Guidelines

Emergency treatment of peri-operative anaphylaxis: Resuscitation Council UK algorithm for anaesthetists

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Summary

Peri-operative anaphylaxis is a rare but potentially catastrophic event which must be considered whenever unexpected and significant cardiovascular or respiratory compromise occurs during anaesthesia. The Resuscitation Council UK algorithm for peri-operative anaphylaxis highlights the importance of early intravenous adrenaline and fluid resuscitation and provides guidance on the treatment of refractory anaphylaxis and immediate follow-up. This algorithm is endorsed by the Royal College of Anaesthetists, Association of Anaesthetists, British Society of Allergy and Clinical Immunology and Clinical Immunology Professional Network of the British Society for Immunology. This document was produced by the Perioperative Allergy Network steering committee in collaboration with the Resuscitation Council UK.

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Key recommendations

1 Consider anaphylaxis whenever unexpected and significant cardiovascular or respiratory compromise occurs.
2 First-line treatment of peri-operative anaphylaxis is intravenous adrenaline (epinephrine). An initial dose of 50 μg (0.5 ml of 1 mg.10 ml^{-1} [1:10,000]) strength is recommended in adults and children aged > 12 y (some patients may respond to smaller doses (10–50 μg) titrated to effect).
3 Adrenaline must be supported by intravenous crystalloid fluid. Administer rapid, large-volume fluid boluses (adults and children aged > 12 y, 500–1000 ml; children aged < 12 y, up to 20 $ml.kg^{-1}$). Multiple fluid boluses may be required.
4 If signs of anaphylaxis persist despite adrenaline boluses, start an adrenaline infusion. A low-dose adrenaline infusion, given via a peripheral venous line, is an effective alternative if central venous access is unavailable.

5 Start cardiopulmonary resuscitation if systolic blood pressure is < 50 mmHg despite initial adrenaline and intravenous fluid.
6 Antihistamines and corticosteroids are not useful in the immediate treatment of anaphylaxis. Do not prioritise these over adrenaline and fluid resuscitation.

What other guideline statements are available on this topic?

The Resuscitation Council UK (RCUK) published an updated guideline in 2021 for the emergency treatment of anaphylaxis by healthcare providers in hospital and community settings [1]. Recommendations for the management and investigation of peri-operative anaphylaxis have been published by the International Suspected Perioperative Allergic Reactions group [2] and the European Academy of Allergy and Clinical Immunology [3].

Why was this algorithm developed?

This algorithm was developed by the RCUK and Perioperative Allergy Network to provide specific guidance on the treatment of anaphylaxis in the peri-operative setting where anaesthetists are providing patient care.

How and why does this statement differ from existing guidelines?

The RCUK guideline for the emergency treatment of anaphylaxis [1] is a generic guideline for healthcare providers and recommends intramuscular adrenaline for the immediate treatment of suspected anaphylaxis. However, the intramuscular route is less appropriate in the peri-operative setting, where patients typically present with more severe and rapid onset reactions, are very closely monitored, have intravenous access and are under the direct care of an anaesthetist. The peri-operative anaphylaxis algorithm emphasises the importance of using early intravenous adrenaline in small doses, titrated to effect, before establishing a low-dose intravenous adrenaline infusion if needed. The algorithm is aligned with the treatment detailed in the *Quick Reference Handbook* of the Association of Anaesthetists [4].

Background

Peri-operative anaphylaxis during anaesthesia is a potentially catastrophic event with a quoted incidence ranging from 1:353 to 1:18,600 anaesthetics and an estimated mortality of around 1–4% [5]. This is higher than the mortality reported for anaphylaxis in other settings [6]. During anaesthesia, patients are exposed to a large number of potential triggers for anaphylaxis, with an average of eight drugs administered, but this can be as many as 20 [7]. These include induction and maintenance drugs; analgesics; antibiotics and anti-emetics. In the UK, almost half of general anaesthetics include the use of a neuromuscular blocking drug [7]. The majority of patients are also exposed to chlorhexidine and many are also exposed to latex. Other potential triggers include radiocontrast and other dyes; surgical materials such as glues and cements; and intravenous colloid fluids [8]. In the 6th National Audit Project of the Royal College of Anaesthetists (NAP6) the most common causes of anaphylaxis were antibiotics (47%); neuromuscular blocking drugs (33%); chlorhexidine (9%) and patent blue dye (3%) [7].

During anaphylaxis degranulation of mast cells and basophils leads to the activation of multiple inflammatory pathways [9]. This results in tissue oedema and smooth muscle contraction in the airways (causing high airway pressures, bronchospasm and wheeze); fluid extravasation, leading to tissue oedema, hypovolaemia, and a profound reduction in venous tone; depressed myocardial function, which can lead to cardiogenic shock and arrhythmias; and fluid leakage into the bowel, as well as smooth muscle contraction, which can result in abdominal and pelvic cramps.

Peri-operative anaphylaxis is a clinical diagnosis. It can be particularly difficult to make a diagnosis in the peri-operative setting because typical presenting features of an allergic reaction (such as urticaria and other skin signs) are absent in around one-third of reactions. There is a wide range of differential diagnoses, including exaggerated physiological responses to induction agents; airway manipulation; and surgical interventions. Peri-operative anaphylaxis occurs most frequently following induction of anaesthesia, with symptom onset typically within minutes of exposure to the culprit drug. Time to cardiac arrest following intravenous exposure is faster than other routes of exposure to a triggering drug, with onset typically within 5–10 min [7].

The modified Ring and Messmer Scale (Table 1) characterises the phenotypes of peri-operative allergic reactions and severity grading [10]. Grades 1 and 2 describe non-life-threatening reactions with skin and or moderate organ involvement. Grade 3 and 4 reactions demonstrate life-threatening organ involvement, fulfilling the criteria for severe anaphylaxis. Grade 3 peri-operative anaphylaxis typically presents with sudden onset, life-threatening hypotension [6, 11], with or without tachycardia or bradycardia [7]. Bronchospasm as a presenting sign is

Table 1 Grading of suspected peri-operative allergic reactions according to the modified Ring and Messmer scale [10].

Grade	Clinical signs
1	Skin, mucosal signs, or both: generalised erythema, extensive urticaria, or both with or without angioedema
2	Moderate multi-organ involvement: skin, mucosal signs or both with or without moderate hypotension; tachycardia; moderate bronchospasm; or gastrointestinal symptoms
3	Life-threatening mono- or multi-organ involvement: life-threatening hypotension; tachycardia, or bradycardia with or without cardiac arrhythmia; severe bronchospasm; skin, mucosal signs, or both; or gastrointestinal symptoms
4	Cardiac or respiratory arrest

more common in patients with underlying airway disease (e.g. asthma or chronic obstructive pulmonary disease) or obesity [7, 12]. In NAP6, hypoxia was an uncommon presenting feature, although was common in the hour following resuscitation. Airway angioedema was uncommon in severe peri-operative anaphylaxis. Skin changes such as generalised erythema or urticaria, are less common, occurring as the presenting feature in 10–40% of peri-operative reactions [6, 11] (Fig. 1) Skin signs may only be seen once adequate perfusion is restored and/or surgical drapes are removed.

Treatment of peri-operative anaphylaxis

Early recognition and treatment of potential anaphylaxis is critical [13]. `If in doubt, treat´ is a useful maxim in the context of any significant, unexpected cardiovascular or respiratory event.

An evidence review for the treatment of anaphylaxis was recently undertaken by the Anaphylaxis Working Group of the RCUK, to support the 2021 update of the guidelines for the emergency treatment of anaphylaxis [14]. Consensus recommendations from the International Suspected Perioperative Allergic Reactions group on the management of peri-operative anaphylaxis outline management specifically in this setting [2]. The cornerstones of treatment are early adrenaline treatment in parallel with airway support; ventilation; supine positioning and volume expansion with intravenous isotonic crystalloid. Treatment of any airway compromise must include checking for correct airway placement to exclude unrecognised oesophageal intubation and patency of the anaesthetic circuit and tracheal tube.

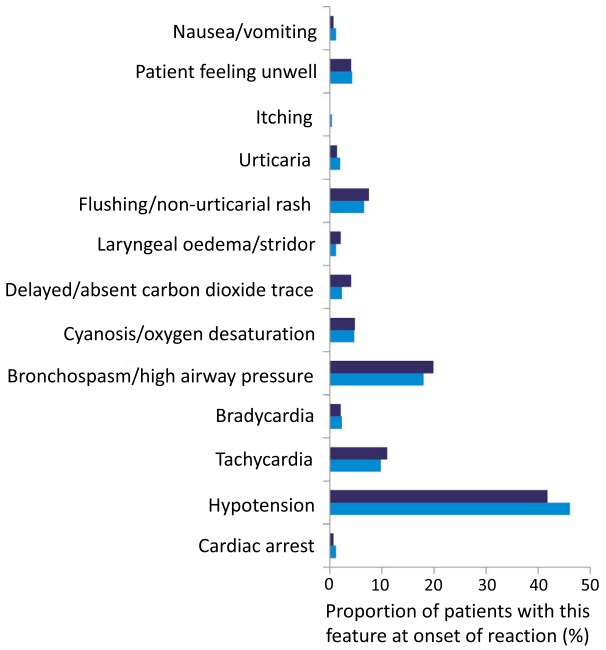

Figure 1 Presenting features of peri-operative anaphylaxis in the NAP6 study [7]. Dark blue, life-threatening/fatal anaphylaxis (equivalent to grades 3–4); light blue, peri-operative allergic reactions (any severity). (Reproduced with permission).

There is international consensus that adrenaline is the first-line treatment for anaphylaxis [1]. Despite the absence of randomised trials, evidence from observational data, clinical experience and animal models support the early use of adrenaline in anaphylaxis. Adrenaline counteracts the effects of anaphylaxis through its vasoconstrictor, bronchodilator, inotropic and mast cell stabilising effects.

The RCUK 2021 guideline recommends that intramuscular adrenaline is the preferred route to be used by most healthcare staff, due to the ease of administration and a favourable safety profile. However, in the peri-operative setting, where patients are closely monitored and under the care of an anaesthetist, there is widespread agreement that intravenous adrenaline is more appropriate [2, 15–17]. The absorption of intramuscular adrenaline is slower, less predictable and dependent on adequate circulation which is more likely to be compromised in peri-operative anaphylaxis [18]. The use of intravenous adrenaline facilitates more rapid improvement than via the intramuscular route and enables the closer titration of doses to effect [11]. For adults, an initial intravenous dose of 50 µg (0.5 ml of 1 mg.10 ml^{-1} [1:10,000] strength) adrenaline is recommended by the RCUK algorithm and *Quick Reference Handbook* [4], although some patients may respond to smaller doses (10–50 µg) titrated to effect.

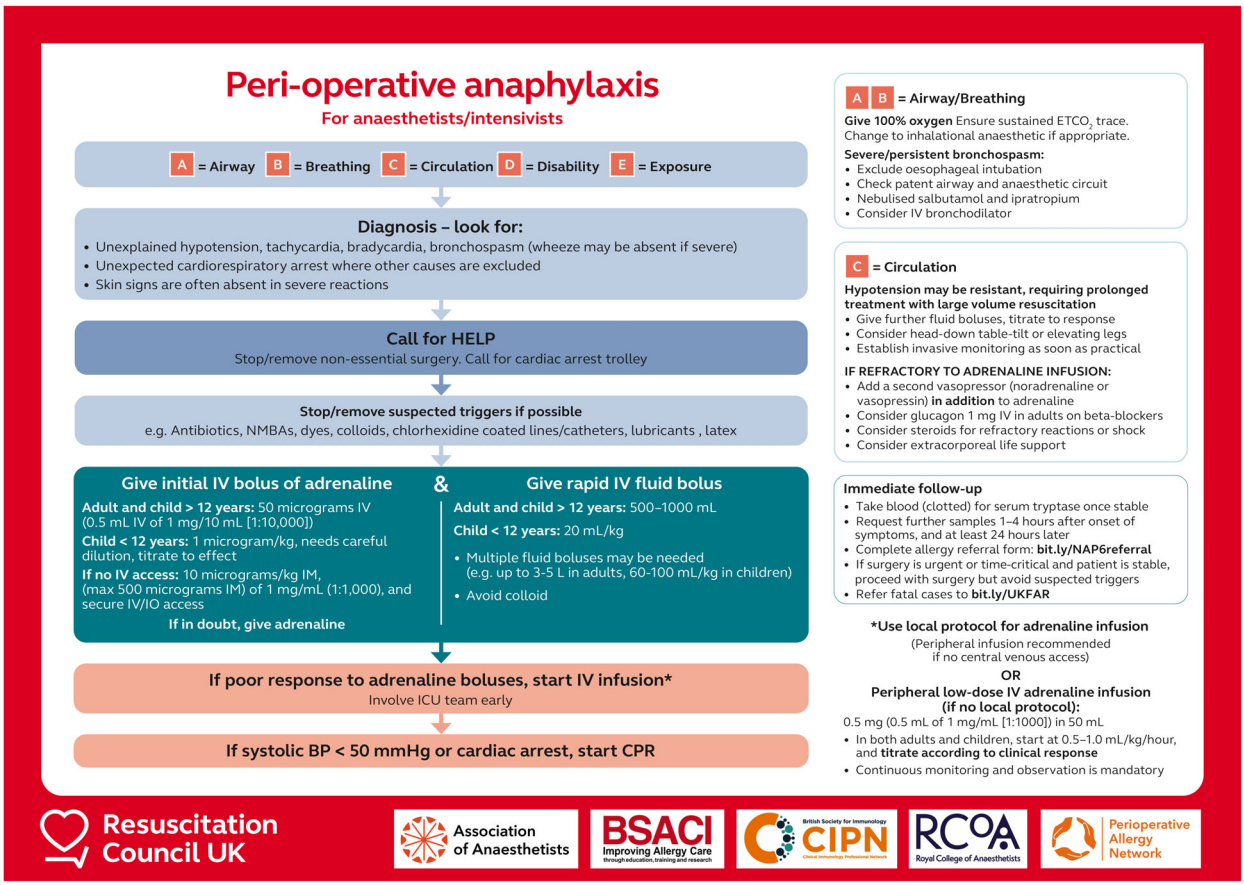

Figure 2 Resuscitation Council UK algorithm for the treatment of peri-operative anaphylaxis. NMBA, neuromuscular blocking drugs; IV, intravenous; IM, intramuscular; BP, blood pressure; CPR, cardiopulmonary resuscitation; $ETCO_2$, end-tidal carbon dioxide.

Refractory anaphylaxis, where signs and symptoms do not resolve following initial adrenaline, is more likely to occur in the peri-operative setting [19]. Data from human case series and animal models of anaphylactic shock show that bolus doses of adrenaline (irrespective of using the intravenous, intramuscular or subcutaneous route) have only a limited effect on haemodynamic recovery [20, 21]. Low-dose intravenous adrenaline infusions were more effective than bolus dosing and were associated with a lower total dose requirement, lower incidence of biphasic reactions and a favourable safety profile [20–22]. For this reason and consistent with international guidelines, the RCUK peri-operative algorithm recommends starting a low-dose intravenous adrenaline infusion if the initial response to intravenous bolus adrenaline is suboptimal [1, 23, 24]. This should be given through a peripheral venous cannula if central venous access is not immediately available. Local protocols for adrenaline infusion should be used. Alternatively, the algorithm describes a protocol for which there is published evidence (Fig. 2) [20].

An important observational study to inform treatment is a case series of 205 episodes of peri-operative anaphylactic shock [25]. In this study, fluid extravasation equivalent to one-third of the circulating blood volume occurred within minutes in severe anaphylaxis. Rapid, large-volume fluid boluses were needed to achieve blood pressure stabilisation, even in those with cardiac disease [25]. In NAP6, intravenous fluid treatment was judged inappropriate due to insufficient fluids in 19% of cases [7].

Rapid, large-volume fluid boluses are recommended in the immediate treatment of anaphylaxis, to restore and maintain adequate circulatory volume. Initial fluid boluses of 500–1000 ml (or 20 $ml.kg^{-1}$ in children aged < 12 y) are recommended. Further fluid boluses should be titrated to respond. Large volumes may be required, up to 3–5 l in adults and 60–100 $ml.kg^{-1}$ in children. There is no clear benefit to volume resuscitation using colloids rather than crystalloid in anaphylaxis, and colloids (particularly if gelatin-based) can themselves induce allergic reactions [26]. In parallel, it can be helpful to improve venous return

by using a head-down table tilt or elevating the patient's legs.

Where the clinical response is suboptimal despite an adrenaline infusion and appropriate fluid resuscitation, a second-line vasopressor should be started (in addition to adrenaline) [2, 27]. There is no clear evidence to recommend one vasopressor over another [28]. In patients taking beta-blockers, glucagon can be considered although the evidence supporting this is limited [2, 29]. Sugammadex has no immediate role in the resuscitation of suspected anaphylaxis [2].

Cardiopulmonary resuscitation should be started in adults with persistent systolic blood pressure < 50 mmHg, especially in the context of bradycardia [30]. In this context, adrenaline doses should be initially titrated based on the response to chest compressions. Intravenous adrenaline should be administered as per cardiac arrest advanced life support protocols if cardiac arrest occurs. Prolonged cardiopulmonary resuscitation (including extracorporeal life support, where available) should be considered for cardiac arrest caused by anaphylaxis, as there is a potentially reversible cause [2].

In patients with severe persistent bronchospasm, nebulised salbutamol and ipratropium, or parenteral bronchodilators, may be considered. These should be used as an adjunct treatment and not as an alternative to an adrenaline infusion. There is no evidence for or against the use of intravenous β-2 agonists or magnesium sulphate in the treatment of anaphylaxis. Ketamine and volatile anaesthetics (e.g. sevoflurane) also have a bronchodilator effect. Although there is no specific evidence for their use in anaphylaxis, this was recommended by the International Suspected Perioperative Allergic Reactions group [2].

The primary action of corticosteroids is the downregulation of the late (rather than early) inflammatory response. However, meta-analyses have confirmed the absence of any evidence that corticosteroids reduce reaction severity or prevent biphasic reactions [31, 32]. Evidence suggests that, in many healthcare settings, corticosteroids delay appropriate treatment with adrenaline [14]. For these reasons, routine administration of corticosteroids is no longer recommended for the initial treatment of anaphylaxis. There is no evidence supporting or refuting their efficacy in refractory anaphylaxis, therefore it is reasonable to consider corticosteroids as an adjunct to adrenaline to treat refractory shock or bronchospasm [2].

Antihistamines are no longer recommended in the initial emergency treatment of anaphylaxis [1, 4]. They are not effective against the cardiovascular and respiratory features of anaphylaxis and do not improve survival [31, 33, 34]. H1-antagonists administered as a rapid intravenous bolus can also precipitate hypotension [35–37]. There is evidence suggesting that giving antihistamines delays the appropriate administration of adrenaline and other treatments in the emergency setting [14]. Antihistamines can be useful to treat angioedema, urticaria and pruritus once patients have been stabilised [2].

Immediate follow-up

During anaphylaxis, mast cell degranulation leads to the release of tryptase into the circulation. Tryptase measurements are key to understanding whether anaphylaxis might have occurred but are omitted frequently [7]. Serum tryptase concentrations may not increase significantly until 30 min or more after the onset of symptoms and peak 1–2 h after onset [38]. The half-life of tryptase is short (approximately 2 h), and concentrations may return to normal within 6–8 h, so the timing of any blood samples is critical. Ideally, three samples should be taken: the first should be taken as soon as the patient is stable (blood sampling must not delay initial treatment and resuscitation); the second within 1–4 h of symptom onset (but ideally 1–2 h after onset) and the third at least 24 h after the event (baseline sample).

An internationally agreed consensus equation for a significant rise in tryptase level is 1.2 × baseline tryptase + 2 $mg.l^{-1}$ [39]. This is known as a dynamic tryptase rise, which may be seen even if the peak level is within the normal range. An absence of a rise in mast cell tryptase does not exclude anaphylaxis.

All patients with suspected peri-operative hypersensitivity reactions should be referred to a specialist allergy service for formal allergy testing, irrespective of mast cell tryptase results. The NAP6 anaesthetic allergy referral form can be found in the online Supporting Information Appendix S1. Guidance on who should be referred has been outlined by the Perioperative Allergy Network and can be found on the British Society of Allergy and Clinical Immunology website.

Fatal cases of anaphylaxis should be referred as soon as possible to the UK Fatal Anaphylaxis Registry. This can provide support and guidance on peri-mortem sample collection. Local laboratories should be advised to retain all peri-mortem samples to allow for post-mortem investigation.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Anaesthetic anaphylaxis referral form.