11 Immediate management and departmental organisation

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Key findings

- All patients were resuscitated by an anaesthetist of appropriate grade and recognition of a critical event was prompt.
- The first clinical feature of anaphylaxis appeared in <5 minutes in 66% of cases, in <10 minutes in 83%, in <15 minutes in 88% and after >30 minutes in 4.6%.
- Recognition of a critical event and of anaphylaxis was generally very prompt.
- There was delay in starting anaphylaxis-specific treatment in 25% of cases, illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis.
- Airway management was generally uncomplicated and without difficulty. A single front of neck airway was judged the only case of airway morbidity associated with anaphylaxis.
- When cardiac compressions were indicated there was delay starting them in more than half of cases.
- Vasopressin and glucagon were very rarely used.
- Fluid administration was frequently judged to be insufficient and was inappropriate in 19%.
- The review panel judged management to be 'good' or 'good and poor' in 85% of cases.
- Careful examination of the role of antihistamines found no evidence of harm or benefit.
- More than half of patients required admission to critical care: of these 70% required level 3 care and most required catecholamine infusions after admission.
- Six per cent of survivors underwent surgery between the index event and the patient being seen in clinic. This was uneventful in every case.

What we already know

Recognition of perioperative anaphylaxis

Recognition that a critical event occurring during anaesthesia is likely to be anaphylaxis may not be straightforward, and the differential diagnosis is wide. The onset may be immediate or delayed, and the patient's medical history rarely provides any clues.

Rash, the classical sign of an allergic reaction, is present in approximately half of cases, but may be delayed or not visible under surgical drapes.

A fall in blood pressure is usually the first sign of perioperative anaphylaxis. A modest fall in blood pressure is a frequent accompaniment of general anaesthesia (Reich 2005) as well as during neuraxial anaesthesia, and vasopressor drugs are often required during routine anaesthesia. It is only when the blood pressure does not respond that less common causes of hypotension are sought, including ischaemic cardiac event, cardiac arrhythmia, embolus, pneumothorax, covert haemorrhage, and anaphylaxis.

There is limited information concerning the frequency with which bronchospasm is the first clinical feature. An acute rise in airway pressure is also not uncommon during routine anaesthesia, especially in patients with asthma and as a response to intubation.

Pharmacological management

There are few studies of the efficacy of individual drugs in the management of perioperative anaphylaxis, and no randomised clinical trials (RCTs), as a result of which the majority of published information derives from case reports.

Adrenaline

It is generally agreed that adrenaline is the mainstay of management, and this drug is recommended in all published guidelines (Krøigaard 2007; Harper 2009; Mirakian 2009; National Institute for Health and Clinical Excellence, 2011, 2014; Simons 2011; Resuscitation Council UK, 2016).

Having both alpha and beta agonist properties, adrenaline has compelling theoretical advantages in the treatment of anaphylaxis. The beneficial actions of adrenaline include venoconstriction which increases venous return, reduced capillary permeability, increased cardiac contractility and cardiac output, bronchodilatation, and inhibition of mast cell and basophil mediator release. These benefits exceed the disadvantages of vasodilatation in skeletal muscle and the potential risk of cardiac arrhythmias. Early administration of adrenaline is associated with improved outcomes in out-of-hospital anaphylaxis (Pumphrey 2000).

McLean-Tooke, reviewing the topic (McLean-Tooke 2003) concluded that adrenaline is not contraindicated in patients with coronary artery disease, as continuing anaphylaxis probably further reduces coronary artery perfusion. However, excessive dose or over-rapid IV administration can cause arrhythmias. Intravenous adrenaline is more likely than intramuscular (IM) adrenaline to result

in cardiac complications in treatment of out-of-hospital anaphylaxis in elderly patients (Kawano 2017) but there is no published information regarding the perioperative setting.

The IV and IM routes are both recommended for the treatment of perioperative anaphylaxis, with the IV route restricted to patients with continuous vital-signs monitoring, including continuous ECG (Resuscitation Council UK 2016). AAGBI guidelines recommend an initial IV dose of 50 mcg, repeated as necessary (Harper 2009). Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) guidance for Grade 3 reactions recommend an initial IV dose of 100 mcg followed, if necessary, by 100-200 mcg every 1-2 minutes and a continuous infusion after three IV boluses (Kolawole 2017). A systematic review informing the European Academy of Allergy and Clinical Immunology (EAACI) Guidelines for Food Allergy and Anaphylaxis considered only out-of-hospital anaphylaxis, and intravenous (IV) adrenaline was not included (Dhami 2014).

Metaraminol

Although metaraminol is not recommended as first-line treatment for anaphylaxis, it is often immediately available in operating theatres for the management of anaesthesia-induced hypotension. There are reports of its efficacy in perioperative anaphylaxis refractory to large doses of adrenaline (Heytman 2004). It is suggested as a second-line treatment in AAGBI guidelines (Harper 2009).

Vasopressin

Several case reports have described survival after use of IV vasopressin (antidiuretic hormone), a potent vasoconstrictor, in the management of intractable perioperative anaphylaxis (Hussain 2008, Meng 2008, Schummer 2008, Bensghir 2013) (Table 1).

Table 1. Case reports describing efficacy of vasopressin in intractable perioperative anaphylaxis

Author	Cases	Total dose of adrenaline before vasopressin	Other vasopressors before vasopressin	Vasopressin dose
Schummer 2008	6	1 mg; 1 mg; 1 mg; 3 mg; 1.6 mg; 0.8 mg	Noradrenaline (5 cases)	2 units (3 cases); 5 units; 8 units; 15 units
Meng 2008	1	1.2 g	Phenylephrine	2 units + infusion
Hussain 2008	1	2 mg	Phenylephrine, noradrenaline	2 units
Bensghir 2013	1	5 mg	Ephedrine, dobutamine	2 units

The mechanisms of action are uncertain, but widespread vasoconstriction is likely to be an important component. Recommendations in guidelines are as follows: AAGBI – not included; Scandinavian 2-10 units in anaphylaxis unresponsive to adrenaline (Krøigaard 2007). ANZAAG 1-2 units, then 2 units per hour (Kolawole 2017).

Glucagon

The benefit of adrenaline is likely reduced in the presence of beta-adrenergic receptor blockade (beta blockade). In patients taking beta-blockers, several guidelines recommend increasing the adrenaline dose and considering glucagon. Both adrenaline and glucagon raise intracellular cAMP concentrations but glucagon bypasses beta receptors. There are single-case reports of glucagon use in beta-blocked patients leading to rapid resolution of hypotension (Zalonga 1986, Javeed 1996). European (Mertes 2011) and ANZAAG (Kolawole 2017) guidelines recommend 1-2 mg every 5 minutes until response.

Corticosteroids

There are no published RCTs investigating the efficacy of corticosteroids in the acute management of anaphylaxis. The rationale for their administration in anaphylaxis appears to be down-regulation of the late-phase response by altering gene expression, and is an extrapolation of their effectiveness in the long-term management of allergic asthma (Liu 2001). Benefit in the acute phase of anaphylaxis in not expected. Hydrocortisone is recommended in published guidelines. Dexamethasone 7.5 mg has an equivalent glucocorticoid effect to hydrocortisone 200 mg. Laboratory animal work suggests pre-treatment may reduce the severity of experimentally-induced anaphylaxis (Choo 2010, Dhami 2014).

Antihistamine drugs

Two RCTs investigating the use of antihistamines in relatively minor out-of-hospital allergic reactions found that combining H1 and H2 antihistamines improved urticaria; H1 antihistamines were better in treating pruritus. A Cochrane review of H1 antihistamines for anaphylaxis was unable to make any recommendations, as a result of lack of evidence (Sheikh 2007). This statement, together with side effects of promethazine, has resulted in some expert groups recommending that antihistamines should not be administered (Kolawole 2017).

Sugammadex

Several case reports may be considered supportive of administration of sugammadex during rocuronium-induced anaphylaxis (McDonnell 2011, Kawano 2012). A large dose, at least 16 mg/kg, has been proposed (Barthel 2012) (Table 2).

Table 2. Case reports of sugammadex use in rocuronium-induced anaphylaxis

Author	Cases	Total dose of adrenaline before sugammadex	Other vasopressors before sugammadex	Sugammadex dose
McDonnell 2011	1	4 mg	-	500 mg
Kawano 2012	1	-	Ephedrine 4 mg	200 mg
Barthel 2012	1	0.1 mg	-	1200 mg + 400 mg

The hypothesis that encapsulating the antigen may halt the clinical features of anaphylaxis is unproven. Leysen *et al* (Leysen 2011) challenged basophils from rocuronium-allergic individuals in vitro, with different mixtures of rocuronium and sugammadex: CD63 expression was used to indicate basophil activation. Sugammadex inhibited basophil activation when pre-administered but not when added to already-activated basophils. Clarke examined the impact of sugammadex on skin wheals during intradermal skin testing in rocuronium-allergic patients (Clarke 2012). Adding sugammadex to rocuronium reduced the wheal size compared to rocuronium alone, but injecting sugammadex into an existing rocuronium-induced wheal had no effect. These studies suggest that sugammadex could lessen a reaction if given before an anaphylactic event, but that once a reaction has been triggered, subsequent administration of sugammadex is unlikely to terminate it.

Platt *et al* (Platt 2015) reported sugammadex administration during immediate management of suspected rocuronium-induced anaphylaxis. Skin testing, subsequently demonstrated that, of 13 cases, five were not rocuronium-induced. Clinical features improved in six patients, including three without rocuronium-induced anaphylaxis: raising the possibility that sugammadex may exert a vasopressor effect via a mechanism other than encapsulating the antigen.

Intravenous fluids

Anaphylaxis is associated with an acute fall in actual and effective circulating blood volume as a result of vasodilatation, increased vascular permeability and fluid sequestration, causing reduced venous return and cardiac output (Figure 1). Although there are no studies reporting the efficacy of different fluid regimens during anaphylaxis, rapid repletion of circulating volume is a logical therapeutic manoeuvre and there is consensus for rapid IV infusion of crystalloid fluids. Recent guidelines emphasise the need to give rapid, repeated IV fluid challenges whilst monitoring the response: ANZAAG guidelines (Kolawole 2017) recommend giving repeated boluses of 20 ml/kg.

Numerical Analysis

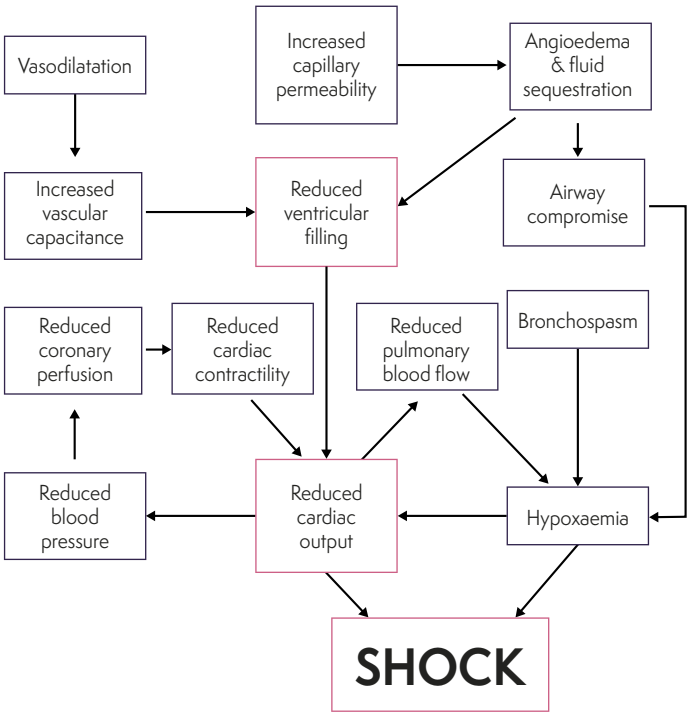
Organisational preparedness for perioperative anaphylaxis

Little is known about how prepared hospitals are for management of perioperative anaphylaxis. To determine this, a brief organisational survey was sent to all hospitals. Results from NHS hospitals are reported here, and those from independent-sector hospitals in Chapter 23, The independent sector.

Responses were received from 217 NHS departments of anaesthesia, covering 323 hospitals (Range 1-7) and employing 12,656 anaesthetists. The response rate was 91%.

Anaesthetic services provided at the locations included general anaesthesia (317 = 98.1%), regional anaesthesia (305 = 99.4%), sedation (310 = 96%) and managed anaesthesia care (274 = 84.8%). Two hundred and thirty-three (72.1%) hospitals had a critical care unit (HDU or ICU) and 205 (63.5%) an emergency department.

Figure 1. Physiological mechanisms responsible for anaphylactic shock



The number of consultant, non-consultant career grade and trainee anaesthetists varied widely from 1-150 (median 32), 0-40 (median 7) and 0-77 (median 19) respectively. Overall medical staffing numbers ranged from 1-228 (median 77).

One hundred and fifty-two (47.1%) hospitals had an anaphylaxis lead anaesthetist. Guidelines for the management of anaphylaxis were immediately available in the majority of theatres in 307 (95.0%) hospitals: predominantly the AAGBI guidelines (88% of those with guidelines) or the RC (UK) guidelines (13%). One hundred and thirty-six (42.1%) hospitals reported having a guideline for immediate investigation of anaphylaxis and 43 (13%) a guideline for referral for investigation. One hundred and sixty hospitals (50%) had readily available anaphylaxis packs. Three hundred and four (94.8%) hospitals were able to provide details of locations where patients would be referred for specialist investigation. One (0.3%) respondent stated the referral would be to the patient's general practitioner or 'consultant dependent'. In 11 (3.5%) hospitals individual anaesthetists performed in-house skin prick testing.

Immediate management of perioperative anaphylaxis

Early management of perioperative anaphylaxis depends on first appreciating that a critical event has occurred, including anaphylaxis in the differential diagnosis, and starting anaphylaxis-specific treatment.

The NAP6 case report form included detailed questions relating to the immediate management of suspected anaphylactic events. These included details of the event, first and subsequent clinical features, speed of recognition of a critical event, recognition of the event as anaphylaxis, and commencement of anaphylaxis-specific treatment. We captured details and timings of drug administrations, IV fluids, cardiac compressions, transfer after resuscitation, and patient outcomes. We asked about availability and use of guidelines and algorithms, contribution of the theatre team, communications with the patient, and referral for investigation.

At panel review, the quality of immediate management was reviewed and classified, including factors such as timeliness, accuracy and completeness. In doing this we also referred to current guidelines of the AAGBI and RCUK on management of perioperative anaphylaxis (Harper 2009; RCUK 2016) and cardiac arrest (Soar 2015) where relevant. The overall initial management was graded as 'good', 'good and poor' or 'poor'.

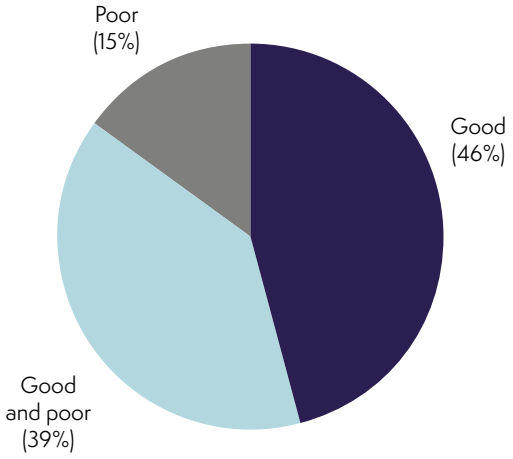
Although administration of adrenaline is the accepted standard for the immediate management of perioperative anaphylaxis, the review panel recognised that anaphylaxis is an uncommon cause of hypotension or bronchospasm during anaesthesia. It is therefore reasonable for anaesthetists to start treatment with vasopressors and bronchodilators such as metaraminol, ephedrine and salbutamol before instituting anaphylaxis-specific treatment unless anaphylaxis was clinically obvious from the outset.

Results here are based on a dataset of the 266 reviewed cases of confirmed anaphylaxis. For some analyses a smaller dataset is used. The quality of delivered care is based on the full panel review of 184 cases.

Overall initial clinical management by the anaesthetist

Resuscitation was performed by an anaesthetist of appropriate grade in all cases. Taking all the elements of clinical management into account, the review panel considered that management by the anaesthetist was good in 46% cases; good and poor in 39%, and poor in 15% (Figure 2).

Figure 2. Quality of the overall initial clinical management by the anaesthetist as judged by the review panel



Recognition of the critical incident, recognising anaphylaxis, and starting specific treatment

Although the suspected trigger agent was not always confirmed by the allergy clinic, the time of administration of the suspected agent was used as the starting point for response times, representing a better indicator of the decision-making process during the anaphylactic event.

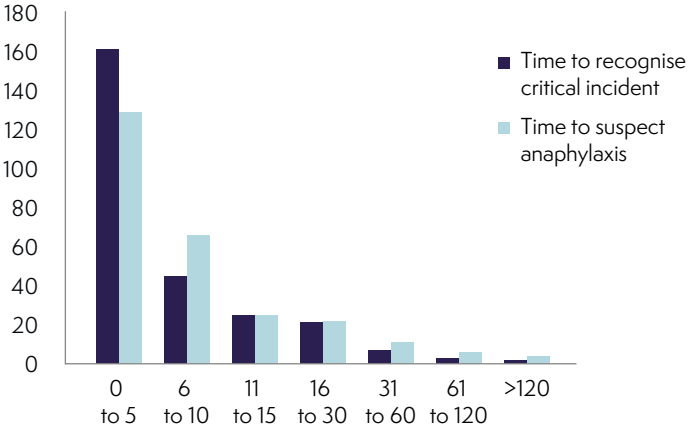
Within five minutes of administration of the suspected trigger agent a critical incident was recognised by the anaesthetist in 60% of cases and anaphylaxis was suspected in 49% of cases (Figure 3). By 10 minutes, the corresponding figures were 78% and 74%.

The first clinical features of anaphylaxis were usually but not always rapid in onset: appearing in <5 minutes after exposure to the suspected trigger agent in 66% of cases, in 6-10 minutes in 16.7% and in 10-15 minutes in 5%. Delayed reactions >30 minutes were seen in 4.6%.

Resuscitation was performed by an anaesthetist of appropriate grade (consultant or career grade anaesthetist) in all cases.

Recognition of the critical incident and suspicion of anaphylaxis was judged to have been prompt in 97.3% and 83.4% of cases respectively.

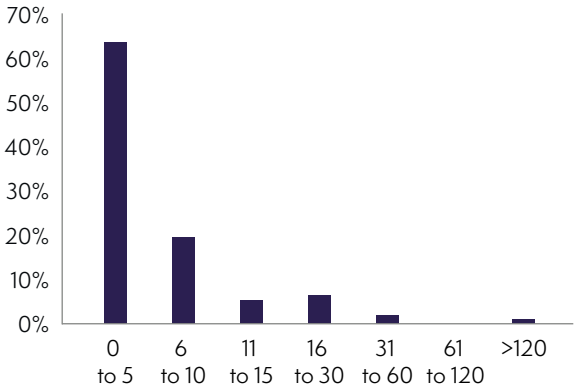
Figure 3. Elapsed time (minutes) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis (number of cases)



Once the first clinical feature of anaphylaxis had appeared, specific treatment for anaphylaxis was started in <5 minutes in 64% of cases and <10 minutes in 83%. (Figure 4). Reported reasons for delay included confounding differential diagnoses such as pulmonary embolism, tension pneumothorax, gas embolism during abdominal endoscopy, primary cardiac events, surgical haemorrhage, and neuraxial blockade-associated hypotension.

Pharmacological treatment was judged prompt and comprehensive in 83.9% and 98.8% of cases respectively.

Figure 4. Speed of starting anaphylaxis-specific treatment after first clinical feature (minutes, % of cases)



Airway management

Airway swelling, airway difficulty and complications were uncommon in NAP6 (see Chapter 10, Clinical features).

Tracheal intubation was performed as part of resuscitation in 13.2% of patients. In the majority this involved removal of a supraglottic airway and replacement by a tracheal tube. In three (1.1%) cases, the tracheal tube was removed and replaced as a result of suspected oesophageal intubation being part of the differential diagnosis. A front of neck airway (FONA) was instituted in one patient who developed laryngeal oedema and stridor, but other details of this case were scarce. In seven patients it was necessary to re-intubate the trachea after completion of the primary surgical procedure; in no case was re-intubation difficult due to airway swelling.

Airway management was judged appropriate in 98.8% of cases (Figure 5); in 1.2% of cases it was judged that tracheal intubation should have been performed. The single case of FONA was judged the only case of airway morbidity associated with anaphylaxis.

Cardiac compressions

The review panel considered that cardiac compressions were indicated if the systolic blood pressure fell below 50 mmHg (see Chapter 5, Methods).

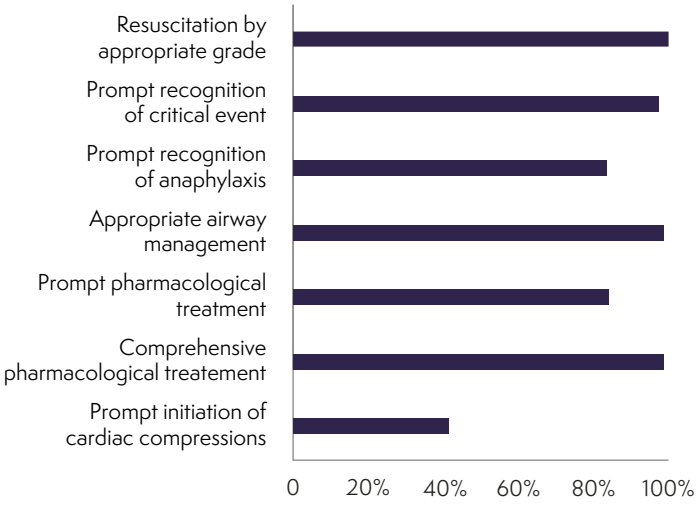
This occurred in 85 (39%) of 216 cases reported as Grade 3 by the anaesthetist, and this group was designated Grade 4 by the review panel.

Cardiac arrest was reported in 40 (15%) patients – in 27% of these within 5 minutes of trigger administration, though others were preceded by prolonged hypotension. All these patients received cardiac compressions; the mean duration was 14 minutes (range 1 to 60 minutes).

These two groups are considered further in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Cardiac compressions were judged to have started promptly in 41.3% of the cases where the review panel deemed this was necessary (Figure 5). This is also discussed in greater detail in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Figure 5. Quality of immediate management determined by the review panel (% of cases). Prompt initiation of cardiac compressions includes all cases in which the systolic blood pressure fell below 50 mmHg

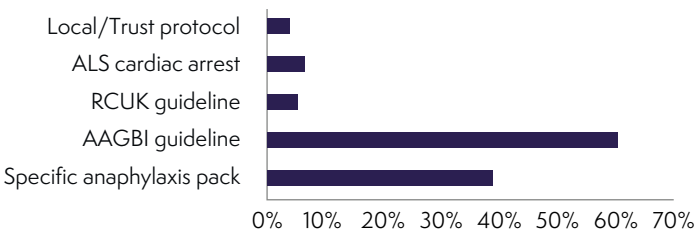


Use of guidelines and algorithms

Eighty-six percent of anaesthetists had immediate access to a guideline on perioperative anaphylaxis, mainly as a laminated sheet; 15% of immediately available guidelines were contained in designated 'anaphylaxis packs'. A smartphone was used to access guidelines in nine cases.

The AAGBI guideline was most commonly used – 60.5% of cases. The RCUK guidelines on management of anaphylaxis and on life support were used in 5.3% and 6.4% of cases, respectively (Figure 6). Local or trust guidelines accounted for 3.8% of cases. In 44 (18.6%) cases no specific guideline was used.

Figure 6. Specific guidance used by the anaesthetist during immediate management (% of cases)



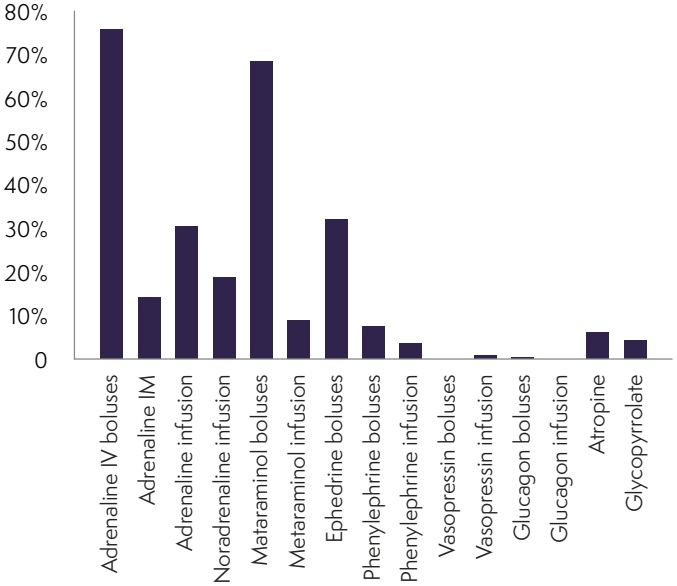
Teamwork

The reporting anaesthetist judged that the theatre team contributed effectively to management in 87% of cases and was partially effective in a further 7.7%.

Vasoactive drugs

Adrenaline was administered in 82.3% of cases (as IV boluses in 75.9%) (Figure 7) and was more likely to be given as severity increased (Figure 8). The IM route was used in 14.1% of cases. Sixteen patients (6%) received both IV and IM adrenaline. There was wide variation in the number of IV doses, ranging from one to thirty (median three doses). In 17.7% of cases no adrenaline was administered at all. Recognition of anaphylaxis was delayed in approximately one-third of these cases.

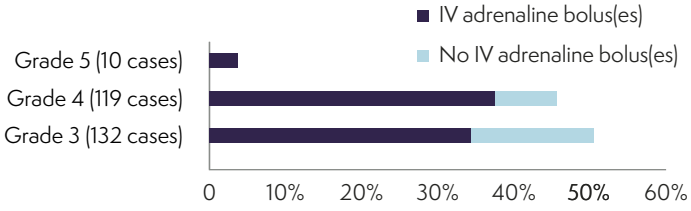
Figure 7. Vasoactive drugs administration during initial management of perioperative anaphylaxis (%)



The dose of IV adrenaline was related to the severity of the anaphylactic event. The median total dose was 0.2 mg, 0.5 mg and 4 mg in severity Grades 3, 4 and 5 respectively (Figure 8).

An IV infusion of adrenaline was started in 30.7% of cases and was preceded by bolus doses in all except a single case.

Figure 8. Proportion of patients (%) receiving IV adrenaline boluses by grade of event in 261 cases with data available (%)



Adrenaline was judged not to have been given when indicated in 19.4% of cases – either not administered (11%) or administered late (8.4%).

An IV infusion of noradrenaline was administered in 18.9% of cases. Of these, 16% did not receive adrenaline at any time.

Metaraminol was a commonly administered drug: 68.7% of patients received IV boluses, 73.6% of whom also received adrenaline. The number of bolus doses ranged from one to 30 (median four doses), and the total dose from 0.1 to 20 mg (median 2 mg).

IV boluses of ephedrine were given in approximately a third of cases.

Phenylephrine was administered by IV bolus in 7.8% of cases and was infused in 3.5%. The number of bolus doses ranged between one and twelve (median three doses). The majority of infusions were not preceded by bolus doses. Most cases were obstetric.

Only two patients received vasopressin (ADH). In both cases the infusion was initiated late in the resuscitation process (2 hours or more) and was preceded by ephedrine, metaraminol, and adrenaline. The total dose was not stated.

There was evidence that taking a beta-adrenergic blocking drug was associated with greater severity of the anaphylaxis – 60% of fatalities were taking a beta-blocker compared with 15% of survivors. A single patient received glucagon 1 mg. This is discussed further in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Bradycardia was present in 13.2% of all cases. Glycopyrrolate was given to treat bradycardia in 4.3% and atropine in 6.2% of cases: approximately a third of patients receiving one of these drugs had experienced cardiac arrest. One patient received both atropine and glycopyrrolate during resuscitation.

Five patients received amiodarone, four cases during cardiac arrest (median dose 300 mg, range 150 to 450 mg). No other patients required drug treatment to treat tachyarrhythmia.

Corticosteroids and antihistamines

IV hydrocortisone was administered in 82.9% of cases (1-4 doses, median dose 200 mg) (Figure 9). Dexamethasone was administered after the anaphylactic event in 16.1% of cases (median dose 6 mg). Both hydrocortisone and dexamethasone were administered in 8.7% of cases. Two patients received methylprednisolone. Thirty-four patients (12.8%) did not receive a steroid, including four fatalities.

IV chlorphenamine was administered in 73.6% and IV ranitidine in 5.3% of cases (median dose 10 mg; range 5-40 mg). Nine (3%) patients received both chlorphenamine and ranitidine.

Figure 9. Administration of corticosteroids and antihistamines after the anaphylactic event (% of cases)

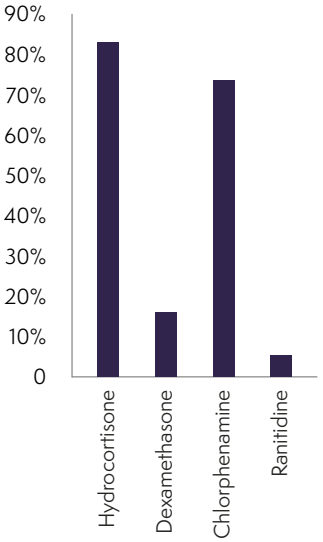


Table 3. ASA grade, level of care and outcomes in patients receiving chlorphenamine or no chlorphenamine for Grade 3-5 perioperative anaphylaxis *physical harm was based on 138 cases and 40 cases with this information available who did or did not receive chlorphenamine, respectively

	Chlorphenamine n=195	No chlorphenamine n=65
ASA 1	17.4%	17.2%
ASA 2	54%	47%
ASA 3	26%	31.3%
ASA 4	2.6%	4.7%
Prompt cardiac compressions	46%	50%
Critical Care		
Level 3 care	42.6%	16.9%
Level 2 care	16.9%	13.8%
Inotropes needed in ICU	31.8%	12.3%
Physical harm*		
None	5.1%	20%
Low	55%	40%
Moderate/ severe/death	39.8%	40%

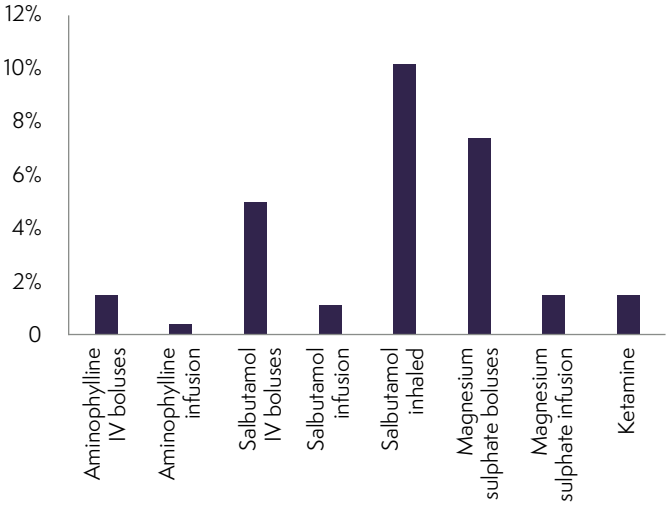
In view of the current interest in, and uncertainty about, the possible benefits or harm of antihistamines during treatment of anaphylaxis, we performed further analysis using a logistic regression model. Variables included: the initial resuscitation drugs (adrenaline bolus, corticosteroids, metaraminol, ephedrine and chlorphenamine), patient factors (age-group intervals excluding children and over 75s due to small numbers), and ASA status (excluding ASA 5 due to small numbers). Outcome was level of harm (no harm, low, moderate/severe harm or death). Despite the univariate findings, in the logistic regression chlorphenamine administration was associated with an increased probability of no harm (odds ratio 2.20; 95% CI 1.05-4.58) and reduced probability of moderate/severe harm or death (odds ratio 0.41; 0.18-0.91). The odds ratios had wide confidence intervals. In order to exclude the possibility that administration of chlorphenamine was simply a surrogate for good (as opposed to 'poor' or 'good and poor') clinical management (noting that chlorphenamine administration was not used as a measure of quality of care during panel discussions) we performed a Fisher exact test. This confirmed a significant association between administration of chlorphenamine and care being judged as good ($P<0.005$). Thus, it was not possible to extricate any potential benefits of chlorphenamine from the presumed benefits of good care.

Bronchodilator drugs

Bronchospasm was present in 48.5% of cases. Specific bronchodilator drugs (excluding adrenaline) were administered in 22.2% of all cases: most commonly inhaled salbutamol (10.2%) and IV magnesium sulphate (7.4%) (Figure 10). The median dose of magnesium sulphate was 2 g. IV salbutamol boluses were administered in 4.2% of cases and a continuous infusion in only three cases. Aminophylline boluses and infusion were used in less than 2% of all cases.

Ketamine was administered to treat intractable bronchospasm (after administration of salbutamol or magnesium sulphate) in four (1.5%) cases (range 40-100 mg).

Figure 10. Administration of bronchodilator drugs after the anaphylactic event (% of cases)



Sugammadex

Sugammadex was administered during the first six hours for treatment of the reaction in 19 (7.1%) cases (median dose 300 mg, range 150–1200 mg). Rocuronium was the suspected trigger agent in nine cases, and the actual culprit in seven: Sugammadex did not terminate the reaction in three cases, and further vasopressors and bronchodilators were needed.

Sugammadex administered for reversal of neuromuscular blockade was the trigger for anaphylaxis in one case. The onset was delayed approximately 15 minutes and the clinical features of anaphylaxis were most marked in the recovery room.

Miscellaneous drugs

Intralipid was administered to two patients in whom the differential diagnosis included local anaesthetic toxicity.

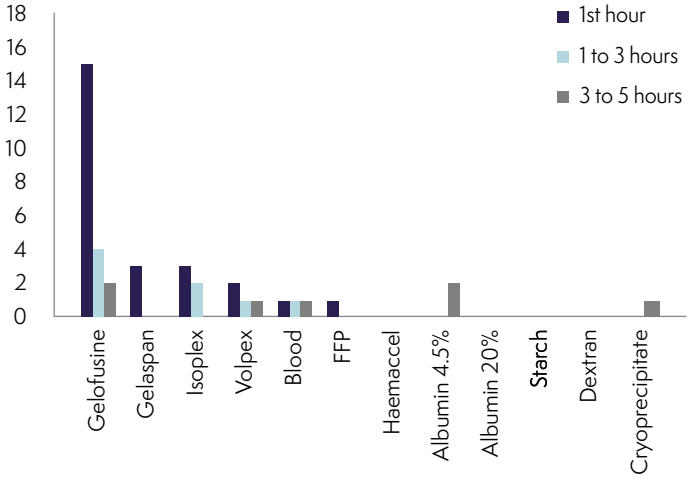
Fluid management

Ninety eight percent of patients received IV crystalloid fluids in the first hour after the reaction, 86% during the subsequent 2 hours, and 69% during the next 2 hours. The median volume administered during each time period was 1L (range 0.1L to 6.0L); 1L (range 0.1 to 3.0L) and 0.5L (range 0.1L to 4.5L)

The only IV colloids administered during the first hour after the anaphylactic event were succinylated gelatin products in 25 (9%) cases (Figure 11).

IV fluid management was judged inappropriate, almost universally as insufficient, in 19% of cases.

Figure 11. Administration of non-crystalloid IV fluids during three time periods after the anaphylactic event



Discontinuation of the trigger agent

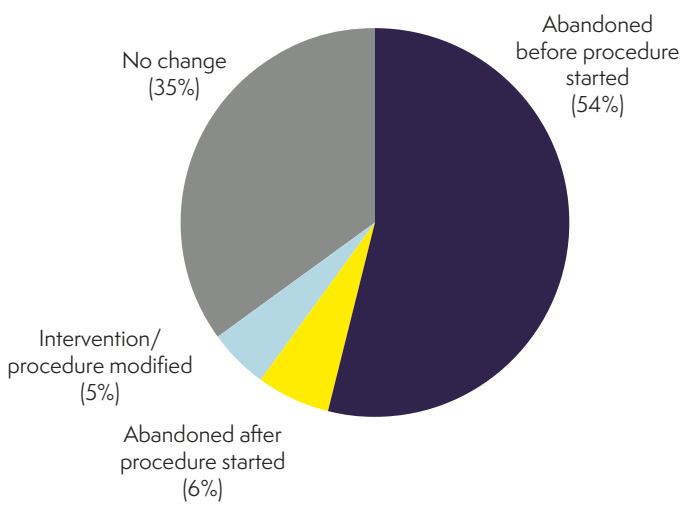
The suspected trigger agent was discontinued in 22 of the 26 cases where this would have been possible. Suspected trigger agents that were not discontinued were IV gelatin, a chlorhexidine-coated central venous line, a second dose of co-amoxiclav and a second dose of protamine.

The actual trigger agent was not discontinued in four of the 14 cases where this would have been possible, these were continuation of IV gelatin, administration of a second dose of protamine and two instances of retained chlorhexidine-coated central venous line.

Impact of anaphylaxis on the interventional procedure

In approximately one third of cases the procedure was unchanged but, in more than half the cases, the intended surgery or other interventional procedure was not started (Figure 12). In a small proportion of cases the procedure was modified or abandoned. Median severity was Grade 4 in the abandoned cases and Grade 3 in continued cases. In two cases cardiopulmonary bypass was used as part of the resuscitation process.

Figure 12. Outcome of the intervention or surgical procedure



In 14% of cases in which the procedure was abandoned it was decided not to re-schedule surgery.

In eleven cases (4.1%), the review panel judged that the surgical procedure was not abandoned when it would have been appropriate to do so; in eight of these the anaphylactic event occurred before surgery had started. Patients were more likely to be admitted to critical care as a result of the anaphylactic event if surgery had started (69% v 49%).

Sixteen patients (6% of survivors) underwent surgery between the time of submitting Part A (ie. after the event) and before the patient being seen in clinic. This was uneventful in every case. In one of these cases the anaesthetist suspected a neuromuscular blocking agent (NMBA), but the true culprit was chlorhexidine.

Unplanned hospital stay and critical care admission

The median unplanned hospital length of stay (LOS) as a result of anaphylaxis was one day, but there was a wide range: 18.4% >2 days; 11.7% >3 days; 8.3% >4 days and 6.6% >5 days. The longest unplanned LOS was 150 days.

One hundred and forty-four (54%) patients were transferred to critical care: the majority (70%) for Level 3 care. The median duration of Level 3 care was one day (range 1-9 days), and of Level 2 care was one day (range 1-25 days). Six patients required Level 3 care and five Level 2 care for >2 days. No patient required an increase in their level of care after admission to critical care while in critical care, 63% required inotropic support, and 5.1% bronchodilator therapy. Of the patients requiring inotrope infusions in critical care, 34.5% received adrenaline, 21.4% both adrenaline and noradrenaline, 15.5% noradrenaline, and the remainder other inotropic drugs.

Discussion

Departmental organisation

Based on the results of our organisational survey, departmental preparedness for management of perioperative anaphylaxis is inconsistent. Many hospitals do not have a lead anaesthetist for

anaphylaxis, guidelines are not always available, and plans for referral are also inconsistent. We have made recommendations about departmental organisation below.

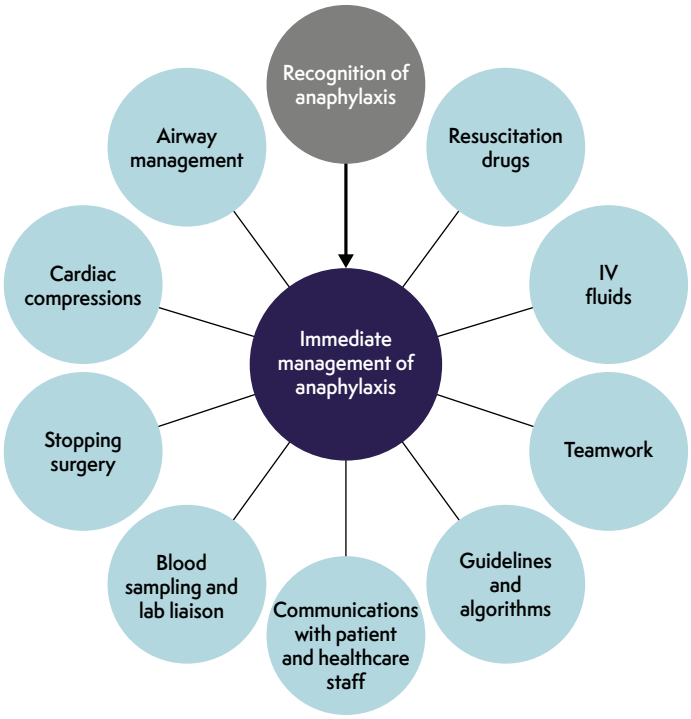
Immediate management

NAP6 is the largest prospective study of perioperative anaphylaxis ever published. Immediate management of perioperative anaphylaxis is a complex process. The anaesthetist not only monitors, minute-by minute, the patient's physiological status, urgently administers a wide range of drugs and assesses the response of the patient, but also leads and directs the resuscitation team.

NAP6 assessed each of the component activities within immediate management (Figure 13).

The large cohort of patients who were reported to the project provides a significant snapshot of the immediate management and outcomes of these cases, and raises, or to an extent tests, certain hypotheses about immediate management.

Figure 13. Processes involved in the immediate management of perioperative anaphylaxis



Recognition of Anaphylaxis

The presence of a critical incident was recognised promptly in almost all cases, but the realisation that the event was likely to be anaphylaxis was judged to have been delayed in one in six cases, suggesting that a period of time was required to exclude more common causes of hypotension or bronchospasm, the most common presenting clinical features of anaphylaxis. Frequent measurement of blood pressure probably reduces the alert time.

With the exception of rash, urticaria and angioedema, the individual clinical features of perioperative anaphylaxis are not specific diagnostic 'pointers', and therefore the diagnosis will be delayed in some cases. It is probable that the late onset (or late recognition) of rash was partially responsible for delaying the diagnosis of anaphylaxis in some cases. Rash was never the first feature in cases where there was a delay in making the diagnosis, although it was the first clinical feature in 46 cases (17.3%) where the diagnosis was not delayed. Several anaesthetists made the observation that rash was noticed only when the surgical drapes were removed at the end of the case.

It has been estimated that bronchospasm occurs in 1.7–16% of patients during anaesthesia (Fisher 2009). Conservatively assuming an incidence of 2% and an incidence of perioperative anaphylaxis of 1:10,000, bronchospasm presenting as an isolated or first clinical feature during anaesthesia is at least 200 times more likely to be due to a mechanism other than anaphylaxis.

The patient felt unwell and complained of facial tingling after a regional block with local anaesthetic. These symptoms were followed by cardiovascular collapse. The differential diagnosis included local anaesthetic toxicity, for which the patient initially received treatment.

Hypotension did not respond to the usual treatment. A rash was noticed only when the level of lighting was increased in theatre at the end of surgery.

A rash was only noticed when the surgical drapes were removed. The blood pressure had been low throughout surgery.

An awake patient developed hypotension during an obstetric procedure. Anaphylaxis was suspected only when she complained of cutaneous symptoms.

Airway management

The review panel considered that airway management was appropriate in almost all cases. It is noteworthy that re-intubation of the trachea was not found to be difficult due to airway swelling, and the panel considered that concerns over the possibility of airway swelling should not be a deterrent when taking a decision whether to re-intubate the trachea.

A notable finding in NAP6 is the relative absence of major airway issues in presentation and in initial management. The single FONA could be considered the only major event.

Cardiac Compressions

There were two settings in which the review panel felt that cardiac compressions were required – the first during cardiac arrest and the second where systolic blood pressure fell to <50 mmHg. In the first setting cardiac compressions were universal and generally prompt, and in the second they were mostly absent. This is discussed in detail in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Guidelines and anaesthesia anaphylaxis packs

Guidelines were not available in one in seven cases, and more work needs to be done to ensure that anaphylaxis guidelines are immediately available at every site where anaesthesia is administered. The AABGI guidelines were the most widely used, and could usefully be adopted as a standard in the UK. An 'anaphylaxis pack' was used in fewer than half of cases and in the organisational survey only half of hospitals had these in theatre. During the review it became apparent that 'anaphylaxis pack' may mean different things – to some it is a pack to guide immediate management in the case of anaphylaxis, and to others it is a pack to guide investigation and referral. It is noteworthy that management of anaphylaxis in the operating theatre is likely to differ from that in other locations, as the allergen is usually administered IV, the patient is fully monitored, and the route of choice for adrenaline is IV and at a significantly reduced dose.

We recommend two sorts of specific Anaesthetic anaphylaxis packs:

- An *Anaesthesia anaphylaxis treatment pack*. This is to facilitate prompt early treatment. We suggest it includes an anaphylaxis management algorithm, adrenaline pre-filled syringes suitable for IV administration, hydrocortisone, and details of the location where glucagon and vasopressin are available. This pack should be available wherever anaesthesia is administered
- An *Anaesthesia anaphylaxis investigation pack*, including tryptase sampling tubes and information sheets describing (a) details of blood tests required and their timing (b) instructions on referral for further investigation and allergy clinic details (c) documentation for the patient. This should be available in all theatre suites.

Pharmacological management

Comprehensive pharmacological management was delivered in three quarters of cases; the review panel determined that adrenaline was not given when indicated in almost one in five fully-reviewed cases. Almost one in five patients did not receive adrenaline by any route. In a Danish study (Garvey 2011), a similar proportion of patients with Grade 3 or 4 anaphylaxis did not receive adrenaline, and the authors suggested that there may be reluctance to administer this drug.

Failure to give adrenaline or delayed administration may be due to late diagnosis, unfamiliarity with treatment guidelines, early resolution as a result of administering 'routine' vasopressors and/or bronchodilators, or non-availability of adrenaline.

Examination of NAP6 narratives suggests that anaesthetists may be reluctant to administer adrenaline in the presence of known coronary artery disease, cardiac valvular disease, or in the presence of cardiac arrhythmias. There is no published evidence on which to base this decision, but it is known that rapidly-administered or large doses of IV adrenaline can precipitate cardiac ischaemia and arrhythmias (Hoshino 2015). However, as patients with cardiac disease appeared more likely to have a poor outcome in NAP6 (see Chapter 12) and we saw very few complications of adrenaline administration (arrhythmias and cardiac ischaemia at any point in the event both occurred in <2% of cases) our findings do not support delaying the administration of adrenaline. It is not known whether a particular patient will respond without adrenaline, and valuable time will be lost due to procrastination. Harm from adrenaline is unlikely.

Immediate availability of guidelines does not appear to be the limiting factor in determining whether adrenaline was administered: anaphylaxis guidelines were immediately available in 87.5% of cases overall and 86% of cases where adrenaline was not given.

AAGBI guidelines were twice as likely to have been used in cases where adrenaline was given, compared with cases where adrenaline was not administered. This observation is open to two interpretations. First, it is possible that consulting AAGBI guidelines during the anaphylactic event resulted in a greater proportion of patients receiving adrenaline. The second possible explanation is that anaesthetists were more likely to consult AAGBI guidelines when the event was particularly severe and had not responded to 'normal' vasopressors. Regardless of the explanation, anaphylaxis guidelines or, as a minimum, a management algorithm, should be immediately available at every anaesthetising site, including radiology departments and emergency departments.

The total dose of bolus IV administration of adrenaline in Grade 4 cases was less than in the Danish study (Garvey 2011) (median 0.5 mg versus 1.95 mg), but comparisons are problematic as there was only a small proportion of Grade 4 cases in that study.

An IV infusion of adrenaline was administered in almost a third of cases. Preparation of an IV infusion takes several minutes and it is suggested that, immediately the first bolus dose of adrenaline has been administered, the need for a vasopressor infusion should be considered.

In a very small minority of cases there was difficulty in maintaining intravenous access during resuscitation and the administration of adrenaline was delayed. In these circumstances, ALS guidelines recommend that adrenaline is administered via the intraosseous route and this good practice was observed in NAP6 (Soar 2015).

> An algorithm was not used and the patient improved without it.
>
> Metaraminol was given as there was a history of coronary artery disease.
>
> The blood pressure was unrecordable and there was bronchospasm. The patient responded to metaraminol, salbutamol and hydrocortisone.
>
> There was a delay in adrenaline being brought, and the patient responded to the usual vasopressors.

It is not possible to establish whether non-administration or delayed administration of adrenaline adversely affected outcome. The panel assessed harm in 184 fully-reviewed cases. Of the patients who did not receive adrenaline by any route, 69% suffered no harm or low harm, compared with 57.7% if adrenaline was

given when indicated. These apparently paradoxical data should be interpreted with caution. Anaphylaxis was generally less severe in those patients in whom adrenaline was withheld, and would be expected to have suffered less harm. The grade of the event not only reflects the severity of the anaphylactic insult but also the extent to which the patient responds to immediate treatment. Anaphylactic reactions in which treatment with adrenaline is rapid and effective may never develop their potential maximum severity.

The pattern of first-line management appeared to reflect the routine anaesthetic practice of drawing-up a vasopressor drug at the beginning of an operating list. Metaraminol was the most commonly used first-line vasopressor, being administered in more than two thirds of cases. It was notable that 21 patients received 10 or more bolus doses of metaraminol. The majority of these also received IV adrenaline, suggesting that metaraminol was only partially effective.

Noradrenaline

Almost 1 in 5 cases received an infusion of noradrenaline to maintain blood pressure, usually after adrenaline administration. It appears that continuing alpha adrenergic agonist activity was required to maintain blood pressure.

Glucagon

Almost 50 patients (18%) were taking a beta-blocking drug but only a single patient received glucagon. This drug is not part of current AAGBI guidelines but is considered in RCUK and several other guidelines. There is sufficient evidence of efficacy in beta-blocked patients to suggest that guidelines should include this drug. Glucagon has a short half-life and repeated doses may be necessary (Kolawole 2017).

Vasopressin

Only two patients received vasopressin. In both cases the patient was only partially responsive to adrenaline and noradrenaline but vasopressin was not given for a considerable period of time. Current evidence is supportive of its use in refractory hypotension caused by anaphylaxis (Hussain 2008; Schummer 2008; Bensghir 2013).

It is unusual for vasopressin and glucagon to be immediately available and the review panel considered that it would be appropriate for 'anaphylaxis packs' to contain these drugs. Anaesthesia anaphylaxis treatment packs could usefully contain advice on when to use glucagon and vasopressin and where to get it urgently.

Corticosteroids

Administration of hydrocortisone is recommended in published guidelines, and it is unexpected that 1 in 6 patients did not receive this drug. As some did receive dexamethasone, a glucocorticoid drug was not administered in 12.9% of cases. Of note, four of the 10 fatalities occurred in patients not receiving a glucocorticoid, but the numbers are too small to draw clear conclusions.

It is notable that dexamethasone is widely used as an antiemetic, and almost half of all patients undergoing general anaesthesia now receive this drug (see Chapter 9). In the NAP6 cohort one in five patients had received dexamethasone prior to the anaphylaxis event. This raises an interesting question as to whether there is any need to give a further glucocorticoid if dexamethasone has already been given, but it provides evidence that corticosteroids given shortly before an anaphylaxis event will not prevent the reaction.

Antihistamines

Intravenous chlorphenamine was administered in almost three quarters of cases. As described above there is current controversy over the value of antihistamines in anaphylaxis. It is likely that antihistamines reduce the severity of epiphenomena such as swelling, rash and urticaria, and may reduce the likelihood of airway swelling.

ANZAAG guidelines (Kolawole 2017) state that administration of promethazine (which has an acidic pH) in perioperative anaphylaxis may be harmful by potentially worsening hypotension and causing tissue necrosis. It is possible that this statement could be over-extrapolated to imply that all antihistamines have no place in the management of perioperative anaphylaxis. In the UK, chlorphenamine for injection is more readily available than promethazine. There do not appear to be any published reports of tissue necrosis after IV injection of chlorphenamine. No patient received promethazine in NAP6.

NAP6 data were analysed using multiple logistic regression, and this indicates no evidence of harm and (somewhat inconsistent) evidence of benefit from administration of chlorphenamine. However, further analysis indicated that there may be a confounding factor in as much as good care was more commonly reported in patients who received chlorphenamine. Overall the NAP6 data do not show a robust reason to stop recommending antihistamine (chlorphenamine) during severe anaphylaxis.

Bronchodilator drugs

Although bronchospasm was present in almost half of cases, only one quarter of patients received a specific bronchodilator drug, suggesting that bronchospasm responded to the administration of adrenaline. It may be the case that adrenaline alone would have been sufficient to reverse bronchospasm in all patients, but evidence is lacking. Nine of the patients receiving nebulised/inhaled salbutamol gave a history of asthma. Both a nebuliser or a metered-dose inhaler are suitable methods to administer salbutamol and are likely to be similarly effective but correct technique is important (Georgopoulos 2000).

Intravenous magnesium sulphate was administered in 7.4% of all cases. Published guidelines recommend considering IV magnesium sulphate if bronchospasm is persistent, but evidence of efficacy in anaphylaxis is lacking although it appears to be effective in acute asthma (British Thoracic Society, 2014). The risk that IV magnesium sulphate will exacerbate hypotension during anaphylaxis is likely to be dose-related. The median total dose was 2 g (range 2 g–5 g) and it is known that an infusion of 40 mg/kg (2.8 g per 70 kg

body weight) over a 10-minute period will reduce blood pressure during deliberate hypotensive anaesthesia (Elsharnouby 2006). Caution should be exercised if magnesium sulphate is used for the treatment of bronchospasm during anaphylactic shock if there is co-existing hypotension.

A small number of patients received ketamine to treat bronchospasm, too few to draw clear conclusions about efficacy or side effects. In acute asthma, ketamine and aminophylline have equal efficacy (Tiwari 2016), but there is no published information relating to the treatment of bronchospasm in anaphylaxis.

Sugammadex

Sugammadex was administered in approximately a quarter of cases when the anaesthetist suspected rocuronium as a trigger for anaphylaxis. Considerable uncertainty surrounds the effectiveness of sugammadex in treating rocuronium-induced anaphylaxis or anaphylaxis in general and we are unable to make any recommendation for clinical practice based on our data.

Intravenous fluid management

The relatively low volumes of IV fluids administered in the acute management of perioperative anaphylaxis were unexpected, and the review panel determined that fluid management was not appropriate in one in five cases. During the critical first hour, based on reported weights and volumes, the median volume of crystalloid in adults was 12.3 ml/kg. This is substantially lower than implied or stated in all published guidelines (see above), and overall the panel was probably insufficiently critical of fluid administration. IV fluid should be given in significant volumes (20 ml/kg – ie, 2L for a patient weighing 100 kg) and repeated regularly while monitoring the physiological response.

Intravenous colloids, mainly succinylated gelatin solutions, were administered in a minority of cases during the first hour. No starches were used at all. In the opinion of the review panel, colloids have no advantages over crystalloids in the management of anaphylaxis, and crystalloids are strongly preferred. In one case, a gelatin infusion was begun before the onset of anaphylaxis and was responsible for anaphylaxis, but was not discontinued. The review panel emphasised that any colloid infusion started before the onset of anaphylaxis should be discontinued and the IV giving-set should be discarded. An intravenous gelatin solution was responsible for anaphylaxis in three cases. Gelatin-derived IV colloids were estimated to be given to 52,000 patients each year (Chapter 9, Allergen Survey), giving an approximate incidence of 5.8 per 100,000 administrations, similar to that of rocuronium (see Chapter 16, NMBAs).

Discontinuation of the trigger agent

In a minority of cases it would have been possible to prevent further trigger exposure. This included two cases of chlorhexidine-induced anaphylaxis where a chlorhexidine-coated central venous catheter remained in place. It is frequently impossible for the anaesthetist to identify the culprit and, in order to avoid re-exposure or continuing exposure, all drugs or other substances administered during the hour before the anaphylactic event should not be re-administered. Potentially-cross-reacting drugs should also be avoided and, if an NMBA was been administered prior to the event, no further muscle relaxant drug should be administered. Chlorhexidine-coated central venous catheters present a considerable problem. Despite MHRA recommendations (Medicines and Healthcare products Regulatory Agency 2012), labelling of chlorhexidine-coated central venous catheters is not always prominent and the risk may remain unnoticed (see also Chapter 17, Chlorhexidine).

Outcome of the interventional procedure

There is little published evidence to support the decision either to continue or to abandon the surgical procedure in perioperative anaphylaxis. In a study which included 167 Grade 3 and 4 cases, Sadleir *et al* (Sadleir 2017) concluded that after initial resuscitation and, if resuscitation could be re-instituted if required, continuing with surgery was not associated with poorer outcomes, except in Grade 4 events in which there was a significant complication-rate irrespective of whether surgery was abandoned or continued.

It is likely that no study, including NAP6, has been able to collect sufficiently detailed postoperative physiological information to enable didactic guidance to be given on whether to proceed with surgery in any particular patient.

Several theoretical factors favour abandonment. The fact that one in three patients required catecholamine infusions might also be considered a clear indication to postpone surgery where practical after a Grade 3 or 4 reaction. If surgery is allowed to continue, severe tissue hypoperfusion associated with anaphylaxis is likely to exacerbate physiological complications of anaesthesia and surgery, including postoperative delirium, renal impairment and cardiac dysfunction, especially in the elderly. Anaphylaxis-induced coagulopathy has been described, which could result in severe surgical haemorrhage. Fibrinolysis (Iqbal 2010), and disseminated intravascular coagulation (Jung 2012) have been reported. Neither of these was seen in NAP6.

Against these considerations must be balanced the degree of urgency of surgery and the wishes of the patient. The former requires clinical judgement. Under some circumstances the risk of a hypersensitivity reaction is sufficiently high to consider discussing preoperatively the patient's wishes regarding continuation of surgery in the event of anaphylaxis, for example, when the patient will be exposed to Patent Blue dye during a surgical procedure for suspected breast cancer.

In some cases surgery continued when the panel felt it should not have. The panel emphasised that anaesthetists should not feel, or be, pressurised to continue in circumstances where it would be appropriate to abandon surgery.

Hospital stay and critical care admission

A small proportion of patients were discharged home on the same day as their anaphylactic event. Regarding anaphylaxis in general, NICE Clinical Guideline 134 (NICE 2011) recommends that "Adults and young people aged 16 years or older who have had emergency treatment for suspected anaphylaxis should be observed for 6–12 hours from the onset of symptoms, depending on their response to emergency treatment". In the setting of

perioperative Grade 3 or 4 anaphylaxis, in view of the high rates of ICU admission, catecholamine infusions and sequelae, the review panel considered that same day discharge may be unwise.

In a three quarters (75.4%) of cases hospital length of stay (LOS) was increased as a result of anaphylaxis. Prolonged LOS stay was related to the severity of anaphylaxis. More than half the patients required admission to critical care, representing a significant demand on scarce resources. Notably, almost a quarter of patients receiving vasopressor drugs in critical care required both adrenaline and noradrenaline infusions, suggesting prolonged vasoplegia. In contrast, only one in 20 patients in critical care required bronchodilators. It is not known why persistent bronchospasm is less frequent than continuing hypotension.

Chapter appendices

To aid departments in preparation for the management of perioperative anaphylaxis we include four appendices:

Appendix A: Anaesthetic anaphylaxis treatment packs.

Appendix B: Anaesthetic anaphylaxis investigation packs.

Appendix C: Management plan for urgent anaesthesia and surgery following perioperative anaphylaxis.

Appendix D: Departmental Lead for Perioperative Anaphylaxis: roles and responsibilities.

Recommendations

National

- Relevant standard setting and examining organisations should ensure that the detection, management and referral for investigation of perioperative anaphylaxis is a core curriculum content for anaesthetists and intensivists.

Institutional

- Procedures should be in place to ensure that an appropriate patient allergy history is sought and recorded before anaesthesia is administered
- There should be a departmental lead for perioperative anaphylaxis in each department of anaesthesia (see Chapter 11, Appendix D). This role should be supported by appropriate time and DCC/SPA allocation
- Department leads and their local allergy clinic should liaise directly to ensure current phone numbers and email contacts for the clinic are readily available to anaesthetists in their department, and kept up to date
- Departments of anaesthesia should have protocols for the detection, management and referral for investigation of perioperative anaphylaxis. These should be readily accessible to all departmental members, widely disseminated and kept up to date
- Clinical Directors of anaesthetic departments should ensure their anaesthetists have been trained in the management of perioperative anaphylaxis
- Perioperative anaphylaxis guidelines and/or a management algorithm should be immediately available wherever anaesthesia is administered
- Anaesthesia anaphylaxis treatment packs, including an anaphylaxis management algorithm, adrenaline pre-filled syringes suitable for IV administration, hydrocortisone and details of the location of glucagon and vasopressin should be immediately available wherever anaesthesia is administered
- Anaesthesia anaphylaxis investigation packs should be available in all theatre suites, including tryptase sampling tubes and paperwork that describes:
    a. Details of blood tests required and their timing
    b. Instructions on referral for further investigation and allergy clinic details
    c. Documentation for the patient
- Vasopressin and glucagon for the management of intractable perioperative anaphylaxis should be available within 10 minutes wherever anaesthesia is administered
- Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the patient's medication and the event, and timings of all drugs administered prior to the event. A standardised form (the NAP6 or AAGBI pro-forma) should accompany the referral
- Investigation of perioperative anaphylaxis should include follow-up, either in hospital or in primary care, to detect adverse sequelae, such as new anxiety, impairment of cognition or activities of daily living or deterioration in cardiorespiratory or renal function. The anaesthetic department lead should coordinate this.

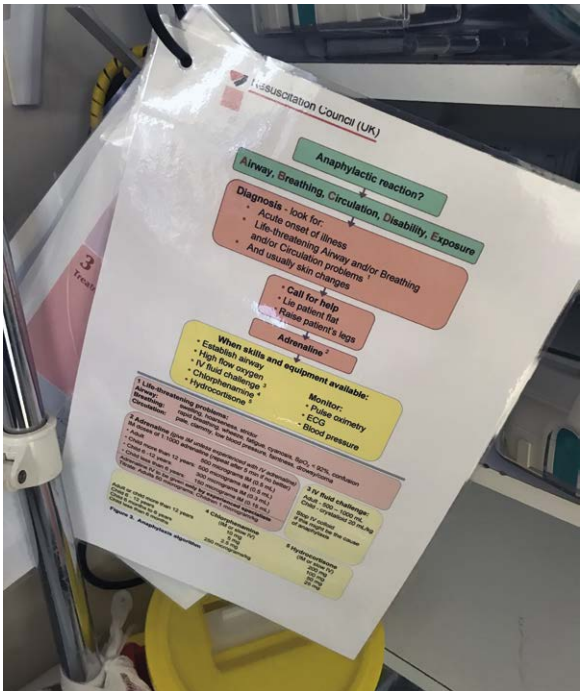
Individual

- All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements
- Adrenaline is the primary treatment of anaphylaxis and should be administered immediately anaphylaxis is suspected. In the perioperative setting this will usually be IV
- Where a critical perioperative hypotensive event occurs and perioperative anaphylaxis is one of several differential diagnoses, treatment for anaphylaxis should start promptly as there is little to be lost and much to be gained
- If IV access is not immediately available, intramuscular or intraosseous routes should be used promptly, until IV access is established
- A rapid IV crystalloid (not colloid) fluid challenge of 20 ml/kg should be given immediately. This should be repeated several times if necessary
- During anaphylaxis with a systolic blood pressure <50 mmHg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with adrenaline and liberal IV fluid administration

- If an IV colloid is being administered at the time of the anaphylactic event, it should be discontinued, and the IV administration set replaced
- Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory
- During perioperative anaphylaxis in patients taking beta-blockers, early administration of IV glucagon 1 mg should be considered, repeated as necessary
- When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one
- A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis
- Chlorphenamine may be given as part of the resuscitation process, but NAP6 found no evidence of either benefit or harm. It may reduce angioedema and urticaria
- Blood samples for mast cell tryptase should be taken in accordance with national guidelines:
  - 1st sample as soon as the patient is stable
  - 2nd sample as close to 1-2 hours as possible after the event
  - 3rd (baseline) at least 24 hours after the event
- All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event, ie. the consultant anaesthetising or supervising the case
- Where a trainee refers a patient to an allergy clinic the contact details of a consultant anaesthetist should be included in the referral
- If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice, as well as making a written referral
- Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules (see Appendix C).

Research

- There remains uncertainty about the benefits or potential harm of administering antihistamine drugs during resuscitation of perioperative anaphylaxis. Clinical trials would provide valuable evidence
- There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium-induced anaphylaxis specifically. Clinical trials would provide valuable evidence
- Research would be of value to investigate the effect of corticosteroids, both given prior to anaphylaxis and for its treatment.



Laminated copies of guidelines can assist management

Airway problems were notably uncommon in NAP6

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Appendix A:

ANAESTHETIC ANAPHYLAXIS **TREATMENT** PACK

Suggested contents

- Adrenaline pre-filled syringe x2 (1 mg/10 ml = 100 mcg/ml).
  Each syringe = 20 doses of 50 mcg, 10 doses of 100 mcg, 1 dose of 1 mg (cardiac arrest)

- Hydrocortisone 100 mg x2.

- Details of where to find glucagon (for patients on beta-blockers) and vasopressin (for protracted hypotension) (less than 10 minutes away)
  Details of doses: glucagon 1–2 mg repeated as required at 5 minute intervals, vasopressin 2 units repeated as needed, consider infusion.

- Anaphylaxis management algorithms (adult and paediatric), for example:

  Resuscitation Council (UK)
  https://www.resus.org.uk/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/

  Or

  AAGBI
  https://www.aagbi.org/sites/default/files/anaphylaxis_2009_0.pdf

  Or

  ANZAAG (Adult – Immediate management)
  http://www.anzaag.com/Docs/PDF/Management%20Guidelines/Adult_Immediate_Management_Card_2016.pdf
  And
  ANZAAG (Adult – Refractory)
  http://www.anzaag.com/Docs/PDF/Management%20Guidelines/Adult_Refractory_Management_Card_2016.pdf
  And
  ANZAAG (Paediatric – Immediate management)
  http://www.anzaag.com/Docs/PDF/Management%20Guidelines/Paediatric_Immediate_Management_Card_2016.pdf
  And
  ANZAAG (Paediatric – Refractory)
  http://www.anzaag.com/Docs/PDF/Management%20Guidelines/Paediatric_Refractory_Management_Card_2016.pdf

- Details of where to find Perioperative Anaphylaxis **Investigation** Packs

Appendix B:

ANAESTHETIC ANAPHYLAXIS INVESTIGATION PACK CHECKLIST

This pack contains:

1. Instructions on taking three timed blood samples for mast cell tryptase.
2. Template for letter to be given to the patient.
3. Urgent-surgery management plan.
4. Template for letter to be sent to the GP.
5. Referral form to be sent to the allergy clinic.

MAST CELL TRYPTASE SAMPLES

- It is the anaesthetist's responsibility to ensure the samples are taken, including the 24-hour sample.
- Use tubes for serum sample, eg. electrolytes (colour coding varies between hospitals). Ensure you date and time the tubes. There is no need to refrigerate the samples.
  - 1st sample – as soon as the patient is stable. (Ideally less than 30 mins)
  - 2nd sample – as close to 1–2 hours as possible after the event. (No more than 6 h)
  - 3rd (baseline) – at least 24 hours after the event.
- Phone your local lab (usually Immunology) when you have taken the 2nd sample so they expect a group of 3 samples.

COMMUNICATION AND FOLLOW-UP

- Refer to critical care for continuing care of the patient.
- Record full details of the anaphylaxis and resuscitation in the patient's medical record.
- Explain to the patient what has happened as soon as practicable and record your conversation in the medical record. Give the patient the completed **Patient Letter**.
- Ensure the event is reported to your local incident reporting system.
- Contact your Departmental Lead for Perioperative Anaphylaxis for advice.
- If postponed surgery is urgent, refer to the **Urgent Surgery Management Plan.**
- Complete all parts of the **Allergy Clinic Referral Form** and send *together with photocopies of anaesthetic record and other relevant documentation*.
- Inform the patient's GP using the **GP Letter**.
- Ensure the event is reported to the MHRA through the Yellow Card system and keep a note of the MHRA Reference Number to update with the Allergy Clinic diagnosis.
- Ensure the patient is followed up for adverse physical and/or psychological effects.

Appendix B2:

LETTER TO THE PATIENT FOLLOWING PERIOPERATIVE ANAPHYLAXIS

[Hospital header] Date ……..

Patient's name .....

Patient's address .....

Medical record number …….

NHS Number ……..…....

Dear .....

You had a suspected severe allergic reaction (anaphylaxis) during anaesthesia on .....
To find out the cause of the reaction I will refer you to the anaesthetic allergy clinic at:

.....

They will contact you with an appointment - this normally takes a few weeks.

- *If you have not heard in six weeks, or if you have any queries, please contact me (details below).*
- *It is important you attend the allergy clinic to prevent a further severe allergic reaction.*

Until you have attended the allergy clinic, you should avoid all the drugs and other potential causes you were exposed to during the hour prior to the allergic reaction. These include:

1) Latex

2) Chlorhexidine, including medical, dental and household products

3) Anaesthetic drugs (SPECIFY) ……..
……..
……..
……..
……
……..

4) Antibiotics (SPECIFY) ……..
……..

5) Analgesics (SPECIFY) ……..
……..

6) Other drugs/substances (SPECIFY) ……..
……..

It is important that you show this letter if you have any medical appointments between now and the time of your clinic appointment

I will write to your GP with this information.

Yours sincerely,

Consultant Anaesthetist Contact phone number……

Appendix B3:

LETTER TO PATIENT'S GP FOLLOWING PERIOPERATIVE ANAPHYLAXIS

[Hospital header] Date ……..

[GP's Name and Address .....]

Dear Dr .....

Your patient .....

Address .....

MRN ……

NHS Number ……

Had a suspected severe allergic reaction (anaphylaxis) during anaesthesia on .....

He/she has been referred for investigation to the anaesthetic allergy clinic at .....

Until the patient has attended the allergy clinic, they should avoid all drugs and other potential allergens to which they were exposed during the hour prior to the allergic reaction. These include:

1) Latex …….

2) Chlorhexidine, including medical, dental and household products ……..

3) Anaesthetic drugs (SPECIFY) ……..
……..
……..
……..
……
……..

4) Antibiotics (SPECIFY) ……..
……..

5) Analgesics (SPECIFY) ……..
……..

6) Other drugs/substances (SPECIFY) ……..
……..
……..

I have given the patient a letter providing the same information as here.

Yours sincerely,

Consultant Anaesthetist

Contact phone number……

Appendix B4:

NAP6 ANAESTHETIC ANAPHYLAXIS REFERRAL FORM (4 pages)

Patient details

Name…….....

Date of birth ….. /…./…….. Hospital / NHS Number ……

Address …….....

…… Telephone …….....

Referring consultant anaesthetist (for clinic correspondence)

Name…….....

Address……..…….……

……...……

Telephone…….. Secure Email …….

Patient's GP (for clinic correspondence)

Name…….....

Address……..…….……

……...……

Telephone…… Secure Email ……

Surgeon (for clinic correspondence)

Name…….....

Address……..…….……

……...……

Telephone…… Secure Email ……...……

Date of the reaction …../…../20.... Time of onset of reaction …../……h (24h clock)

<u>Suspected cause of the reaction</u>

1) ……..... 2) ……..…… 3) ……..…..…

Proposed surgery or other procedure : ……

Was surgery/procedure completed? Yes ☐ No ☐

If 'no', has another date for surgery being scheduled? Yes ☐ No ☐

Urgency/Date of future surgery……...

Drugs administered IN THE HOUR BEFORE THE REACTION (including premed). Please include any other relevant events or exposures, e.g. Patent Blue dye

Drug or Event	Time (24 hr clock)	Route of drug administration	Comments

IV Colloids/blood products given *BEFORE the onset of the reaction* with start times

1 …… _____:_____ 2 …….. _____:_____

3 …….. _____:_____ 4 …… _____:_____

Neuraxial blockade Spinal ☐ Epidural ☐ CSE ☐

Drug/Procedure	Time (24 hr clock)	Route

Peripheral nerve/regional block Type of block(s) .....……

Drug	Time (24 hr clock)	Route

Latex free environment? Yes ☐ No ☐

Chlorhexidine skin prep (by anaesthetist) Yes ☐ No ☐ Time(s) .....

Chlorhexidine skin prep (by surgeon) Yes ☐ No ☐ Time .....

Chlorhexidine medical lubricant gel Yes ☐ No ☐ Time .....

Chlorhexidine-coated intravascular catheter Yes ☐ No ☐ Time .....

Drugs and IV fluids given to treat the reaction

Drug /IV fluid	Time (24 hour clock)	Route	Comments on response to treatment

CPR required Yes ☐ No ☐ Duration of CPR .....

Adverse sequelae from this reaction e.g. cardiac, renal, neurological, respiratory, anxiety.....

Investigations performed before referral (please give results)

N.B. It is the anaesthetist's responsibility to obtain the results from the laboratory

Were blood samples taken for Mast Cell Tryptase? Yes ☐ No ☐

First MCT sample Time___:___ Date___/___/____ Result…….....…….

Second MCT sample Time___:___ Date___/___/____ Result…….....

Third MCT sample Time___:___ Date___/___/____ Result…….....…….

Other bloods tests:

Test:…….....…… Time___:___ Date___/___/____ Result……

Test:…….....…… Time___:___ Date___/___/____ Result……

Case discussed at a multidisciplinary meeting? Yes ☐ No ☐

Reported to the MHRA Yes ☐ No ☐

By whom? ……

MHRA Reference Number .....

Please send the completed form to the allergy clinic together with:

- Photocopy of the anaesthetic record and any previous anaesthetic records
- Photocopy of the prescription record if relevant
- Photocopy of relevant recovery-room documentation
- Photocopy of relevant ward documentation

Please file a copy of this form in the patient's medical record

Appendix C:

Urgent surgical intervention after suspected perioperative anaphylaxis and prior to allergy investigations: NAP6 suggested management plan

It is possible to provide safe anaesthesia in almost every case and unnecessary to postpone urgent surgery.

- ✓ It is important to discuss the case with a consultant Allergist or Clinical Immunologist as soon as possible after the suspected anaphylactic event
- ✓ Regional anaesthesia, where practical, may be a sensible option to enable avoidance of most drugs suspected to have caused anaphylaxis during previous general anaesthesia
- ✓ If anaesthesia was induced with propofol and general anaesthesia is required, the choice of induction agents includes inhalational agents, thiopental, etomidate (non-lipid formulation) and ketamine.
- ✓ If tracheal intubation is required and an NMBA is contra-indicated:
    - A remifentanil infusion, magnesium sulphate and topical anaesthesia are helpful adjuncts to deep anaesthesia in facilitating laryngoscopy and intubation
    - Where remifentanil was used in the previous anaesthetic, consider the use of alfentanil
    - Awake intubation under topical anaesthesia is an alternative
- ✓ If local anaesthetics are not contra-indicated, sufficient surgical muscle relaxation can usually be provided if necessary with an adequate depth of anaesthesia and adjunct neuraxial block, transversus abdominis blocks, rectus sheath blocks or other peripheral nerve block
- ✓ Pre-warn the theatre team beforehand, and be prepared to diagnose and treat anaphylaxis promptly. Consult appropriate guidelines in advance
- ✓ Premedication with antihistamines and steroids may reduce the severity of reactions caused by non-specific histamine release but will not prevent anaphylaxis.

Avoid the following if administered/exposed during the 60 minutes prior to the suspected anaphylactic event:

- All drugs to which the patient was exposed, with the exception of inhalational anaesthetic agents
- All antibiotics of the same class that was administered (beta lactams; macrolides; fluoroquinolones; aminoglycosides; monobactams; carbapenems). The surgical and anaesthetic team should discuss antibiotic choice with a microbiologist
- If an NMBA was administered during this period, all NMBAs should be avoided unless it is absolutely impossible to do so, due to the risk of cross-sensitivity
- Chlorhexidine (including chlorhexidine antiseptic wipes, medical gel (e.g. used before catheter insertion) and chlorhexidine-coated intravascular lines/catheters)
- IV colloids
- Radiological contrast and dyes used for lymph node identification
- Latex
- Local anaesthetics of the same class (amides; esters)
- Histamine-releasing drugs (morphine and codeine) as the previous reaction may have been due to non-specific histamine-release

If past anaesthetic records are not available, in addition to the above:

- Assume that the patient previously received an antibiotic. Antibiotics are the most common cause of perioperative anaphylaxis in the UK. Discuss antibiotic prophylaxis with a microbiologist beforehand
- Assume that the patient was previously exposed to propofol, morphine, chlorhexidine, latex, IV colloid, and an NMBA

Appendix D:

ANAESTHETIC DEPARTMENTAL ANAPHYLAXIS LEAD: ROLES AND RESPONSIBILITIES

If any of these responsibilities are delegated, the Departmental Lead should ensure that tasks have been completed. The role of departmental lead should be supported by job planning to determine allocation of appropriate time (direct clinical care and or supporting professional activity).

- Lead on anaphylaxis education and training in the department.
- Disseminate relevant updates as necessary.
- Engage with the local specialist allergy clinic and ensure up to date contact details (named contact, direct phone number and email).
- Act as a reference point for anaesthetists in the department who encounter perioperative anaphylaxis.
- Provide advice on referring patients for specialist investigation.
- Ensure that the patient and the GP have been given adequate, timely information in each case.
- Ensure that cases have been reported to the trust or board (Scotland) incident reporting system.
- Ensure that cases have been reported to the MHRA and that after investigation the data held by the MHRA is updated and accurate (using MHRA reference number)
- Coordinate, with primary care, appropriate follow-up of patients who have experienced perioperative anaphylaxis to identify physical or psychological adverse sequelae. This will usually take place in an outpatient setting. Refer onwards for specialist management if appropriate.
- Liaise with the hospital resuscitation team where appropriate
- Maintain a record of cases (within data protection regulations), and carry out annual audit and quality improvement as appropriate.
- Ensure that anaphylaxis guidelines are present at all sites where anaesthetics are given.
- Ensure the introduction of:
    - anaesthesia anaphylaxis treatment packs
    - anaesthesia anaphylaxis investigation packs.
- Ensure that cases are presented at departmental meetings, and that learning points are acted upon and audited if appropriate.