Perioperative anaphylaxis

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Abstract

Anaphylaxis is defined as a 'severe life-threatening generalized or systemic hypersensitivity reaction'. Anaphylactic shock is characterized by generalized vasodilation and increased capillary permeability, leading to reduction in cardiac output. The pathophysiology of anaphylaxis can be described as immunologic and non-immunologic. The National Audit Project 6 (NAP 6) has recently investigated perioperative anaphylaxis and this article will outline some key updates from their report. Common triggers include antibiotics, followed by neuromuscular blocking agents, chlorhexidine and patent blue dye. Invasive lines impregnated with chlorhexidine are frequently missed as a cause of anaphylaxis. Patients at high risk of adverse outcomes include the elderly and those with pre-existing cardiopulmonary disease. The diagnosis is clinical and can be confounded by physiological changes commonly experienced after induction or airway manipulation. Key management principles include early administration of intravenous adrenaline, CPR if the systolic blood pressure is <50 mmHg and fluid resuscitation. Follow-up investigations are essential to guide future patient care and this is the responsibility of the anaesthetist.

Keywords Adrenaline; anaphylaxis; pathophysiology of anaphylaxis; tryptase

Royal College of Anaesthetists CPD Matrix: 1B01, 2A06, 2C04

Learning objectives

After reading this article, you should be able to:

- define and classify hypersensitivity and perioperative anaphylaxis
- describe the pathophysiology of anaphylaxis
- understand the diagnostic criteria and common perioperative triggers
- appreciate the impact that various comorbidities and medications have on the response to treatment in patients with anaphylaxis
- describe the immediate and secondary management of a patient with anaphylaxis
- understand the need for further investigations and appropriate onward referral

Hypersensitivity

When a stimulus that is normally tolerated in the general population (e.g. insect stings, certain foods) causes an undesirable immune response, it is labelled as a hypersensitivity reaction. These reactions are graded (Box 1), and once features of grade 3 and above are present it is considered anaphylaxis. Grades 1 and 2 are not considered life threatening.

Anaphylaxis

Anaphylaxis is defined as a 'severe life-threatening generalized or systemic hypersensitivity reaction'. It is derived from the Greek 'ana' (backward) and 'phylaxis' (protection/immunity). The death of an Egyptian pharaoh after a wasp sting (2640 BC) is the first documented episode of anaphylaxis. The majority of anaphylactic reactions occur in the community, with 10% arising from insect stings. However, more than one-third of patients with anaphylactic reactions requiring admission to intensive care originate from the theatre environment. This article will focus on perioperative anaphylaxis, recently studied by the National Audit Project (NAP) in their 6th report (Box 2). These audit projects aim to illuminate important anaesthetic topics of low incidence.

Perioperative anaphylaxis has an estimated incidence of about 1:10,000 anaesthetics. The true incidence, however, may well be higher due to incomplete or delayed reporting. The chance of facing this critical incident during a career is low (about once every 7 years). Significant morbidity and mortality can be avoided with prompt and simple measures.

Hypersensitivity grading

Grade 1: cutaneous features such as rash, itch or peripheral swelling
Grade 2: mild hypotension or wheeze (usually not requiring treatment) ± Grade 1 features
Grade 3: severe grade 1 or 2 features, and may include airway swelling
Grade 4: fulfils the requirements for initiating cardiopulmonary resuscitation (CPR)
Grade 5: a fatal reaction

Box 1

Pathophysiology

The World Allergy Organization has proposed that anaphylaxis be described in the form of immunological versus non-immunological, discarding the vague term 'anaphylactoid'.

The pathophysiology underlying either mechanism, however, results in generalized vasodilation and increased capillary permeability leading to a cascade of physiological deterioration culminating in a reduction in preload and cardiac output (Figure 1).

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Key lessons from NAP 6.

- Bronchospasm and hypotension are the most common presenting features
- Patients at high risk of adverse outcomes include the elderly, asthmatics, obese, ASA $\geq$3, prolonged CPR or taking ACE inhibitors/beta-blockers
- Immediate resuscitation includes IV fluids and early administration of adrenaline
- Start CPR if systolic BP $<$50 mmHg
- 'Test doses' of antibiotics are not recommended
- Consider administration of antibiotics prior to anaesthesia if possible as this allows earlier detection of symptoms and simplifies investigation of the allergen
- Teicoplanin causes significant anaphylaxis so ensure that patients truly are allergic to penicillin
- Invasive lines impregnated with chlorhexidine are frequently missed

Box 2

Immunological anaphylaxis

IgE mediated reactions

Anaphylaxis is most commonly caused by immunological mechanisms- specifically IgE mediated mechanisms. On the first exposure to the allergen, the B cells of allergy-prone people will start to produce allergen-specific IgE immunoglobulins. The differentiation of B-cells into IgE producing cells is influenced by CD4 Helper T-Cell (Th2 cells) activity. This process takes place in the peripheral lymphoid tissue, followed by systemic spread of IgE throughout the tissues and vasculature. The IgE immunoglobulins bind to the Fc receptor on mast cells and/or basophils and 'prime' these cells. A second exposure of allergen will interact with surface bound IgE specific to that allergen, resulting in widespread mast cell/basophil degranulation of pre-formed vasoactive mediators, enzymes and cytokines (tryptase, histamine, tumour necrosis factor). Cytokines such as interleukin-4 and interleukin-13 further contribute to the IgE response. These mediators either act directly on tissue or indirectly by activating eosinophils to cause symptoms of allergy. It is the result of a complex cascade of vasoactive substances; histamine release alone will not suffice.

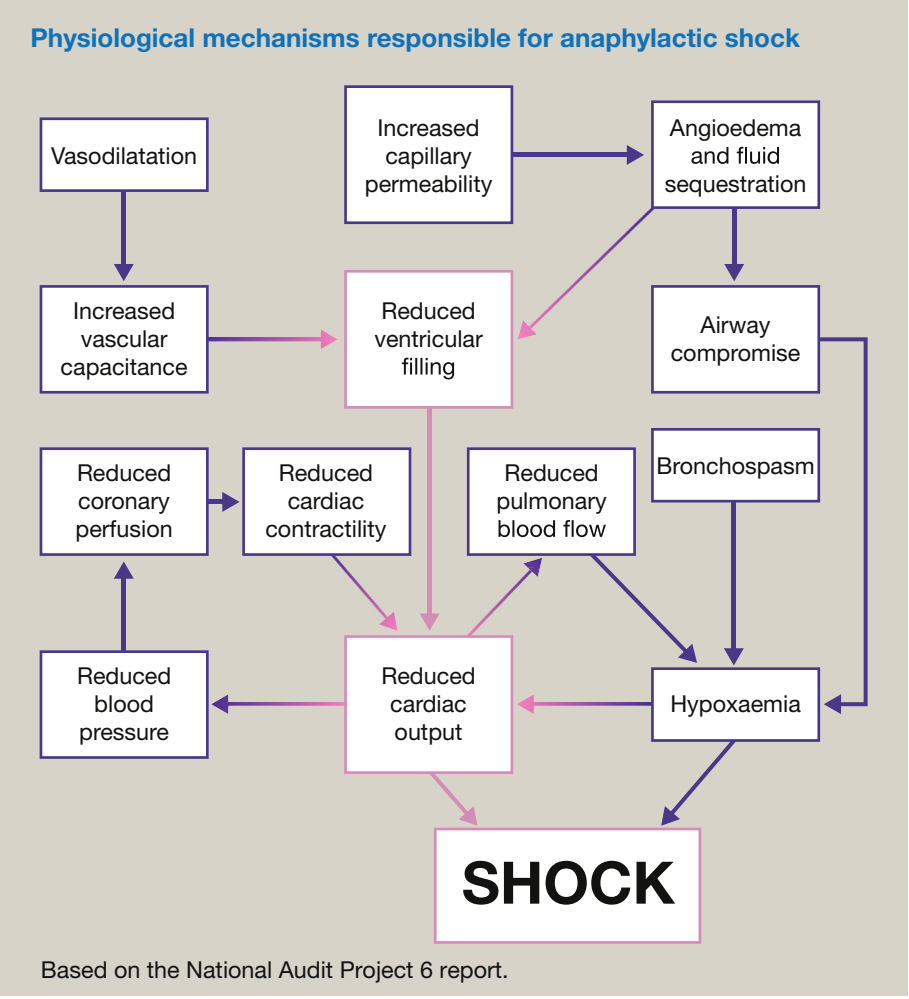


Figure 1

Non-IgE mediated reactions

Although IgG mediated reactions have not been demonstrated in humans, IgG receptors are involved in activating macrophages and neutrophils to secrete platelet activating factor (PAF) which activates mast cells causing immune-complex mediated anaphylaxis. This has been implicated in life-threatening reactions to many drugs (e.g. protamine).

Non-immunological anaphylaxis

These reactions are caused by agents or events that bypass immunoglobulins and induce sudden and massive mast cell or basophil degranulation. Proposed mechanisms include:

- activation of complement in the absence of immune complex formation (e.g. peanut-induced anaphylaxis)
- direct activation of receptors on mast cells and/or basophils. Implicated in 'red man syndrome' reaction to vancomycin and degranulation by drugs such as opiates
- excess bradykinin can cause rare anaphylactic reactions or isolated angioedema from angiotensin-converting enzyme inhibitors (ACEi).

Diagnosis

The diagnosis of perioperative anaphylaxis is based on clinical findings and confirmed later by immunological testing. Clinical suspicion is complicated by the presence of multiple overlapping physiological changes expected in response to administered drugs, airway instrumentation and patient comorbidities. Hypotension and bronchospasm frequently occur due to common anaesthetic interventions. Reassuringly, recognition of a critical incident was considered 'prompt' in 97% of cases in NAP 6. However, the actual diagnosis of anaphylaxis and initiation of specific treatment was delayed in 15% of cases. This delay is understandable as time is needed to exclude the more common differentials such as occult haemorrhage and acute pulmonary or cardiac pathology. This is emphasized in the Association of Anaesthetists of Great Britain & Ireland (AAGBI) guideline, which advises the consideration of anaphylaxis when faced with unexplained adverse clinical signs (Box 3). *Severe perioperative anaphylaxis* is when systolic BP < 50 mmHg is present or CPR has been required.

When anaphylaxis should be considered

- Unexplained hypotension
- Unexplained bronchospasm (wheeze may be absent if severe)
- Unexplained tachycardia or bradycardia
- Angioedema
- Unexpected cardiac arrest where other causes are excluded
- Cutaneous flushing in association with one or more of the signs above

From AAGBI Quick Reference Handbook available at https://anaesthetists.org/.

Box 3

Table 1 outlines how the features of perioperative anaphylaxis observed by NAP 6 at presentation differ from those seen overall. Hypotension is common in all episodes of anaphylaxis, but is the sole feature in 46%. Asthmatics are more likely to present with high airway pressures; this is the patient population that you are likely to attribute bronchospasm to their underlying lung disease. It is well recognized that the development of the pathognomonic urticarial rash is a late feature (sometimes only after resuscitation), but absence of a rash not exclude anaphylaxis.

Clinical features of perioperative anaphylaxis

Presenting Features	Clinical features overall
Hypotension (46%)	Hypotension (100%)
Bronchospasm/high airway pressures (20%)	Flush/non-urticarial rash (60%)
Tachycardia (10%)	Bronchospasm/high airway pressures (50%)
Flush/non-urticarial rash (7%)	Tachycardia (50%)
Low sats (5%)	Low sats (40%)
Reduced/absent capnography (2%)	Reduced/absent capnography (30%)

From the National Audit Project 6 report.

Table 1

Triggers

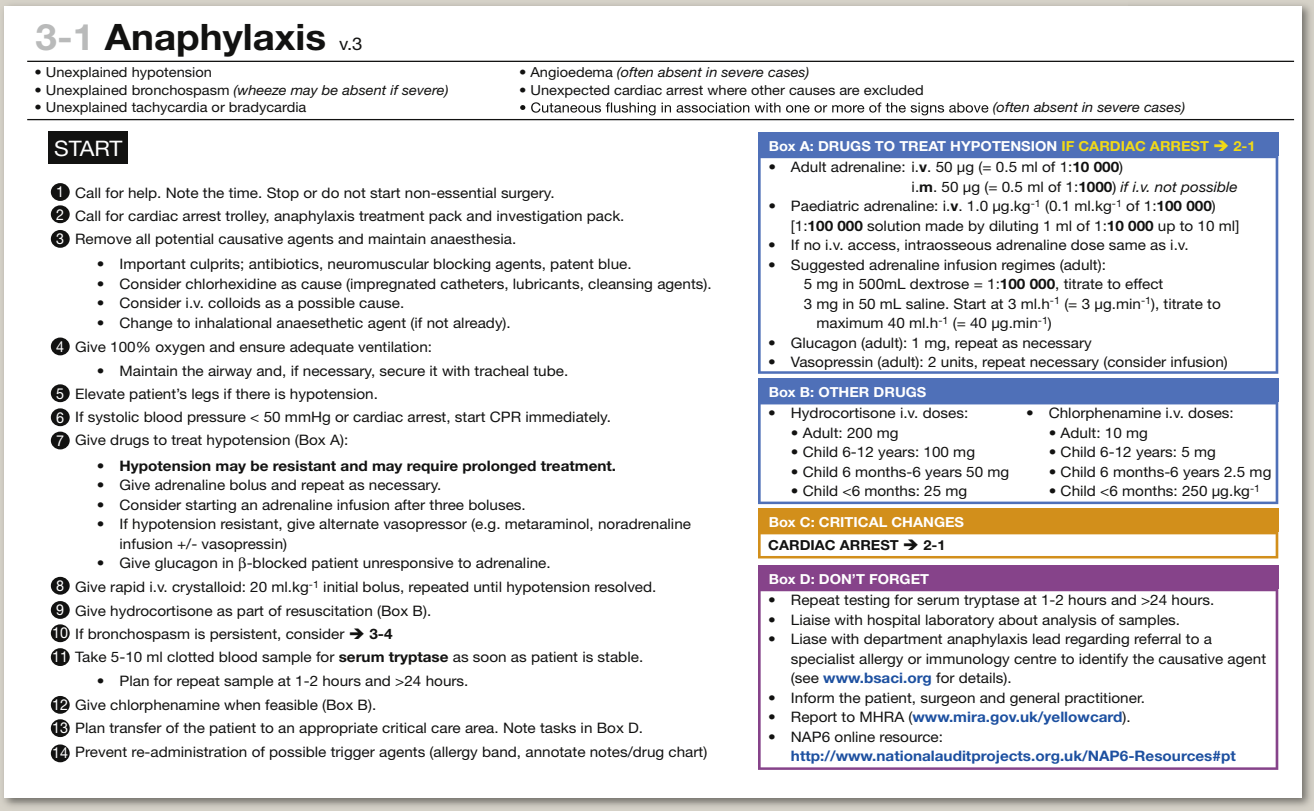
Anaphylaxis can be precipitated by a multitude of triggers; the most commonly identified triggers include food, drugs and venom. Perioperative anaphylaxis is driven by drug exposure. NAP 6 reported that the most commonly *identified* agents in anaesthesia are antibiotics (47%) followed by neuromuscular blockers (33%), chlorhexidine (9%) and patent blue dye (5%). Interestingly, no latex-induced anaphylaxis was identified; this may reflect an increased awareness of this allergen with subsequent reduction of occupational latex use.

Allergens such as neuromuscular blockers and IV antibiotics are typically associated with the onset of clinical features within 10 minutes. Others may be more delayed, including patent blue dye, chlorhexidine and colloids.

Antibiotics are given in almost 60% of surgical procedures. Penicillin is a well-recognized trigger, but increasingly teicoplanin is being identified as a culprit and together, co-amoxiclav and teicoplanin caused 90% of all antibiotic related reactions in NAP 6. Interestingly, patients labelled with penicillin allergy were often given teicoplanin as an alternative. There were several case reports in NAP 6 describing patients suffering an anaphylaxis to teicoplanin who, on allergy testing, were actually not allergic to penicillin. This highlights the importance of taking thorough allergy histories and recognizing that common alternatives may be equally allergenic.

In terms of neuromuscular blockers, suxamethonium is almost twice as likely to cause anaphylaxis than its non-depolarizing counterparts. The incidence of anaphylaxis was very similar amongst the non-depolarizing agents, which means that perceived risk of anaphylaxis should not be a factor when making a choice between them. Use of sugammadex is rising and there was a single case of anaphylaxis reported in NAP 6. It has been used in resuscitation in anaphylaxis presumed to be caused by rocuronium, with no clear evidence base for success.

Anaphylaxis algorithm based on AAGBI guidelines



3-1 Anaphylaxis v.3

- Unexplained hypotension
- Unexplained bronchospasm *(wheeze may be absent if severe)*
- Unexplained tachycardia or bradycardia
- Angioedema *(often absent in severe cases)*
- Unexpected cardiac arrest where other causes are excluded
- Cutaneous flushing in association with one or more of the signs above *(often absent in severe cases)*

START

1. Call for help. Note the time. Stop or do not start non-essential surgery.
2. Call for cardiac arrest trolley, anaphylaxis treatment pack and investigation pack.
3. Remove all potential causative agents and maintain anaesthesia.
   - Important culprits; antibiotics, neuromuscular blocking agents, patent blue.
   - Consider chlorhexidine as cause (impregnated catheters, lubricants, cleansing agents).
   - Consider i.v. colloids as a possible cause.
   - Change to inhalational anaesethetic agent (if not already).
4. Give 100% oxygen and ensure adequate ventilation:
   - Maintain the airway and, if necessary, secure it with tracheal tube.
5. Elevate patient's legs if there is hypotension.
6. If systolic blood pressure < 50 mmHg or cardiac arrest, start CPR immediately.
7. Give drugs to treat hypotension (Box A):
   - **Hypotension may be resistant and may require prolonged treatment.**
   - Give adrenaline bolus and repeat as necessary.
   - Consider starting an adrenaline infusion after three boluses.
   - If hypotension resistant, give alternate vasopressor (e.g. metaraminol, noradrenaline infusion +/- vasopressin)
   - Give glucagon in β-blocked patient unresponsive to adrenaline.
8. Give rapid i.v. crystalloid: 20 ml.kg^{-1} initial bolus, repeated until hypotension resolved.
9. Give hydrocortisone as part of resuscitation (Box B).
10. If bronchospasm is persistent, consider ➔ **3-4**
11. Take 5-10 ml clotted blood sample for **serum tryptase** as soon as patient is stable.
    - Plan for repeat sample at 1-2 hours and >24 hours.
12. Give chlorphenamine when feasible (Box B).
13. Plan transfer of the patient to an appropriate critical care area. Note tasks in Box D.
14. Prevent re-administration of possible trigger agents (allergy band, annotate notes/drug chart)

Box A: DRUGS TO TREAT HYPOTENSION IF CARDIAC ARREST ➔ 2-1

- Adult adrenaline: i.**v.** 50 µg (= 0.5 ml of 1:**10 000**)
  i.**m.** 50 µg (= 0.5 ml of 1:**1000**) *if i.v. not possible*
- Paediatric adrenaline: i.**v.** 1.0 µg.kg^{-1} (0.1 ml.kg^{-1} of 1:**100 000**) [1:**100 000** solution made by diluting 1 ml of 1:**10 000** up to 10 ml]
- If no i.v. access, intraosseous adrenaline dose same as i.v.
- Suggested adrenaline infusion regimes (adult):
  5 mg in 500mL dextrose = 1:**100 000**, titrate to effect
  3 mg in 50 mL saline. Start at 3 ml.h^{-1} (= 3 µg.min^{-1}), titrate to maximum 40 ml.h^{-1} (= 40 µg.min^{-1})
- Glucagon (adult): 1 mg, repeat as necessary
- Vasopressin (adult): 2 units, repeat necessary (consider infusion)

Box B: OTHER DRUGS

- Hydrocortisone i.v. doses:
  - Adult: 200 mg
  - Child 6-12 years: 100 mg
  - Child 6 months-6 years 50 mg
  - Child <6 months: 25 mg
- Chlorphenamine i.v. doses:
  - Adult: 10 mg
  - Child 6-12 years: 5 mg
  - Child 6 months-6 years 2.5 mg
  - Child <6 months: 250 µg.kg^{-1}

Box C: CRITICAL CHANGES

CARDIAC ARREST ➔ 2-1

Box D: DON'T FORGET

- Repeat testing for serum tryptase at 1-2 hours and >24 hours.
- Liaise with hospital laboratory about analysis of samples.
- Liase with department anaphylaxis lead regarding referral to a specialist allergy or immunology centre to identify the causative agent (see **www.bsaci.org** for details).
- Inform the patient, surgeon and general practitioner.
- Report to MHRA (**www.mira.gov.uk/yellowcard**).
- NAP6 online resource: **http://www.nationalauditprojects.org.uk/NAP6-Resources#pt**

From AAGBI *Quick Reference Handbook,* available at: https://anaesthetists.org/.

Figure 2

Test dose

'Test doses' of IV antibiotics were implicated in 20% of all reported anaphylaxis cases in NAP 6, 50% of which caused the actual anaphylactic reaction. There is no evidence to support the practice of giving test doses in an attempt to reduce the severity of anaphylaxis. Test doses in theatre are typically not consistent with the allergen-challenge given in allergy clinics and the use of test doses is not advised.

Management

The AAGBI have updated their guidance on the management of anaphylaxis to include several key points from NAP 6 (Figure 2). The numbered references within Figure 2 refer to the updated *Quick Reference Handbook* available on the AAGBI website (https://anaesthetists.org/). Initial management should follow the well-established ABCDE approach. Key early considerations should be to remove potential causative agents including invasive devices impregnated with chlorhexidine and management of hypotension.

Management of hypotension

Considering that hypotension is the dominant feature in anaphylaxis, NAP 6 reported that it was managed surprisingly poorly. This is likely multifactorial, arising predominantly due to a paucity of data on the implications and management of perioperative hypotension. Clinical factors include a reluctance to administer early adrenaline (preferring more common vasopressors) and insufficient fluid resuscitation.

Adrenaline has advantageous alpha and beta agonism which will be beneficial in the management of the pathophysiology driving anaphylactic shock. These effects include increased preload (due to venoconstriction), increased contractility which increases cardiac output, and inhibition of mast cell/basophil degranulation and bronchodilation. ECG monitoring is advised as there is a concern about cardiac arrhythmias developing, but the benefits far outweigh the risks in anaphylaxis.

NAP outlines four key factors contributing to the reluctance to administer adrenaline:

- Anaphylaxis is uncommon.
- Most causes of hypotension respond well to commonly used vasopressors and anaesthetists will typically persist with these more familiar agents.
- Adrenaline is a relatively unfamiliar drug outside critical care.
- Administering adrenaline confirms that a crisis is occurring.

Adrenaline doses are outlined in Figure 2. Admittedly, the evidence base for adrenaline dosing in anaphylaxis is poor and wide variations internationally exist. UK guidelines use IV

boluses of 50 micrograms initially, with consideration of glucagon in patients on beta-blockers and vasopressin in those poorly responsive to catecholamines.

The success of vasopressor and inotropic support relies on adequate fluid resuscitation, especially in anaphylaxis which is characterized by intravascular volume depletion. NAP 6 reported that fluid management was suboptimal in 20% of cases. Guidelines now suggest an initial fluid bolus of 20 ml/kg which should be repeated until hypotension is resolved.

The NAP 6 report suggests CPR should commence with systolic BP of <50 mmHg during perioperative anaphylaxis, welcoming debate on the matter as there is currently a lack of universally accepted management and CPR guidance for the hypotensive anaesthetized patient. Arguments against this action include the fact that initiating compressions could distract from the prompt initiation of anaphylaxis-specific treatment which will counter the real cause of the reduced cardiac output.

Corticosteroids and antihistamines should be considered, but two Cochrane papers reviewing their use have failed to make any firm recommendations. Antihistamines may reduce swelling, rash and urticaria. See Figure 2 for doses and timings.

Laboratory analysis

Blood samples should be sent for serum mast cell tryptase (MCT) levels to enable retrospective confirmation/refutation of the diagnosis. Blood for MCT levels should be taken immediately during event, 1–2 hours post-event and 24 hours post-event. Current adherence to this regime is poor; NAP 6 report that only 45% of early samples met the standards set by the British Society for Allergy and Clinical Immunology.

Thorough investigation following suspected anaphylaxis is essential to avoid future re-exposure to the allergen, and it is the responsibility of the anaesthetist to organize appropriate investigation and referral to allergy clinic. This includes a letter which should be given immediately to the patient on discharge with an estimate of the triggering agent; this prediction turns out to be correct in about 75% of cases and proves how important our input is in terms of securing future patient safety.

When to abandon surgery

This decision is dependant on multiple clinical factors and based on a risk–benefit analysis. If a procedure is cancelled, it may be indeterminately delayed to first accommodate allergy screening. Delays in emergency or cancer surgery are unacceptable and consideration to continue surgery once the patient has been stabilized should be made. NAP 6 have published the first set of guidelines to aid the re-organization of surgery in patients with suspected anaphylaxis not yet tested formally.

Follow-up

Anaphylaxis has classically been described in phases, with up to 90% of presentations quoted to be 'uniphasic' with features peaking 30–60 minutes after exposure to allergens. Biphasic responses were characterized by a uniphasic peak, followed by an asymptomatic period of an hour or more with the subsequent recurrence of symptoms despite no re-exposure to allergen. NAP 6 failed to demonstrate any examples of biphasic responses in perioperative anaphylaxis.

Nevertheless, most patients will typically be monitored postoperatively in a high dependency area and rarely require re-escalation of care following the initial event. NICE (CG 134) recommends a period of 6–12 hours of observation following onset of symptoms treated as anaphylaxis. The mortality of perioperative anaphylaxis is quoted as 4%; fatalities are more common in high risk patients with cardiac and pulmonary co-morbidities. ◆

FURTHER READING

Association of Anaesthetists of Great Britain & Ireland (AAGBI) Quick reference guidebook available on (https://anaesthetists.org/).

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