Titrate** up or down according to response, aiming for the lowest effective rate.
  - Steady state is reached 5-10 minutes after a change in rate.
  - Monitor infusion site regularly to ensure patency of cannula
- **Tachycardia, tremor, pallor with a normal or raised BP** may indicate excessive adrenaline treatment : reduce the infusion rate (or stop infusion if severe).
- If refractory to adrenaline infusion, seek urgent further expert help. Patients will require central venous access for prolonged infusions; follow local protocols.

WEANING

- **As symptoms improve, reduce the infusion**, aiming for 50% of the starting rate.
- One hour after resolution of all symptoms and signs, wean the infusion over 30 minutes and then stop; monitor closely for recurrence, and restart if necessary.

6.6 Other supportive measures

6.6.1 AIRWAY

Severe upper airways obstruction is uncommon in refractory anaphylaxis. Evidence from autopsy show significant laryngeal oedema in under 10% of cases.[77] This may be due to laryngeal oedema being responsive to adrenaline treatment.

Tissue oxygenation is more important than tracheal intubation.

If tracheal intubation is indicated, it should be performed by the most experienced clinician available, following a difficult airway protocol (das.uk.com/guidelines).

Nebulised adrenaline can be used to treat upper airways obstruction[10] but should not be prioritised over an adrenaline infusion or delay tracheal intubation in cases of critical upper airways obstruction.

6.6.2 BREATHING

Severe bronchospasm is common in food-induced anaphylaxis,[78] and in children; in these cases, cardiac arrest is usually secondary to hypoxia. Treat severe respiratory symptoms with an adrenaline infusion as first line therapy, in addition to nebulised and intravenous bronchodilator therapy.

Magnesium sulphate is not recommended as it causes significant vasodilation.

6.6.3 CIRCULATION

Reduced venous return is common in anaphylaxis, even in the absence of obvious circulatory compromise (e.g. in those with severe bronchospasm). An adrenaline infusion should be the first line treatment alongside a fluid bolus.

Give further fluids as necessary. A large volume (up to 3-5 litres) may be needed for severe anaphylactic shock. Use a non-glucose-containing crystalloid (e.g. Hartmann's and Plasma-Lyte®) rather than 0.9% sodium chloride to reduce the risk of hyperchloraemia.

In considering second line vasopressor treatment, there is insufficient evidence to recommend any particular vasopressor; expert advice and local protocols should be followed.[9,10] Doses should be titrated to clinical response, and only administered where there is sufficient expertise and monitoring available to minimise the risk of potential side effects (e.g. hypertensive crises and pulmonary oedema).

CARDIAC ARREST

Recognise cardiac arrest has occurred if the person becomes unresponsive or unconscious, and breathing is absent or abnormal. Other signs of cardiac arrest in a person with advanced monitoring include reducing or absent $ETCO_2$ and absent arterial waveform.

Cardiac arrest following anaphylaxis is a situation when prolonged CPR should be considered (including extra-corporeal CPR). This is because the patients have usually arrested rapidly from a previously well state and a potentially reversible cause.

In adults, start chest compressions early in the peri-arrest patient.[36] Recommendations for the management of peri-operative anaphylaxis are to start chest compressions if peripheral sBP remains below 50mmHg, especially in the context of bradycardia.[79]

6.6.4 OTHER MEDICATIONS

STEROIDS

The routine administration of corticosteroids to treat anaphylaxis is NOT recommended (see Section 5.5).

However, there is no evidence for or against their use for refractory anaphylaxis. It is reasonable to consider corticosteroids (such as hydrocortisone) for refractory reactions after initial resuscitation (conditional recommendation). Corticosteroids must not be prioritised over an adrenaline infusion and fluid resuscitation.

GLUCAGON

Adrenaline may be less effective in patients treated with beta-blockers.[10,80] In these cases, consider giving glucagon where symptoms continue to be refractory to adrenaline infusion and adequate fluid resuscitation.[10,55,80] Monitor for adverse events which including hyperglycaemia, vomiting, hypokalaemia and hypocalcaemia.

7. Investigations

Undertake investigations appropriate for a medical emergency, e.g. 12- lead ECG, chest X-ray, urea and electrolytes, arterial blood gases etc.

7.1 Mast cell tryptase

The specific test to help confirm a diagnosis of anaphylaxis is measurement of mast cell tryptase. Tryptase is the major protein component of mast cell secretory granules. During anaphylaxis, mast cell degranulation leads to an increase in blood tryptase concentrations (Figure 4), although this may not be obvious in food-induced anaphylaxis.[81] Tryptase levels can be useful in the follow-up of suspected anaphylaxis, but not in the initial recognition and treatment:[82] measuring tryptase levels must not delay initial resuscitation. Tryptase concentrations in the blood may not increase significantly until 30 minutes or more after the onset of symptoms, and peak 1-2 hours after onset.[83] The half-life of tryptase is short (approximately 2 hours), and concentrations may return to normal within 6-8 hours, so timing of any blood samples is very important.

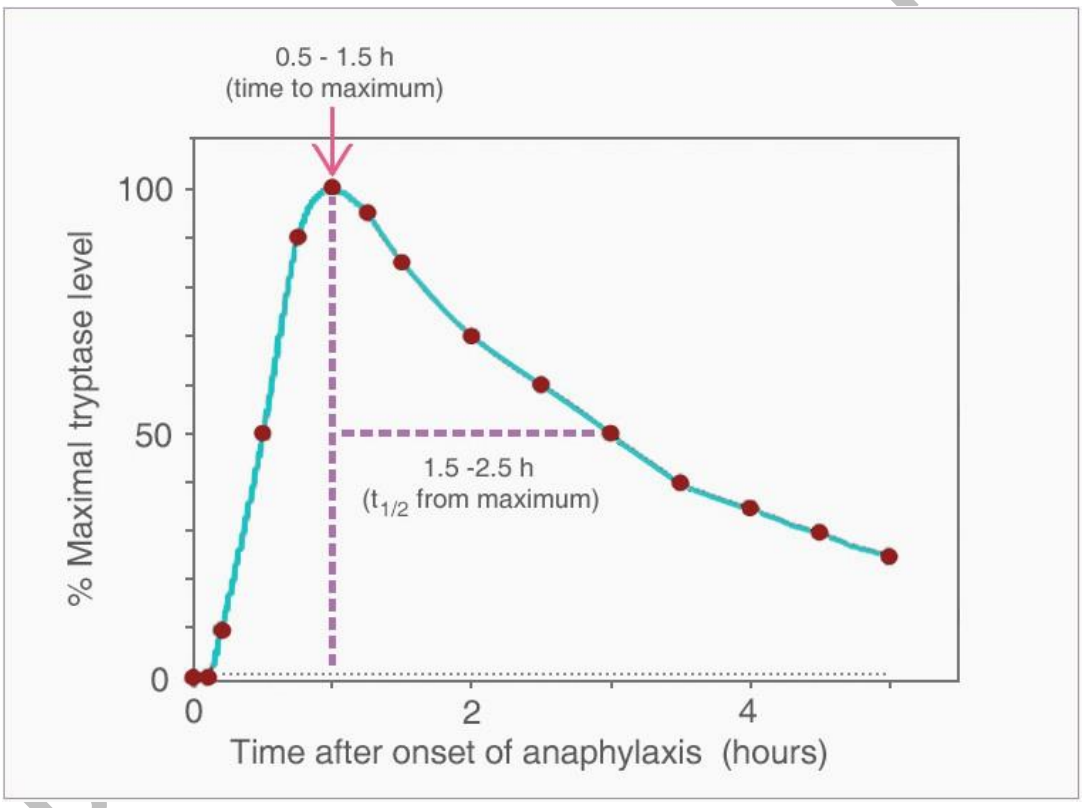

Figure 7. Suggested time course for the appearance of tryptase in serum or plasma during systemic anaphylaxis.[83] (Reproduced with permission).

7.2 Sample timing

The time of onset of anaphylaxis is the time when symptoms were first noticed. It is important that this time is accurately recorded.

a) Minimum: one sample ideally within 1-2 hours (but no later than 4 hours) **from the onset of symptoms** (when peak tryptase levels generally occur)
b) Ideally: Three ***timed*** samples:
   1) Initial sample as soon as feasible after resuscitation has started – do not delay resuscitation to take sample.
   2) A second sample at 1-2 hours (but no later than 4 hours) **from the onset of symptoms.**
   3) A third sample at least 24 hours after complete resolution, or in convalescence (for example, at a follow-up allergy clinic). This sample is important as it provides a baseline tryptase value - some individuals have an elevated baseline level and may be at greater risk of anaphylaxis to some triggers.

Serial samples have better specificity and sensitivity than a single measurement in the confirmation of anaphylaxis.[82,84]

7.3 Sample requirements

1. Either serum ('liver function test' tube) or plasma samples are acceptable in most laboratories.
2. Sample volumes as little as 0.5 mL of sample are usually sufficient, but >2mL is preferred.
3. ***Record the timing of each sample accurately*** on the request form and in the clinical notes. State on the request form (and in the clinical notes) how many minutes/hours after the onset of symptoms the sample was taken. This will enable staff to track the change in tryptase levels over time which is essential for interpretation.
4. Specimens are stable for up to 2 days at room temperature, 7 days refrigerated at 2-8°C, and for longer frozen at –20°C.85 However, samples beyond these times may still provide useful information and should therefore be submitted for analysis, regardless.
5. Consult your local laboratory if you have any queries.

8. Discharge and follow up

8.1 Recovery from anaphylaxis

Patients who have had suspected anaphylaxis (i.e. an Airway/Breathing/Circulation problem) should be treated and then observed in a clinical area with facilities for treating life-threatening ABC problems.

1. **Some patients experience further symptoms following resolution** of the initial reaction. This may be a true biphasic reaction (see Section 8.2) but can also represent further allergen absorption e.g. if there is residual food allergen present in the gut, eating may cause further gastrointestinal absorption of the allergen, resulting in further symptoms.[86]
   - It may be advisable for patients to eat a snack at least one hour prior to discharge to mitigate against this.
2. **Postural hypotension** has been reported after both anaphylaxis and more mild allergic reactions in some patients.[87]
   - Stand patients and monitor for dizziness (and measure blood pressure if indicated) prior to discharge.

8.2 Biphasic reactions

Anaphylaxis can appear to resolve but then exhibit a recrudescence of symptoms several hours later in the absence of further allergen exposure. This is known as a biphasic reaction, and occurs in around 5% of patients.[63,88]

Biphasic reactions can be difficult to distinguish from protracted anaphylaxis with a transient response to adrenaline, or progression due to further allergen absorption from residual food in the gastrointestinal tract. Published studies report the median time to biphasic symptoms (i.e. time by which 50% of biphasic reactions have occurred) as around 12 hours.[63,88-90]

The optimal duration of observation following anaphylaxis to monitor for biphasic reactions is unknown. In 2011, NICE recommended observation for 6–12 hours from the onset of symptoms in individuals over 16 years, on the basis of expert opinion,[91] but recent evidence suggests that this strategy may miss over 50% of biphasic reactions in the 5% of patients who experience them. [63,88-90]

Biphasic reactions can also occur following more mild allergic reactions; this may be at the same rate as biphasic reactions after anaphyalxis.[92]

Risk factors for biphasic reactions following anaphylaxis include[66]

- More severe initial presentation of anaphylaxis
- Initial reaction needed more than one dose of adrenaline
- A delay in adrenaline administration (>30-60 minutes from symptom onset)[93]

Patients with a history of prior biphasic reaction may also be at an increased risk.

Fatal outcomes due to biphasic reactions are very rare: over 9000 cases of anaphylaxis were reported to the European Anaphylaxis Registry between 2011 and 2019: there were

435 cases with biphasic reactions and XX fatalities. No fatality occurred in a patient with a biphasic reaction.[88]

8.3 Discharge from hospital

All patients should be reviewed by a senior clinician and a decision made about the need for further treatment and duration of observation. There is no reliable way of predicting who will have a biphasic reaction,[66] so decisions about discharge must be made for each patient by an experienced clinician.

Patients should be warned of the possibility of a biphasic reaction causing recurrence of symptoms.

NICE recommends that prior to discharge, a healthcare professional with the appropriate skills and competencies should offer people (or, as appropriate, their parent and/or carer) the following:

- Information about anaphylaxis, including the signs and symptoms of anaphylaxis.
- Information about the risk of a biphasic reaction (and clear instructions to return to hospital if symptoms return).
- Information on what to do if anaphylaxis occurs (use the adrenaline injector and call emergency services).
- Considered for an adrenaline auto-injector (see Section 8.5) or given a replacement.
- If prescribed, a demonstration of the correct use of the adrenaline injector and when to use it.
- Advice about how to avoid the suspected trigger (if known).
- Information about the need for referral to a specialist allergy service and the referral process.
- Information about patient support groups (e.g. Anaphylaxis Campaign, Allergy UK).

On the basis of a review of the available evidence, the working group proposed a risk-stratified approach to the length of in-hospital observation recommended following anaphylaxis:

Consider fast-track discharge (after 2 hours observation) if:	Minimum 6 hours observation after resolution of symptoms recommended if:	Observation for at least 12 hours following resolution of symptoms if any one of the following:
• Good response to a single dose of adrenaline given within 30 minutes of symptom onset; AND • Complete resolution of symptoms; AND • The patient already has adrenaline auto-injectors (AAI) and has been trained how to use them. • There is adequate supervision following discharge	• 2 doses of IM adrenaline needed to treat reaction OR • Previous biphasic reaction	• Severe reaction requiring >2 doses of adrenaline. • Patient has severe asthma or reaction involved severe respiratory compromise. • Possibility of continuing absorption of allergen e.g. slow release medicines. • Patient presents late at night, or may not be able to respond to any deterioration. • Patients in areas where access to emergency care is difficult.

8.4 Record keeping

To help confirm the diagnosis of anaphylaxis and identify the most likely trigger, it is useful for the allergy clinic to have:

- A description of the reaction with circumstances and timings to help identify potential triggers.
- A list of administered treatments.
- Copies of relevant patient records, e.g., ambulance charts, emergency department records, observation charts, anaesthetic charts.
- Results of any investigations already completed, including the timings of mast cell tryptase samples.

The Association of Anaesthetists recommends that anaesthetists follow a referral pathway as outlined in the Sixth National Audit Project (NAP6) for follow-up of patients who have experienced peri-operative anaphylaxis.[13] The pathway includes a list of the relevant patient records which are required for the referral.

A list of clinics with a specific interest in peri-operative anaphylaxis is available at the BSACI and Association of Anaesthetists websites (https://www.bsaci.org/ and https://anaesthetists.org/)

8.5 Reporting of reaction

An Anaphylaxis Registry has been established in the UK. Healthcare professionals are encouraged to report all anaphylaxis events at XXX

Adverse drug reactions that involve anaphylaxis should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) using the yellow card scheme (https://www.gov.uk/report-problem-medicine-medical-device).

All cases of fatal anaphylaxis must be reported to the coroner.

8.6 When to prescribe an adrenaline auto-injector

Emergency departments should liaise with their nearest specialist allergy service to devise a local guideline for which patients should be given an adrenaline auto- injector on discharge.

Prescription of adrenaline auto-injectors is appropriate for patients:

- at high risk of future exposure to the index allergen e.g. to triggers such as venom stings and food-induced reactions (unless easy to avoid).
- at risk of idiopathic anaphylaxis

An auto-injector is not usually necessary for patients who have suffered drug- induced anaphylaxis, unless it is difficult to avoid the drug.

Ideally, all patients should be assessed by an allergy specialist and have a treatment plan based on their individual risk.[9,10]

Individuals provided with an adrenaline auto-injector at discharge from hospital must be given instructions and training, and have appropriate follow-up including contact with the patient's general practitioner.

NICE guidelines currently recommend that patients with adrenaline auto-injectors should have TWO devices available at all times. Patients (and those close to them e.g. immediate family members, friends, carers) should receive training in their use, and practise regularly using a suitable training device so that they will know what to do in an emergency.

8.7 Specialist referral

All patients presenting with anaphylaxis should be referred to an allergy clinic to identify the cause, and thereby reduce the risk of future reactions and prepare the patient to manage future episodes themselves.

A list of specialist clinics is available at the British Society for Allergy and Clinical Immunology (BSACI) website.

8.8 Patient education

Patients at risk of anaphylaxis should be referred to an appropriate allergy clinic. Patients need to know the allergen responsible and how to avoid it. For food allergens, patients need information on dietary avoidance (including what products are likely to contain it and alternative names for the allergen).

Patients should be provided with an Emergency Management or Action Plan (these can be downloaded at www.bsaci.org), to facilitate recognition of the early symptoms of anaphylaxis, request help early and use the appropriate emergency medication.

Patients must always seek urgent medical assistance when experiencing anaphylaxis and after using an adrenaline auto-injector. Information about managing severe allergies can be obtained from their allergy specialist, general practitioner, other healthcare professional, or patient helplines/websites (the Anaphylaxis Campaign, Allergy UK).

Specific guidance and training is available for schools with children at risk of allergic reactions (www.sparepensinschools.uk).

Individuals at high risk of anaphylaxis should consider wearing a warning device (e.g., MedicAlert band), that provides information about their history of reaction.

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Appendices

Appendix 1 Legal aspects of administering adrenaline for anaphylaxis in an Emergency

There is no legal problem in a healthcare professional administering an adrenaline injection to treat anaphylaxis, that:

- has either been prescribed to a specific person (such as an adrenaline auto-injector), or
- is from an emergency drug supply, for example, a “crash trolley” or emergency bag.

Adrenaline is a prescription-only medicine (POM). Under Regulation 214 of The Human Medicines Regulations 2012 (which can be found at www.legislation.gov.uk), “a person may not parenterally administer (otherwise than to himself or herself) a prescription-only medicine unless the person is “an appropriate practitioner” (e.g. doctor, dentist, nurse prescriber) or acting in accordance with the directions of such a practitioner.

However, a number of medicines are exempt from this restriction, where “this is for the purpose of saving life in an emergency” (Regulation 238). This includes adrenaline.

Where adrenaline is held as an Emergency drug (and not specifically provided on a named-patient basis), any qualified healthcare professional may administer adrenaline (1mg/ml strength) at the doses recommended in this guideline, without the need for it to be prescribed first. However, the individual must be:

- working within the standards of the relevant regulator (e.g. Nursing & Midwifery Council; Health & Care Professionals Council)
- competent in being able to recognise anaphylaxis and administer adrenaline, either using a needle/ampoule/syringe or an auto-injector device that has not been prescribed on an individual patient basis.

In addition, under Schedule 17 of the Human Medicines Regulation (as amended in 2017), “generic” adrenaline auto-injectors can now be supplied to schools without being issued against a prescription. The legislation allows for any person who is “carrying on the business of a school” and who is suitably trained to do so, to administer such an auto-injector for the emergency treatment of anaphylaxis. Further information can be found at www.sparepensinschools.uk.

Where the adrenaline has been prescribed for a named person (e.g. as an auto-injector), the auto-injector can be administered by any person competent to do so, but only to the person for whom the auto-injector has been prescribed. The law does not allow a non-prescriber to administer an adrenaline auto-injector device – which has been specifically prescribed to a named person – to another individual.

Appendix 2. Choice of needle and technique for intramuscular (IM) injection

There is no specific evidence for any particular technique of intramuscular injection when treating anaphylaxis. This guidance is based on the recommendations for intramuscular injections for vaccination (Immunisation against infectious disease. Department of Health UK, 2006). For IM injections, the needle needs to be long enough to ensure that the drug is injected into the muscle.

A 25mm needle is best and is suitable for all ages. In pre-term or very small infants, a 16mm needle is suitable for IM injection. In some adults, a longer length (38 mm) may be needed.

Standard UK needle gauges and lengths		
Brown	26G	10 mm
Orange	25G	16 mm or 25 mm
Blue	23G	25 mm
Green	21G	38 mm

Appendix 3. Suggested drug doses for refractory anaphylaxis

	Adult	Paediatric
Adrenaline infusion	Where a local protocol is not readily available, the following can be used: Mix 1mg (1mL of 1mg/ml [1:1000]) adrenaline in 100 mL of 0.9% sodium chloride. Start at 0.5 mL/kg/hour (~0.1 microgram/kg/min) and titrate according to response. This dilution can be given via peripheral venous cannula. Continuous monitoring mandatory: ECG, Pulse oximetry, non-invasive BP at least every 5 minutes	
Adrenaline (IV bolus, until infusion is ready) **To be given only by experienced specialists.**	50 micrograms, if repeated, start an IV adrenaline infusion. Prefilled syringes of 1:10,000 adrenaline contain 100mcg/mL. 0.5mL is equivalent to 50 micrograms and is the smallest dose that can be given accurately. **Do not use 1:1000 adrenaline undiluted**	There is no evidence on which to base a dose recommendation – a child may respond to a dose as small as 1 microgram/kg. This requires very careful dilution and checking to prevent dosing errors.
Aminophylline	Loading dose: • 5mg/kg (max 500mg) IV over 20 mins (omit if on theophylline) IV Infusion: • <12 years 1mg/kg/hr • >12 years: 0.5-0.7mg/kg/hr (0.3mg/kg/hr in elderly)	
Atropine	0.5mg IV, repeat if necessary Consider if severe persistent bradycardia despite adequate fluid resuscitation.	
Glucagon	1mg IV [11] Can be repeated or followed by an infusion of 1-2mg/hour.	20-30micrograms/kg (max 1mg) can be repeated every 5 minutes
Hydrocortisone	200mg IV as initial dose	4mg/kg IV (maximum 200mg)
Ipratropium	Nebulised: 500micrograms	Nebulised: <2 years: 125micrograms; 2-12 years: 250micrograms; >12 years: 500micrograms
Metaraminol	IV bolus: 0.5mg, repeat as required Infusion: seek local expert advice	IV bolus: 10microgram/kg, repeat as required and titrate to response
Noradrenaline	Seek local expert advice. IV infusion: 0.05-0.5 micrograms/kg/min	Seek expert advice. Commence at 0.1 micrograms/kg/min
Salbutamol	Nebulised: 5mg IV bolus (give over 5 minutes): 250 micrograms	Nebulised: <5 years 2.5mg >5 years 5mg IV bolus (give over 5 minutes): <2 y: 5mcg/kg over 5 mins 2-18y: 15 mcg/kg (max 250mcg)
Vasopressin	IV bolus: 2 units [11] (repeat as needed, consider infusion)	Infusion: 0.02 - 0.06 units/kg/hr [77] Mix 1 unit/kg in 50 mL Give 2mL bolus, then 1-3mL/hr

Resuscitation Council UK

Appendix 4. Useful websites

https://www.resus.org.uk/
Resuscitation Council UK

https://www.bsaci.org/
British Society of Allergy & Clinical Immunology

https://www.anaphylaxis.org.uk/
The Anaphylaxis Campaign

https://www.allergyuk.org/
Allergy UK

https://www.eaaci.org/
The European Academy of Allergology and Clinical Immunology

https://erc.edu/
European Resuscitation Council

https://anaesthetists.org/
Association of Anaesthetists

https://www.cochrane.org/
The Cochrane collaboration

https://www.sparepensinschools.uk/
Website to support the use of adrenaline auto-injectors (including “generic” devices”) in schools and other educational settings.

Resuscitation Council UK

Appendix 5. Glossary of terms and abbreviations

- The term ‘patient’ is used to describe an individual suffering from anaphylaxis in any setting instead of alternative terms e.g., victim or casualty.
- **ABCDE**: Airway, Breathing, Circulation, Disability, Exposure (see Appendix 1).
- **ALS:** Advanced Life Support.
- **Anaphylactic shock:** poor perfusion of the body’s vital organs caused by an anaphylaxis.
- **BLS:** Basic Life Support, i.e., CPR without the use of equipment except for airway protective devices.
- **CPR:** cardiopulmonary resuscitation, which refers to chest compressions and ventilations.
- **IM:** intramuscular.
- **IV:** intravenous.

Appendix 6. Equality Impact Statement

RCUK is committed to promoting equality, eliminating unlawful discrimination and actively considering the implications of its guidance for human rights. It aims to comply fully with the Equality Act (2010).

		Yes/No	Comments
1.	**Does the guidance affect one group less or more favourably than another on the basis of:**		
	• Race	NO	
	• Ethnic origins (including gypsies and travellers)	NO	
	• Nationality	NO	
	• Gender	NO	
	• Culture	NO	
	• Religion or belief	NO	
	• Sexual orientation including lesbian, gay and bisexual people	NO	
	• Age	NO	Guidance covers all age groups
	• Disability – learning disabilities, physical disability, sensory impairment and mental health problems	NO	
2.	**Is there any evidence that some groups are affected differently?**	YES	Causes of anaphylaxis can vary with age. This is addressed in the guidelines
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	NO	
4.	**Is the impact of the policy/ guidance likely to be negative?**	NO	
5.	**If so, can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	