

Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6)

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This article is accompanied by two editorials: Where audit meets science: role of reporting and recommendations guidelines in service evaluations by Pearse & Hopkins, *Br J Anaesth* 2018;121:118–120, doi: [10.1016/j.bja.2018.05.007](https://doi.org/10.1016/j.bja.2018.05.007) and Perioperative anaphylaxis – Management and outcomes in NAP6 by Garvey & Mertes, *Br J Anaesth* 2018;121:120–123, doi: [10.1016/j.bja.2018.05.010](https://doi.org/10.1016/j.bja.2018.05.010).

Editorial decision: April 16, 2018; Accepted: April 16, 2018

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Abstract

Background: Anaphylaxis during anaesthesia is a serious complication for patients and anaesthetists. There is little published information on management and outcomes of perioperative anaphylaxis in the UK.

Methods: The 6th National Audit Project of the Royal College of Anaesthetists (NAP6) collected and reviewed 266 reports of Grade 3–5 anaphylaxis from all UK NHS hospitals over 1 yr. Quality of management was assessed against published guidelines.

Results: Appropriately senior anaesthetists resuscitated all patients. Immediate management was 'good' in 46% and 'poor' in 15%. Recognition and treatment of anaphylaxis were prompt in 97% and 83% of cases, respectively. Epinephrine was administered i.v. in 76%, i.m. in 14%, both in 6%, and not at all in 11% of cases. A catecholamine infusion was administered in half of cases. Cardiac arrests (40 cases; 15%) were promptly treated but cardiac compressions were omitted in half of patients with unrecordable BP. The surgical procedure was abandoned in most cases, including 10% where surgery was urgent. Of 54% admitted to critical care, 70% were level 3, with most requiring catecholamine infusions. Ten (3.8%) patients (mostly elderly with cardiovascular disease) died from anaphylaxis. Corticosteroids and antihistamines were generally administered early. We found no clear evidence of harm or benefit from chlorphenamine. Two patients received vasopressin and one glucagon. Fluid administration was inadequate in 19% of cases. Treatment included sugammadex in 19 cases, including one when rocuronium had not been administered. Adverse sequelae (psychological, cognitive, or physical) were reported in one-third of cases.

Conclusions: Management of perioperative anaphylaxis could be improved, especially with respect to administration of epinephrine, cardiac compressions, and i.v. fluid. Sequelae were common.

Keywords: allergy; anaesthesia; anaphylaxis; outcome; perioperative

The 6th National Audit Project of the Royal College of Anaesthetists (NAP6) was performed to characterise the incidence, risk factors, current management, clinical outcomes, and investigation of perioperative anaphylaxis in the UK. This paper describes the management and outcome data, and, based on this, makes recommendations for future practice. Successful management of perioperative anaphylaxis is critically dependent on early recognition and prompt initiation of specific treatment. Recognition that a critical event occurring during anaesthesia is likely to be anaphylaxis might not be straightforward and the differential diagnosis is wide. Rash, the classical sign of an allergic reaction, is present in approximately half of cases, but might be not visible under surgical drapes or be delayed, especially in more severe cases. Hypotension requiring vasopressor drugs, which is usually the first sign of perioperative anaphylaxis,¹ is also common during uncomplicated general² or neuraxial anaesthesia. It is only when the BP does not respond to treatment that less common causes of hypotension are sought, including: myocardial ischaemia; cardiac arrhythmia; thrombotic, amniotic fluid, fat, bone cement, air, or carbon dioxide embolism; pneumothorax; covert haemorrhage; and anaphylaxis. Similarly, bronchospasm is the first clinical feature in 18% of cases of perioperative anaphylaxis,¹ but is not uncommon during general anaesthesia, especially in asthmatic patients, and anaphylaxis might not be the first differential diagnosis.

It is generally agreed that epinephrine (adrenaline) is the mainstay of management and is recommended in all published guidelines.^{3–11} Having both α - and β -agonist properties, epinephrine has compelling theoretical advantages in the treatment of anaphylaxis by ameliorating many of the pathophysiological processes (Fig. 1).

Although metaraminol is a second-line treatment in Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines,³ it is widely available in UK anaesthesia settings for management of hypotension. Several case reports

describe survival after use of i.v. vasopressin (antidiuretic hormone) 2–15 units in the management of intractable perioperative anaphylaxis,^{12–15} and this drug is included in the Australasian guidelines.¹⁰ The benefit of epinephrine is likely to be reduced in the presence of β -blockade. There are single case reports of glucagon use in β -blocked patients leading to rapid resolution of hypotension.^{16,17} European¹¹ and Australasian¹⁰ guidelines recommend epinephrine every 5 min until response, but it is not known how commonly glucagon and vasopressin are used to treat perioperative anaphylaxis in UK practice.

There are no published randomised controlled trials investigating the efficacy of corticosteroids in the acute management of anaphylaxis and few published observational data on the pattern of their use in practice. The rationale for corticosteroid administration in anaphylaxis is an extrapolation of their effectiveness in the long-term management of allergic asthma,¹⁸ and hydrocortisone is recommended in published guidelines.

The use of antihistamines in relatively minor out-of-hospital allergic reactions benefits urticaria and pruritus. A Cochrane review of H1 antihistamines for anaphylaxis was unable to make any recommendations because of lack of evidence.¹⁹ This statement, together with side-effects of promethazine, has resulted in some expert groups recommending that antihistamines should not be administered.¹⁰ We aimed to establish whether administration of chlorphenamine, the most commonly used antihistamine in the UK, influenced outcome. We also sought to determine to what extent sugammadex has been incorporated in current management of perioperative anaphylaxis.

Anaphylaxis is associated with an acute decrease in venous return and cardiac output (Fig. 1), and there is consensus for rapid i.v. infusion of crystalloid fluids. Recent guidelines emphasise the need to give rapid, repeated i.v. fluid challenges whilst monitoring the response: Australasian guidelines

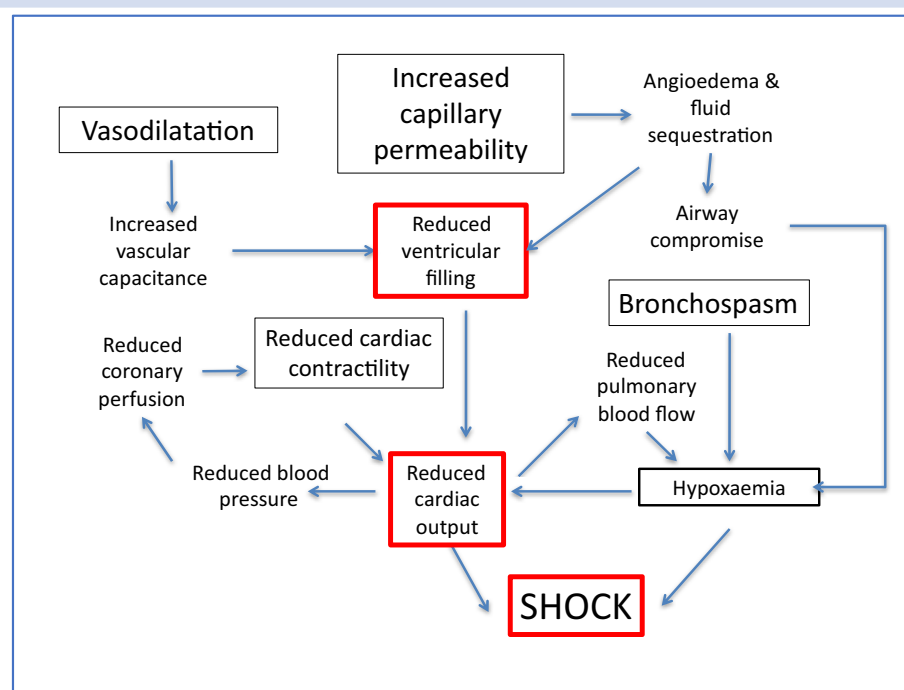


Fig 1. Pathophysiological mechanisms involved in anaphylactic shock.

recommend giving repeated boluses of 20 ml kg^{-1} .¹⁰ There are few data concerning i.v. fluid management in management of perioperative anaphylaxis, and we sought to obtain this information.

Little is known about the outcomes of perioperative anaphylaxis. We sought to establish the influence of patient characteristics, concomitant medication, comorbidities, and the quality of resuscitation. Lastly, we aimed to characterise perioperative anaphylaxis in two important groups: obstetric patients and children.

Methods

Methods are described briefly here but are discussed in detail in an accompanying paper.²⁰ All UK NHS hospitals took part and each had a Local Coordinator, a consultant anaesthetist, responsible for delivering the project. There were four elements to the project (reported in previous^{21,22} or accompanying papers^{1,20,23,24}); relevant here was a 1 yr prospective collection of anonymised case reports of life-threatening perioperative anaphylaxis, undertaken in 2015–16. Submission of cases entailed completion of a detailed form that included patient characteristics, description of the event, its management, patient outcomes, and allergy clinic investigations. Analysis of allergy clinic investigation is reported in another paper and therefore not discussed in detail here.²⁵ Eligible cases were reviewed by a multidisciplinary panel, details of which are described in the methods paper.²⁰ The quality of immediate management was assessed and classified including factors such as timeliness, accuracy, and completeness. Promptness of treatment was assessed on a case-by-case basis (generally <5 or <10 min) based on difficulty in making the diagnosis. In

doing this we also referred to current guidelines of the AAGBI and Resuscitation Council of the United Kingdom (RCUK) on management of perioperative anaphylaxis⁹ and cardiac arrest²⁶ where relevant.

Regarding resuscitation, after taking external expert advice, the panel used a systolic BP threshold of <50 mm Hg as the point at which chest compressions were indicated in adult patients. The rationale for this is discussed in detail in the accompanying paper²⁰ but is based on the findings that invasively measured systolic BP <50 mm Hg is associated with pulselessness with a 90% positive predictive value²⁷ and that non-invasive methods will underestimate hypotension when it is severe.²⁸ When the lowest recorded BP was <50 mm Hg and cardiopulmonary resuscitation (CPR) was not started, this was deemed to be suboptimal care.

The overall initial management was graded as ‘good’, ‘good and poor’, or ‘poor’,²⁰ taking into account airway management, prompt and comprehensive anaphylaxis-specific pharmacological treatment, administration of i.v. fluids and initiation of cardiac compressions, if required.

Although administration of epinephrine 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 an in-depth panel review of 184 cases.²⁰

Statistical analysis

Data are presented as median and range.

To examine the impact of chlorphenamine on outcome, we performed a logistic regression model. Variables included initial resuscitation drugs (epinephrine bolus, corticosteroids, metaraminol, ephedrine, and chlorphenamine); patient factors (age group intervals excluding children and age >75 yr because of small numbers) and ASA physical status (excluding ASA 5 because of few cases). Outcome was level of harm (no harm, low, moderate/severe harm/death).²⁰ A Fisher exact test was used to examine association between chlorphenamine administration and good quality care as judged by the review panel. A Fisher exact test was used to compare incidences of anaphylaxis between adults and children and between non-obstetric and obstetric adult patients.

Results

Quality of resuscitation

Resuscitation was performed by an anaesthetist of appropriate grade in all cases. The review panel considered that overall management was good in 46% cases; good and poor in 39%, and poor in 15% (Fig. 2).

Recognition of a critical incident and suspicion of anaphylaxis was within 5 min in 60% and 49% of cases, respectively. By 10 min, the corresponding figures were 78% and 74%, respectively. Recognition of anaphylaxis and treatment were judged prompt in 97% and 83% of cases, respectively (Fig. 3).

Specific treatment for anaphylaxis after the first clinical feature was started in <5 min in 64% of cases and <10 min in 83% (Fig. 4). Reported reasons for delay in starting anaphylaxis-specific treatment included confounding differential diagnoses such as pulmonary thromboembolism, tension pneumothorax, gas embolism during laparoscopy, primary cardiac events, surgical haemorrhage, and hypotension associated with neuraxial block.

Airway management

Airway management was judged appropriate in 98.8% of cases; in 1.2% of cases, it was judged that tracheal intubation should have been performed. Airway swelling, airway

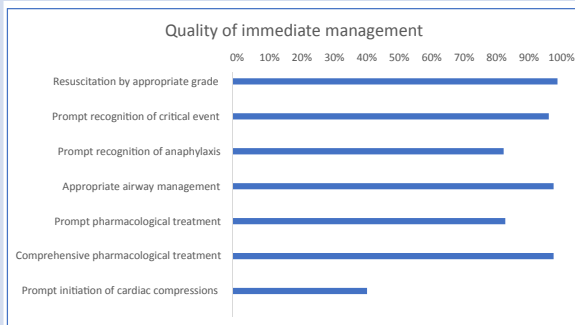


Fig 2. Proportion of cases (%) in which clinical management conformed to NAP6 quality of management indices.

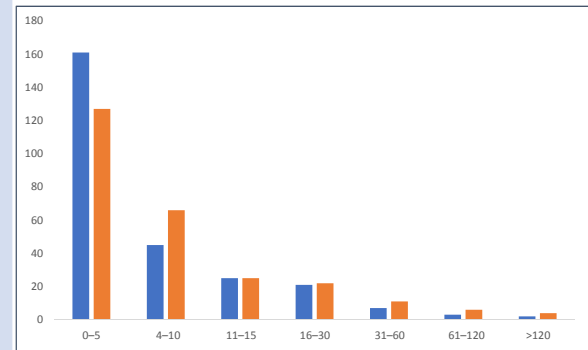


Fig 3. Number of patients (y-axis) and elapsed time (min, x-axis) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis. Blue: time to recognise critical incident; orange: time to suspect anaphylaxis.

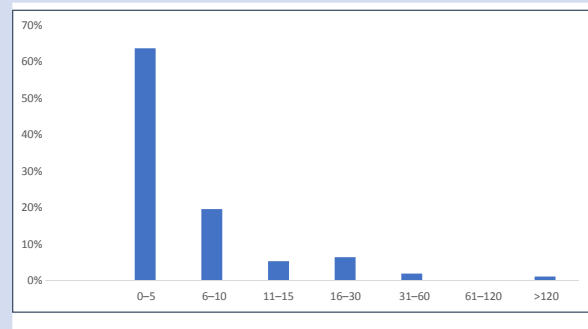


Fig 4. Proportion (%) of cases in which anaphylaxis-specific treatment was delayed (min) after appearance of the first clinical feature.

difficulty, and complications were uncommon. Tracheal intubation was performed as part of resuscitation in 13% of patients; in the majority this involved removal of a supra-glottic 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 as part of the differential diagnosis. A front of neck airway 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 because of laryngeal swelling.

Vasoactive drugs

Pharmacological treatment was judged prompt in 84% and comprehensive in 99% of cases. The vasoactive drugs administered are shown in Figure 5. Epinephrine was administered in 82% of cases, as i.v. boluses in 76%, with administration and doses administered increasing as reaction severity increased. The median i.v. total dose was 0.2 mg,

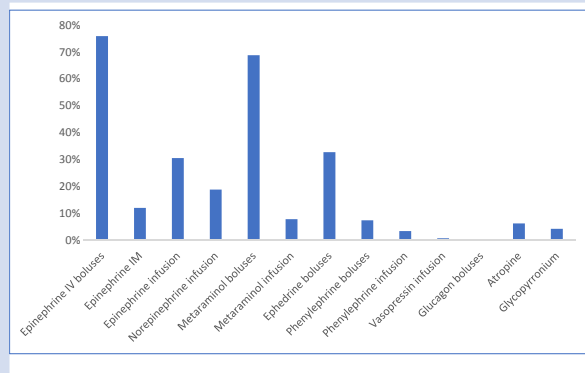


Fig 5. Proportion (%) of cases receiving vasoactive drugs administered during initial management of perioperative anaphylaxis.

0.5 mg, and 4 mg in severity-grades 3, 4, and 5, respectively. There was wide variation in the number of i.v. doses administered, ranging from 1 to 30 (median three doses). The i.m. route was used in 14% of cases, and 16 patients (6%) received both i.v. and i.m. epinephrine. An i.v. infusion of epinephrine was used in 31%, preceded by bolus doses in all except one case. Epinephrine was judged not to have been given when indicated in 19% of cases, either not administered (11%) or given late (8.4%).

Metaraminol boluses were administered in 69% of patients, of whom 74% also received epinephrine. Phenylephrine (mostly in obstetric cases) was administered by i.v. bolus in 7.8% of cases and by infusion in 3.5%. An i.v. infusion of norepinephrine (noradrenaline) was administered in 19% of cases. Only two patients received vasopressin (antidiuretic hormone) and one received glucagon. In both cases these drugs were given late in the resuscitation process and each was preceded by ephedrine, metaraminol, and epinephrine.

Bradycardia, which was present in 13% of all cases, was treated with glycopyrronium in 4.3% and atropine in 6.2%, a third in association with cardiac arrest. Tachyarrhythmia was rare, being treated once with amiodarone, which was also used during the management of four cases of cardiac arrest. No other antiarrhythmic drugs were used to treat tachyarrhythmia.

Intravenous fluids

Fluid management was judged inappropriate, almost always as insufficient, in 19% of cases. Most (98%) of patients received i.v. crystalloids in the first hour after the reaction, 86% during the subsequent 2 h and 69% 3–5 h after the event. The median volume administered during each of these time periods was 1 L (range 0.1–6.0 L), 1 L (range 0.1–3.0 L), and 0.5 L (range 0.1–4.5 L). The only i.v. colloids administered during the first hour after the anaphylactic event were succinylated gelatin products in 25 (9%) cases.

Corticosteroids

I.V. hydrocortisone was administered in 83% of cases (one to four doses, median dose 200 mg) and dexamethasone (administered after the event) in 16% of cases (median dose

6 mg). In 8.7% of cases, both drugs were administered during the event. Two patients received methylprednisolone. Of note, dexamethasone was also given before the event in 19% of cases. Thirty-four patients (12.8%) did not receive a steroid, including four fatalities.

Antihistamine drugs

Intravenous chlorphenamine was administered in 74% (median 10 mg, 5–40 mg; Table 1) and i.v. ranitidine in 5.3% of cases. Nine (3%) patients received both drugs. Chlorphenamine administration was associated with an increased probability of 'no harm' and a decreased probability of a 'moderate/severe harm and death': odds ratios 2.20 (1.05–4.58) and 0.41 (0.18–0.91), respectively. Chlorphenamine had no effect on the probability of 'low harm'. However, in order to exclude chlorphenamine as 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, we were not able to determine with any clarity whether administration of antihistamine was associated with harm or benefit.

Sugammadex

Sugammadex was administered within 6 h of the event in 19 (7.1%) cases (median dose 300 mg, range 150–1200 mg). Patients had received rocuronium in all but one case, in which atracurium had been administered. The suspected trigger agent was rocuronium in nine cases, and the actual culprit in seven. The other culprits were teicoplanin, co-amoxiclav, and atracurium. In the seven cases of rocuronium-induced anaphylaxis, after administration of sugammadex, no

Table 1 ASA physical status, level of care, and outcomes in patients receiving chlorphenamine or no chlorphenamine for Grade 3–5 perioperative anaphylaxis

	Chlorphenamine (n=195), %	No chlorphenamine (n=65), %
ASA physical status		
ASA 1	17	17
ASA 2	54	47
ASA 3	26	31
ASA 4	2.6	4.7
Prompt cardiac compressions	46	50
Critical care		
Level 3 care	42.6	20
Level 2 care	17	14
Inotropes needed in ICU	32	12
Physical harm^a		
None	5.1	20
Low	55	40
Moderate/severe/death	40	40

^a Physical harm was based on 138 cases and 40 cases with this information available in which the patient did or did not receive chlorphenamine, respectively.

further vasopressor was required in four cases, while further vasopressors and bronchodilators were needed in three.

Guideline access

A management guideline was immediately accessible in 86% of cases, 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% of cases). The RCUK guidelines on management of anaphylaxis and on life support were used in 5.3% and 6.4% of cases, respectively. Local or Trust guidelines accounted for 3.8% of cases. In 44 (19%) cases, no specific guideline was used. 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%.

Fatal cases

Immediate management was prompt in all but one of the 10 fatal cases and all resuscitations followed a guideline and were managed by a consultant. Nine had a cardiac arrest during the event and one did not. Resuscitation from cardiac arrest, in the nine relevant cases, was prompt, prolonged, and extensive. CPR took place for a median 39 min, and in all cases for >25 min. Resuscitation included extracorporeal membrane oxygenation in one patient and immediate cardiac catheterisation to explore or manage an acute coronary syndrome in two patients. Epinephrine i.v. was administered in all cases including an infusion in five. A median of five doses (5 mg) epinephrine was administered (range 2–13 mg). No patient received i.m. or intraosseous epinephrine. Ephedrine, metaraminol, glycopyrronium, and atropine were used early in resuscitation and five patients received norepinephrine, two vasopressin, and one glucagon (administered 65 min after the reaction). Half of cases received chlorphenamine and hydrocortisone. Sugammadex was not used. Fluid resuscitation volumes were relatively modest 1–4.5 L (median 1.5 L) in the first hour and 1–9.5 L, (median 1.5L) in the first 5 h: only one

patient received >4 L in total. Five patients did not survive initial resuscitation, while five did, one of whom died soon after. Of the four remaining patients, all were admitted to ICU and all survived at least 1 week, but all deaths occurred in <30 days. Four patients developed multiple organ failure.

A mast cell tryptase sample was sent in all cases and a dynamic change was identifiable in five cases. Mast cell tryptase results are discussed elsewhere.²⁵ There were no episodes of recrudescence of anaphylaxis.

Good elements of care were: appropriately senior resuscitators (10/10); prompt recognition of the critical event (9/10); prompt recognition of anaphylaxis (9/10); appropriate airway management (10/10) and prompt initiation of cardiac compressions (9/10, one uncertain). Inadequate fluid administration was a recurrent theme.

Cardiac arrest

Cardiac arrest was reported in 40 (15%) patients: five did not survive the cardiac arrest, four died after admission to critical care and 31 survived. In 11 patients, cardiac arrest occurred within 5 min of trigger administration, although others were preceded by prolonged hypotension. All these patients received cardiac compressions for a mean duration of 14 min (range 1–60 min). It was generally prolonged in those who died (see above) but brief in those who survived: median 8 min (interquartile range 2–8 min) in survivors. The event was generally promptly recognised and treated. Delay in managing anaphylaxis was a result of slow diagnosis or uncertain diagnosis (one case each) and loss of i.v. access (one case). Quality of resuscitation is summarised in Table 2. On average, five doses of epinephrine i.v. were administered (total mean 5 mg, range 0–12 mg), notably similar in those patients who died or survived. Half of survivors received an epinephrine infusion after initial resuscitation. Second-line drugs included norepinephrine to 15 patients, vasopressin to two (one of whom died and one survived), glucagon to one (who died), lipid emulsion to two and sugammadex to one. Chlorphenamine and steroid were given to approximately 75% of patients during resuscitation. Fluid volumes were modest; median volume 1.8 L (range 0–4.5 L) during

Table 2 Quality of resuscitation and outcomes in patients who died compared with those who survived cardiac arrest, and those who experienced profound hypotension or did not *One patient who subsequently died did not have a cardiac arrest at the time of the event

	Deaths (n=10), %	*Non-fatal cardiac arrest (n=31), %	BP <50 mm Hg but not cardiac arrest or death (n=79), %	All others (n=135), %
Quality of resuscitation				
Appropriate resuscitator	100	100	100	98
Prompt recognition	100	91	98	99
Prompt diagnosis of anaphylaxis	88	82	80	85
Prompt treatment of anaphylaxis	70	83	65	78
Epinephrine administered as needed	90	100	76	77
Prompt cardiopulmonary resuscitation when indicated	90	91	2	67
Appropriate fluid	67	81	78	83
Good initial management	60	65	8	58
Poor initial management	0	9	34	8
Outcomes				
Outcomes where known (median)	Severe	Moderate	Moderate	Low
% experiencing any harm	100	74	59	60
ICU for vasopressors (% of all cases)	n/a	67	32	23
Time on ICU (median, all cases)	n/a	2	0	1
Unplanned hospital length of stay	n/a	2	1	1

the first hour and 3.2 L (range 0–9.5 L) during the first 5 h. Panel judgements on quality of care are included in Table 2.

Profound hypotension

In >40% of cases the lowest systolic arterial pressure was <50 mm Hg or unrecordable. Chest compressions were initiated in 28 (50%) of those with an unrecordable BP and in five (9%) with systolic arterial pressure <50 mm Hg. Prompt initiation of chest compressions for arterial pressure <50 mm Hg or unrecordable was reported in 23% of cases. In the group with profound hypotension without cardiac arrest, failure of prompt and complete pharmacological treatment and fluid administration was noted somewhat more frequently than in other groups and care was more frequently judged to be poor. Patient characteristics, outcomes, and quality of care are summarised in Table 2.

Discontinuation of the trigger agent

The suspected trigger agent was discontinued in 22 of the 26 cases where this would have been possible. Agents that were not discontinued were i.v. 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 fourteen cases where this would have been possible: i.v. gelatin, administration of a second dose of protamine, and two instances of retained chlorhexidine-coated central venous line.

Continuation of surgery

In one-third of cases the procedure was unchanged but, in more than half of cases the intended surgery was not started. 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.

Unplanned hospital stay and critical care admission

The median unplanned hospital length of stay as a result of anaphylaxis was 1 day, but there was a wide range: 18% >2 days; 12% >3 days; 8.3% >4 days; and 6.6% >5 days. The longest unplanned length of stay was 150 days.

Of 144 (54%) patients transferred to critical care, the majority (70%) were for level 3 care. The median duration of level 3 care was 1 day (range 1–9 days), and of level 2 care was 1 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. Data on the use of vasopressors and bronchodilators were available for 135 and 119 patients, respectively. While in critical care, 84/135 (63%) of patients received vasopressors or inotropes and 6/119 (5.0%) bronchodilators. Of 84 patients requiring vasopressor or inotrope infusions in critical care, 29 (34%) received epinephrine, 19 (23%) both epinephrine and norepinephrine, 13 (15%) norepinephrine, and the remainder other inotropic drugs.

Outcomes (cases of all severity)

The severity of physical harm (see accompanying paper for definitions)²⁰ identified by the review panel was none in 8%; low in 51%; moderate in 34%; severe in 0%; death in 4%; and uncertain in 3%. Concomitant β -adrenergic blocking drugs

were associated with greater severity: 60% of fatalities were taking a β -blocker compared with 18% of all cases although causality cannot be proved.

We asked about physical and psychological sequelae after the event. Data were recorded poorly, so any estimates must be judged as minima. More complications were recorded in the section of the case report form completed before allergy clinical referral (104 sequelae: 67 mild, 29 moderate and eight severe) than in that completed after the allergy clinic visit (73 sequelae: 41 mild, 27 moderate, and five severe). Anxiety about future anaesthetics was the most commonly reported consequence, accounting for more than half of longer-term consequences, in three cases this extended to symptoms of post-traumatic stress disorder. Ten patients reported problems with mood, memory, or coordination. There were 13 reports of myocardial infarction, acute kidney injury, or new shortness of breath.

As a result of anaphylaxis, cancer surgery was delayed in 19 (7.1%) cases, urgent non-cancer surgery in eight (3%), non-urgent surgery in 76 (29%), and other treatment was delayed in nine (3.4%) cases. Total hospital stay was extended as a result of anaphylaxis in 75% of patients (median 1 day, range 0–150 days).

Obstetric cases

We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey²³ estimated that 233 886 obstetric anaesthetics are administered per annum in the UK, giving an incidence of severe obstetric perioperative anaphylaxis of 3.4 per 100 000 (95% CI: 1.5–6.7 per 100 000). The incidence in obstetric patients is therefore lower than in non-obstetric adult patients (247 cases in 2 489 428 patients: 9.9 per 100 000, 95% CI: 8.7–11.2 per 100 000, Fisher exact $P < 0.001$).

Six patients received neuraxial anaesthesia and two general anaesthesia. Six cases occurred in association with anaesthesia for Caesarean section, most commonly after delivery of the baby. There were no cardiac arrests, maternal, or neonatal deaths. All patients developed hypotension, in some cases profound. In four of six patients who developed severe anaphylaxis during neuraxial anaesthesia, a common feature was the patient complaining of feeling unwell before the onset of hypotension or other clinical signs. Hypotension commonly developed at a time when spinal-induced hypotension would have been anticipated to have settled.

A consultant anaesthetist was involved in the management of all the cases. In five cases there was prompt treatment, but in three cases there was a delay in diagnosis and treatment was delayed. Resuscitation drugs differed from those used in non-obstetric cases: six patients received phenylephrine, four epinephrine, and three both drugs. Fluid management was appropriate in all cases. An anaphylaxis pack was used to assist management in only two cases. In four cases, overall care was judged as good and in one case was judged as good and poor.

Mast cell tryptase tests were sent in all cases. In six cases, these were raised or there was a dynamic change. The reaction was allergic anaphylaxis in five cases, anaphylaxis not-specified in one case and uncertain in two. Identified culprits were chlorhexidine, atracurium, succinylcholine (suxamethonium), and ondansetron and in four cases no trigger was identified.

Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during

neuraxial anaesthesia required tracheal intubation. For three women hospital discharge was delayed and one patient reported anxiety about future anaesthesia.

Paediatric cases

Eleven cases of perioperative anaphylaxis in patients aged <16 yr were reported, three of which were emergency procedures. With an estimated 403 000 paediatric cases performed per annum, the incidence of Grade 3–4 anaphylaxis is 2.7 per 100 000 paediatric anaesthetics (95% CI: 1.4–4.9 per 100 000). The incidence in paediatric patients is therefore lower than in adult patients (255 cases in 2 723 314 patients: 9.4 per 100 000, 95% CI: 8.4–10.6 per 100 000, Fisher exact $P < 0.001$).

Two patients had well-controlled asthma. Six cases presented in the operating theatre, three in the anaesthetic room, one during transfer from the recovery room to the ward and one in the radiology department. Seven cases presented after induction and before surgery. The first clinical feature was bronchospasm, or high airway pressures in seven (64%) cases with hypotension being the presenting feature in two, tachycardia in one, and non-urticarial rash in the remaining case.

Bronchospasm presented within 5 min, whereas hypotension was generally slower in onset. A decrease in end-tidal carbon dioxide concentration was noted in three cases with an absent capnography trace in two of these at some point. Two cases exhibited non-laryngeal oedema, which was delayed in one case. There were no fatalities in children. The clinical features present at any time during the reaction are shown in Figure 6. All cases were judged Grade 3 by the index anaesthetist: on panel review, six were judged as Grade 4.

The review panel judged that clinical management was good in four cases, good and poor in two cases, and was poor in a single case (where epinephrine was not administered). A consultant was present during resuscitation in all cases. AAGBI guidelines were used in five and RCUK guidelines in one. In seven cases, there was immediate access to a guideline as a laminated document.

Specific treatment for anaphylaxis was started within 5 min in six of the seven cases where bronchospasm or high

airway pressures were the presenting feature. When hypotension or tachycardia were the presenting features, specific treatment tended to be started later. Epinephrine was administered in 10 cases, either i.v. or i.m., and an infusion was required in four cases. Other vasopressors were used in small numbers of cases. Eight patients received chlorphenamine and eight hydrocortisone. Two patients did not receive a corticosteroid. One patient received atropine. No patients received phenylephrine, vasopressin, glucagon, glycopyrronium, sugammadex, or magnesium sulfate. Ten patients received i.v. crystalloid, one i.v. gelatin, and one no i.v. fluid. The volume of crystalloid administered during the first hour was 12–75 ml kg⁻¹ (median 20 ml kg⁻¹), between 1 and 3 h 3–25 ml kg⁻¹ (median 9 ml kg⁻¹), and during the subsequent 2 h 6–20 ml kg⁻¹ (median 8 ml kg⁻¹).

In six cases the procedure was abandoned and four of these were rescheduled, in all cases except one judged to be appropriate. Three patients were transferred to HDU/ICU as a result of the event, including one to a different hospital.

Eight cases had at least one mast cell tryptase sample obtained, with four showing elevation or dynamic changes. The reaction was allergic anaphylaxis in three cases, non-allergic anaphylaxis in one case, anaphylaxis not-specified in two cases and uncertain in five. Culprit agents were: atracurium in three cases and one each of succinylcholine, aprotinin, cefuroxime, ibuprofen, and cryoprecipitate. The trigger was not confidently identified in the three remaining cases. The mechanism of the reaction to ibuprofen was judged to be non-allergic anaphylaxis. Overall allergy clinic investigation for eight fully reviewed cases was good in one, good and poor in three, and poor in four.

Following resuscitation and clinical recovery, one child was reported as being withdrawn and angry and one child reported anxiety about potential further anaesthesia. Seven cases were reported through the Trust's local critical incident reporting system but only one case was recorded as being reported to the Medicines and Healthcare products Regulatory Agency, and two patients were issued with a hazard alert by the anaesthetist.

Concordance

Concordance between triggers suspected by the anaesthetist and identified by the panel is discussed in greater detail in a paper exploring allergy clinic investigation of the NAP6 cohort.²⁵ Amongst cases with an identified trigger, overall concordance was 75% between the anaesthetist and the panel. However, anaesthetists were likely to over-identify neuromuscular blocking agents as triggers and to fail to recognise chlorhexidine-induced anaphylaxis.

Communication

The panel judged that there were considerable shortcomings in communication between the anaesthetist and the patient after the event. Information given to the patient by the anaesthetist about which drugs or other substances they should avoid before attending an allergy clinic for investigation was oral in 27%, written in 20%, both in 39%, and none in 14%. In 222 cases where this information was available, 29% were issued with a hazard warning card, 39% of these by the index anaesthetist.

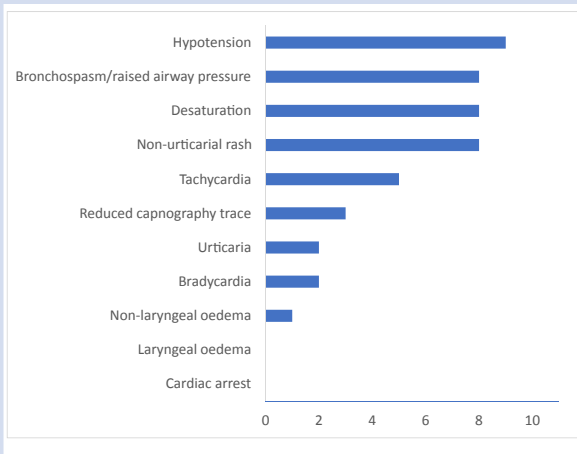


Fig 6. Number of children exhibiting clinical features at any time during the anaphylactic episode.

Discussion

Key findings

The key findings of the NAP6 survey of anaphylaxis are summarised as follows:

- (i) All 266 patients were resuscitated by an anaesthetist of appropriate grade and recognition of a critical event was prompt.
- (ii) Recognition of anaphylaxis was generally prompt.
- (iii) Immediate management was judged 'good' in 46% and 'poor' in 15% of cases.
- (iv) There was delay in starting anaphylaxis-specific treatment in 67 cases.
- (v) Fluid administration was frequently judged to be insufficient and was inappropriate in 19% of cases.
- (vi) When cardiac compressions were indicated there was delay starting them in more than half of cases.
- (vii) Airway management was generally uncomplicated and without difficulty. A front of neck airway was performed in a single case as a result of anaphylaxis.
- (viii) Sugammadex was administered in seven rocuronium-induced cases and no further pharmacological treatment was needed in four.
- (ix) Vasopressin and glucagon were very rarely used. Careful examination of the role of chlorphenamine found no evidence of harm or benefit.
- (x) Of 54% of patients requiring admission to critical care, 70% were for level 3 care, and most required catecholamine infusions after admission.
- (xi) One-third of patients experienced sequelae from anaphylaxis: 34% of patients experienced moderate physical harm, anxiety about future anaesthetics was common, and three patients experienced symptoms of post-traumatic stress disorder.

Immediate management: all cases

We are unaware of any previous study investigating the management of perioperative anaphylaxis in such detail. It is reassuring that resuscitation involved a consultant or other career grade anaesthetist in all cases. The majority (89%) of UK patients are anaesthetised by consultant or career grade anaesthetists²³; nevertheless, trainees were willing to call for help and the theatre team contributed effectively to management in almost 90% of cases. Recognition of perioperative anaphylaxis may be difficult but nevertheless was prompt in 83% of cases.

Overall quality of management was judged 'good' in slightly less than half of the cases. The deficits were multifactorial and included insufficient i.v. fluids (19% of cases), non-administration or late administration of epinephrine (18%), delays in recognising anaphylaxis and starting specific treatment, and lack of cardiac compressions where there was profound hypotension.

Epinephrine and fluids

The beneficial actions of epinephrine include vasoconstriction which increases venous return, reduced capillary permeability, increased cardiac contractility and cardiac output, bronchodilatation, and inhibition of mast cell and basophil mediator release. Early administration of epinephrine is associated with improved outcomes in out-of-hospital anaphylaxis.²⁹ McLean-Tooke and colleagues³⁰ concluded that

epinephrine is not contraindicated in patients with coronary artery disease as continuing anaphylaxis is likely to reduce coronary artery perfusion further. However, excessive dose or over-rapid i.v. administration can cause arrhythmias. We found no evidence that epinephrine caused arrhythmia and the dose in survivors and non-survivors of cardiac arrest did not differ. I.V. epinephrine is more likely than i.m. to result in cardiac complications in treatment of out-of-hospital anaphylaxis in elderly patients,³¹ but there is no previous published information regarding the perioperative setting. The i.v. and i.m. routes are both recommended for the treatment of perioperative anaphylaxis; the i.v. route restricted to patients with continuous vital-signs monitoring, including continuous electrocardiography.⁹ The AAGBI guidelines recommend an initial i.v. dose of 50 µg, repeated as necessary.³ The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) guidance for Grade 3 reactions recommend an initial i.v. dose of 100 µg followed, if necessary, by 100–200 µg every 1–2 min and a continuous infusion after three i.v. boluses.¹⁰ We were not able to determine whether larger doses are more effective, but we found no important complications of repeated doses of 50 µg. However, those patients who died were more likely to be elderly and to have cardiac disease than survivors. Several died after prolonged cardiac arrest with approximately half developing multiorgan failure after transfer to critical care.

In one in five cases, epinephrine was either not administered or was delayed. An apparent reluctance to give epinephrine has been previously reported, although this was not common.³² We suggest that four factors operate. First, anaphylaxis is very uncommon: an anaesthetist will see perioperative anaphylaxis on average only once every 7.25 yr.²¹ Second, when faced with hypotension, it has been the anaesthetist's previous experience that repeated doses of the 'usual' vasopressors will eventually restore arterial BP, encouraging a 'more of the same' approach. Third is the phenomenon of crisis-denial and the realisation that giving epinephrine will affirm that a crisis exists. Fourth, unless the anaesthetist has a critical care background, administration of epinephrine can be outside their usual experience. It is also possible that the anaesthetist has unfounded concerns that epinephrine is contraindicated in patients with coronary artery disease or in obstetric patients. In addition to immediate availability of management guidelines, overcoming these barriers to epinephrine administration might benefit from frequent practice drills and, ideally, simulator training.³³

Reluctance to administer large volumes of i.v. fluids was observed more commonly, including in elderly patients and those with cardiac disease, perhaps through misplaced fears of causing fluid overload and precipitating heart failure.

Risk factors for fatal reactions

The mortality rate (3.8%) observed in NAP6 corresponds with other large series. A significant finding was the association with increased age, increased ASA physical status, morbid obesity, coronary artery disease and β -blocker and angiotensin converting enzyme inhibitor use. These factors are likely to interact and might not each be independent predictors of poor outcome but are worthy of further research.

Management of profound hypotension

Patients with profound hypotension had poorer quality of care than any other patient group. They were more likely to have

delayed diagnosis and administration of epinephrine, and chest compressions were a rarity. Significant numbers of patients in this group came to harm. Early recognition of these patients as at high risk of harm, early management with epinephrine and fluids, and chest compressions provide an opportunity to improve outcomes.

Critical care

Gibbison and colleagues³⁴ showed that perioperative anaphylaxis accounted for a third of all cases of anaphylaxis admitted to critical care units³⁴; this is a similar proportion to that admitted from the emergency department after community anaphylaxis. Our data for 144 admissions over a 1 yr period are compatible with these findings. A novel finding is that while almost two-thirds of patients admitted to critical care required continuing inotropic support, only 5% needed continuing bronchodilator therapy. Of note, there were no cases of so-called biphasic anaphylaxis.

Vasopressin and glucagon

Vasopressin is recommended for intractable hypotension in several guidelines,^{5,10} but was administered in only two cases despite the presence of persistent hypotension, evidenced by the administration of norepinephrine infusion in almost one in five cases. Several cardiac arrests were preceded by prolonged hypotension. Of note, earlier guidelines omitted this drug³ and it is likely that awareness of its role is limited. It is also likely that vasopressin is unavailable in many anaesthetising sites, a situation addressed by our recommendations. Similar comments apply to glucagon.

Chlorphenamine

We sought to be in a position to make firm recommendations about the administration of chlorphenamine. Using level of harm as the outcome and including all putative factors, logistic regression identified chlorphenamine administration was associated with increased probability of 'no harm' and decreased probability of 'moderate/severe' harm. However, the confidence intervals were wide and a Fischer exact test demonstrated that anaesthetists who gave overall good care as determined by the review panel were more likely to have administered chlorphenamine, presumably as a result of following UK guidelines (i.e. we were unable to demonstrate causality). The review panel considered that chlorphenamine should continue to be recommended, although mainly to reduce angioedema/urticaria.

Sugammadex

Several case reports may be considered supportive of administration of sugammadex during rocuronium-induced anaphylaxis.^{35–37} The hypothesis that encapsulating the antigen might halt the clinical features of anaphylaxis is unproved, despite *in vitro* and clinical studies.³⁸ Platt and colleagues³⁹ reported sugammadex administration for immediate management of suspected rocuronium-induced anaphylaxis in 13 cases, of which five were not rocuronium-induced. Clinical features improved in six patients, including three without rocuronium-induced anaphylaxis. This raises the possibility that sugammadex exerts a vasopressor effect

via a mechanism other than encapsulating the antigen. Our data do not support the efficacy of sugammadex in rocuronium-induced anaphylaxis. Of seven proved cases, four required no further pharmacological treatment after sugammadex was given, but three required further vasopressor or bronchodilator therapy.

Anaphylaxis packs

Anaphylaxis packs^{5,40} can refer to packs designed to assist either treatment or in initiating investigation and referral. We have recommended both anaesthetic anaphylaxis treatment packs and anaesthetic anaphylaxis investigation packs. The suggested contents of these are described in [Supplementary material A and B](#), respectively.

Decision whether to continue surgery

The majority of patients in our cohort required transfer to critical care, mostly for level 3 care, and half of patients required catecholamine infusions and a substantial number of patients were harmed by their anaphylactic event. While the decision to abandon or continue surgery needs to be a balanced one based on individual circumstances, the review panel suggest that it is inadvisable for surgery to proceed after life-threatening anaphylaxis (Grades 3 and 4), unless there are over-riding reasons to do so. Sadleir and colleagues⁴¹ demonstrated that patients with Grade 3 anaphylaxis who continued with surgery did not require more intra-operative epinephrine or longer postoperative ventilation than those in whom the procedure was abandoned. However, surgery was more likely to be abandoned in the more severe Grade 3 cases. The authors attempted to control for this effect by using the degree of mast cell tryptase increase as a surrogate for severity, but NAP6 data show no relationship between acute mast cell tryptase concentrations and indices of clinical severity.²⁵ In the Sadleir and colleagues⁴¹ study, continuing with surgery in Grade 4 anaphylaxis was not recommended because of poor outcomes in all patient groups.

When surgery is abandoned there might be a need to reorganise it before allergy clinic investigation can be undertaken. Balancing the risks of deferring or proceeding with surgery after perioperative anaphylaxis will often require careful multidisciplinary discussion. The potential risks of this are underlined by a NAP6 case in which an neuromuscular blocking agent was the suspected culprit but chlorhexidine was demonstrated to be the cause on allergy testing. In most circumstances, genuinely urgent surgery can be performed before allergy clinic assessment by applying some simple, cautious rules, and we have developed a management plan ([Appendix 1](#)) for patients in whom surgery is needed before a clinic diagnosis has been obtained. However, we emphasise that this applies only to genuinely urgent surgery and that elective surgery should be deferred until after investigation. This might require multidisciplinary discussion to balance the benefits and risks of early surgery and anaesthesia.

Obstetric cases

Anaphylaxis in the obstetric setting was half as frequent as in the general adult population. Anaphylaxis during pregnancy is very uncommon including during Caesarean delivery (≈ 1.6 – 3.0 per 100 000 maternities and 2.1 per 100 000

Caesarean sections).^{42–44} Widespread use of neuraxial techniques is likely to limit exposure to many trigger agents associated with general anaesthesia. Previous studies have highlighted latex, succinylcholine, and antibiotics as culprits.⁴⁵ Of note, the obstetric setting leads to numerous other (more common) obstetric causes of profound hypotension that might complicate diagnosis and delay treatment. Treatment of perioperative obstetric anaphylaxis demands safety of both patients and raises concerns of the potential impact of both maternal hypotension and epinephrine administered to the mother on uteroplacental haemodynamics. The placenta is metabolically active and metabolises histamine and other endogenous mediators,⁴⁶ potentially protecting the fetus from mediator-related morbidity.

Management and outcomes of these patients was good. Phenylephrine was more widely used in obstetric anaphylaxis than in other settings; it is widely available and recommended for management of hypotension associated with spinal anaesthesia.⁴⁷ However, epinephrine remains recommended for the management of obstetric anaphylaxis, and any theoretic impact on the uteroplacental circulation is likely to be short lived⁴⁸ and less dangerous than the impact of maternal hypotension.

Paediatric cases

Perioperative anaphylaxis is uncommon in children, and reported incidences vary considerably.^{49–51} We found a rate that is a quarter of that in adults. Latex and neuromuscular blocking agents have historically been prominent triggers and antibiotics less commonly cited. This is probably influenced by differences in both procedures commonly undergone by children and by anaesthetic techniques.

The low incidence of paediatric perioperative anaphylaxis could have several causes. Latex exposure has reduced significantly in recent years. It is also likely that children are both less sensitised to allergens before anaesthesia and less exposed than adults to allergens during the perioperative period. NAP6 indicates that neuromuscular blocking agents and antibiotics were used in 25% and 26% of paediatric general anaesthetics, compared with 47% and 57% in adults.²⁴ The NAP6 allergen survey also showed that 14% of children received only sevoflurane for induction and maintenance, which is a low anaphylaxis-risk anaesthetic.²⁴

Unlike in adult patients, bronchospasm or high airway pressures were the most common presenting feature in children. Cardiopulmonary resuscitation was not performed in any paediatric case: in four cases, systolic arterial pressure was <50 mm Hg, but expert opinion did not favour setting a BP below which CPR should be initiated in children.

Given the small number of cases reported in children, it is not possible to make confident conclusions concerning risk rates with different drugs. However, the number of cases of atracurium and succinylcholine appears to be proportionate to the number of exposures. Atracurium was the most-used neuromuscular blocking agent in children (57%) by a large margin, followed by rocuronium, and succinylcholine. Paediatric cases are increasingly intubated without an neuromuscular blocking agent.⁵² There were no cases of latex-induced anaphylaxis, which might reflect its declining presence in the workplace⁵³ and an increased awareness

as a potential hazard following historical paediatric case reports.⁵⁴

In both obstetric and paediatric anaesthesia, we noted statistically significantly lower rates of perioperative anaphylaxis than in non-obstetric adults and adults, respectively. However, given the relatively small numbers of cases involved, these results must be interpreted with caution and require further confirmation in other series.

Recommendations

We are not aware of other studies that investigated a wide range of physical and psychological adverse sequelae. Severe anxiety and mood changes, mild/moderate memory impairment, and impaired mobility were observed. Physical harm was uncommon but did include one front of neck airway and a small number of patients who experienced myocardial infarction, acute kidney injury, or new shortness of breath as a consequence of perioperative anaphylaxis or during their recovery. It is likely that these sequelae are underdiagnosed. We recommend that all patients should be followed-up after perioperative anaphylaxis. In order to facilitate this and the many other tasks that are needed for a department of anaesthesia to be 'institutionally prepared' to manage perioperative anaphylaxis, we recommend that all departments of anaesthesia should have a 'Departmental Lead for Anaphylaxis'. The suggested roles and responsibilities are set out in [Supplementary material C](#).

We list the complete series of NAP6 recommendations intended to improve care in [Appendix 2](#). They are numerous and some simply reinforce known good practice. However, each recommendation is founded on the direct and indirect findings of NAP6. We hope that (as with previous NAPs)^{55,56} the many recommendations we have made will be largely implemented. Others might stimulate discussion or provide hypotheses for future research. We hope this will both increase awareness of the topic and improve institutional and individual preparedness for these infrequent but life-threatening events. This will have the potential to make inroads into avoiding avoidable anaphylaxis, improving the quality of care patients receive when it occurs and afterwards, both by anaesthetists and in allergy clinics.

Authors' contributions

Co-designed methodology of the study: N.J.N.H., T.M.C., T.G., S.F., N.L., M.T., K.-L.K., S.K., S.M., J.H., K.F., M.B., H.T.

Results analysis: N.J.N.H., T.M.C., T.G., S.F., N.L., M.T., K.-L.K., S.K., S.M., J.H., K.F., M.B., H.T.

Collated draft sections, wrote all drafts of the paper and the final draft: N.J.N.H.

Reviewed and revised drafts of the paper and the final draft: T.M.C.

Wrote draft sections of the paper: T.G., S.F., N.L., M.T., K.-L.K., S.K., S.M., J.H., K.F., M.B., H.T.

Contributed to the design and methodology of the study, reviewed the results and took part in review of draft manuscripts leading to finalisation: all other panel members.

Contributed to design and methodology of the study: L.F.

Administered study: L.F.

Took part in review of draft manuscript leading to finalisation: L.F.

Acknowledgements

We thank all anaesthetists who engaged with the NAP6 project and all Local Coordinators who administered the project at each of the participating hospitals. Particular thanks to M. Shields, Belfast Health and Social Care Trust, who acted as NAP6 Moderator throughout the project. At the Royal College of Anaesthetists, we thank J. Goodwin, Research Manager, J. Lourtie, Research Supervisor, and S. Drake, Director of Education and Research. We also acknowledge the contributions of the following NAP6 panel review members: A. McGlennan, Royal Free London NHS Foundation Trust, London, UK; S.R. Moonesinghe, Perioperative and Intensive Care Medicine, University College Hospital London NHS Trust (Health Services Research Centre), London UK; G. Scadding, Imperial College Healthcare NHS Trust, London UK; T. Krishna, Heart of England NHS Foundation Trust, Birmingham, UK; R. Collins, Hillsborough Private Clinic (The Association for Perioperative Practice), London, UK; M. East, Former National Coordinator of the Anaphylaxis Campaign (Anaphylaxis Campaign), London UK.

Declarations of interest

T.M.C. is a member of the associate editorial board of the *British Journal of Anaesthesia*. He is not aware of any financial conflicts.

N.J.N.H., T.G., D.N.L., M.T., H.K., K.-L.K., S.M., S.K., K.Fe., J.H., H.T., A.W., W.E., S.N., N.M., K.Fl., M.B., L.F., and S.F. have no conflicts to declare.

Funding

The Royal College of Anaesthetists.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.bja.2018.04.015>.

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Appendix 1.

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

It is possible to provide safe anaesthesia in most cases and unnecessary to postpone urgent surgery. However, we emphasise that this guideline applies only to genuinely urgent surgery and that elective surgery should be deferred until after investigation.

- ✓ 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 inhalation agents, thiopental, etomidate (non-lipid formulation), and ketamine
- ✓ If tracheal intubation is required and a neuromuscular blocking agent is contraindicated:
 - A remifentanyl infusion, magnesium sulfate and topical anaesthesia are helpful adjuncts to deep anaesthesia in facilitating laryngoscopy and intubation
 - Where remifentanyl was used in the previous anaesthetic, consider the use of alfentanil
 - Awake intubation under topical anaesthesia is an alternative
- ✓ If local anaesthetics are not contraindicated, 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 and be prepared to diagnose and treat anaphylaxis promptly. Consult appropriate guidelines in advance
- ✓ Premedication with antihistamines and steroids might 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 min before the suspected anaphylactic event:

- All drugs to which the patient was exposed, with the exception of inhalation anaesthetic agents
- All antibiotics of the same class administered (β -lactams; macrolides; fluoroquinolones; aminoglycosides; monobactams; carbapenems). The surgical and anaesthetic team should discuss antibiotic choice with a microbiologist
- If a neuromuscular blocking agent was administered during this period, all neuromuscular blocking agents should

be avoided unless it is absolutely impossible to do so, because of the risk of cross-sensitivity

- Chlorhexidine [including chlorhexidine antiseptic wipes, medical gel (e.g. used before catheter insertion) and chlorhexidine-coated intravascular lines/catheters]
- I.V. 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 might have been a result of 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, i.v. colloid, and a neuromuscular blocking agent
- If possible, use local or regional anaesthesia in patients who have had a previous suspected anaphylactic event during general anaesthesia, and vice versa

Appendix 2.

NAP6 recommendations for anaesthetists

Recommendations regarding allergy clinic investigations can be found in the accompanying paper,²³ and all recommendations including those for research are in the main report at <http://www.nationalauditprojects.org.uk/NAP6Report#pt>

Departmental organisation and immediate management

National

1. 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.
2. Allergy history-taking should be included in core curricula for medical and nursing training. Nurses in preoperative assessment clinics require particular skills and training.

Institutional

3. Procedures should be in place to ensure that an appropriate patient allergy history is sought and recorded before anaesthesia is administered.

4. There should be a *departmental lead for perioperative anaphylaxis* in each department of anaesthesia. This role should be supported by appropriate time and direct clinical care and supporting professional activity (DCC/SPA) allocation.
 5. 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.
 6. 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.
 7. Clinical Directors of anaesthetic departments should ensure their anaesthetists have been trained in the management of perioperative anaphylaxis.
 8. Perioperative anaphylaxis guidelines, a management algorithm, or both, should be immediately available wherever anaesthesia is administered.
 9. *Anaesthesia anaphylaxis treatment packs*, including an anaphylaxis management algorithm, epinephrine pre-filled syringes suitable for i.v. administration, hydrocortisone and details of the location of glucagon and vasopressin, should be immediately available wherever anaesthesia is administered.
 10. *Anaesthesia anaphylaxis investigation packs*, including tryptase sampling tubes and information sheets that describe: (a) details of blood tests required and their timing; (b) instructions on referral for further investigation and allergy clinic details; and (c) documentation for the patient, should be available in all theatre suites.
 11. Vasopressin and glucagon for the management of intractable perioperative anaphylaxis should be available within 10 min, wherever anaesthesia is administered.
 12. Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the patient's medication, the event and timings of all drugs administered before the event. A standardised form (e.g. the NAP6 or AAGBI proforma) should accompany the referral.
 13. 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 co-ordinate this.
- Individual**
14. All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.
 15. Epinephrine is the primary treatment of anaphylaxis and should be administered immediately once anaphylaxis is suspected. In the perioperative setting, this will usually be i.v.
 16. 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.
 17. If i.v. access is not immediately available, i.m. or intraosseous routes should be used promptly, until i.v. access is established.
 18. A rapid i.v. crystalloid (not colloid) fluid challenge of 20 ml kg⁻¹ should be given immediately. This should be repeated several times if necessary.
 19. During anaphylaxis with a systolic BP <50 mm Hg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with epinephrine and liberal i.v. fluid administration.
 20. If an i.v. colloid is being administered at the time of the anaphylactic event, it should be discontinued, and the i.v. administration set replaced.
 21. Administration of i.v. vasopressin 2 units, repeated as necessary, should be considered when hypotension because of perioperative anaphylaxis is refractory.
 22. During perioperative anaphylaxis in patients taking beta-blockers early administration of i.v. glucagon 1 mg should be considered, repeated as necessary.
 23. When anaphylaxis occurs after recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one.
 24. A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis.
 25. 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.
 26. Blood samples for mast cell tryptase should be obtained in accordance with national guidelines:
 - a. First sample as soon as the patient is stable.
 - b. Second sample as close to 1–2 h as possible after the event.
 - c. Third (baseline) at least 24 h after the event.
 27. 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 (i.e. the consultant anaesthetising or supervising the case).
 28. Where a trainee refers a patient to an allergy clinic, the contact details of a consultant anaesthetist should be included in the referral.
 29. If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice as well as making a written referral.
 30. Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules.
- Research**
31. There remains uncertainty about the benefits or potential harm of administering antihistamine drugs during resuscitation of perioperative anaphylaxis. Clinical trials would provide valuable evidence.
- Patient experience**
- Institutional**
32. Consent should always be informed. Therefore, patients should be informed of the risk of anaphylaxis before the operation. Patient information leaflets may be suitable as part of this process.
 33. Following a perioperative anaphylactic event and before discharge from hospital, the patient should be provided with a letter from their anaesthetist. This letter should be in addition to the discharge summary and a copy should be sent directly to the patient's GP.

Research

34. The effect of a perioperative anaphylactic event on a patient's physical and psychological well-being in both the medium and the long term is not well understood. Research into this topic and dissemination of the outcomes could be of great benefit to patients.

Clinical features**Institutional**

See recommendation 14.

Individual

35. Perioperative anaphylaxis can present with a single clinical feature, in particular isolated hypotension. Anaesthetists should exercise a high index of suspicion in recognising perioperative anaphylaxis and commence treatment promptly.
36. In patients with asthma, the occurrence of bronchospasm or high airway pressures should not automatically be attributed to acute asthma as in these patients this may be the presenting feature of life-threatening anaphylaxis.
37. As anaphylaxis may be delayed, particularly with some oral drugs, referrals to allergy clinics should include details of all agents that the patient has been exposed to within at least the previous 2 h.

Also see recommendation 22.

Research

38. Further studies are required to clarify the role of a decrease in end-tidal CO₂ concentration in the early recognition and management of severe perioperative anaphylactic reactions.
39. The role of glucagon and vasopressin in refractory anaphylaxis [particularly in high risk groups such as the elderly, and those taking beta-blockers or angiotensin-converting-enzyme (ACE) inhibitors] needs further investigation.
40. Studies are indicated to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.
41. Research would be of value to investigate the effect of corticosteroids, both given before anaphylaxis and for its treatment.

Deaths, cardiac arrest, and profound hypotension

Severe perioperative anaphylaxis here refers to perioperative anaphylaxis requiring CPR or with profound hypotension (e.g. systolic arterial BP <50 mm Hg).

42. In patients who experience perioperative anaphylaxis with a high risk of adverse outcome (elderly, obese, ASA_≥3, patients taking beta-blockers or ACE inhibitors, prolonged CPR), anaesthetists should be prepared to escalate treatment early.
43. During anaphylaxis with a systolic BP <50 mm Hg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with epinephrine and liberal i.v. fluid administration.
44. The need for a vasopressor infusion should be anticipated after severe perioperative anaphylaxis.
45. Non-essential surgery should not be started after severe perioperative anaphylaxis.
46. Where severe perioperative anaphylaxis occurs during non-essential surgery the operation should be curtailed unless there is an overriding reason to continue.

47. Patients with severe anaphylaxis should be admitted to critical care (HDU/ICU).
48. While it is not possible to be definitive about how long a patient should be observed after Grade 3–4 perioperative anaphylaxis, it would seem imprudent for them to be discharged on the same day as the event.
49. All cases of severe perioperative anaphylaxis, including fatalities, should be discussed with an allergy clinic at the first available opportunity.

Also see recommendations 21 and 22.

Reporting**National**

50. The Medicines and Healthcare products Regulatory Agency (MHRA) should improve communication with clinicians; for example, providing an annual report that includes perioperative anaphylaxis.

Institutional

51. The departmental lead should ensure all cases have been reported to the Trust incident reporting system.
52. The departmental lead should ensure all cases are reported (by the anaesthetist encountering the reaction, or the departmental lead) to the MHRA as soon as possible after the event and record the MHRA case identifier for future reference.
53. The department lead should (using the MHRA case identifier) ensure the MHRA record is updated after allergy clinic investigation is completed, to ensure the information held is accurate.

Individual

54. The departmental lead should be informed of the case.
55. The MHRA case identifier should be included in the referral to the allergy clinic.
56. All cases of Grade 3–5 perioperative anaphylaxis should be presented and discussed at local morbidity and mortality meetings, for purposes of education and familiarisation.

Neuromuscular blocking agents**Individual**

57. Except in cases of known or suspected allergy to specific neuromuscular blocking agents, the risk of anaphylaxis should not be an over-riding factor in choice of neuromuscular blocking agents, as this varies little between neuromuscular blocking agents.

Research

58. Further research on population sensitisation by pholcodine is needed. If a causal association is confirmed, withdrawal of pholcodine-containing medicines from the UK market should be formally considered.
59. Uncertainty remains 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.

Antibiotics**Institutional**

60. Patients with reported allergy to a beta-lactam antibiotic and at least one other class of antibiotics should be referred for specialist allergy investigation, before elective surgery, in line with NICE CG183: *Drug allergy: diagnosis and management*.

61. If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed.
62. Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

Individual

63. Antibiotic administration should strictly follow national or local guidelines.
64. A test dose of antibiotic should not be used, as it will not prevent or reduce the severity of anaphylaxis.
65. Ninety percent of anaphylaxis because of antibiotics presents within 10 min of administration. When perioperative antibiotics are indicated they should be administered as early as possible, where practical at least 5–10 min before induction of anaesthesia, providing this does not interfere with their efficacy.
66. The anaesthetist should consider co-amoxiclav or teicoplanin amongst the likely culprits when anaphylaxis occurs after their administration.
67. Broad beta-lactam avoidance advice should be discouraged, and patients should be further investigated to clarify the drug(s) to avoid and to identify safe alternatives.

Chlorhexidine

National

68. The MHRA should work with manufacturers of medical devices (e.g. central venous and other intravascular catheters) to ensure that products are labelled clearly and prominently, to identify whether they contain chlorhexidine or not.

Institutional

69. Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy.
70. Investigation of suspected perioperative anaphylaxis should include chlorhexidine.

Individual

71. Chlorhexidine allergy should be included in the allergy history obtained by anaesthetists, nurses and other healthcare professionals.
72. Clinical teams should be aware of 'hidden chlorhexidine' such as in urethral gels and coated central venous catheters and should consider this as a potential culprit if perioperative anaphylaxis occurs.

Also see recommendation 23.

Patent Blue dye

Individual

73. If administration of Patent Blue dye is planned during surgery, the surgical team should discuss the risk of anaphylaxis as part of the consent process for surgery.
74. If anaphylaxis occurs in a patient who has received Patent Blue dye, it should not be assumed that this is the culprit, and the patient should be referred for specialist allergy investigation.
75. Where pulse oximeter saturations decrease during anaphylaxis in a patient who has received Patent Blue dye, hypoxia should be assumed to be real. A blood gas sample should be obtained, when the patient is stable enough for this.

Investigation

76. Specialist perioperative allergy clinics should adopt a multidisciplinary team approach, including where practical having an anaesthetist-with-a-special-interest in the allergy clinic. Where this is not practical cases should be discussed with an anaesthetist before the patient attends the clinic.
77. Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the event and a full list of the patient's medication and drugs administered before the event. A standardised form (e.g. the NAP6 or AAGBI proforma) should accompany the referral.

Individual

78. The anaesthetist referring the patient for investigation of perioperative anaphylaxis should explain the importance of attending and allay any fears to improve uptake of allergy clinic appointments.

Also see recommendation 27.

Obstetric

Institutional

79. Obstetric units should ensure immediate availability of anaesthetic anaphylaxis treatment and investigation packs wherever general or regional anaesthesia is administered.

Individual

80. An allergy history should be obtained even when there is extreme urgency to deliver the baby.
81. Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients.
82. Anaphylaxis in obstetric patients should be managed following the same principles as in non-obstetric patients. Epinephrine should not be withheld for fear of a detrimental effect on placental perfusion.
83. Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase concentrations should be measured.
84. Anaesthetists should be aware that hypotension as a result of anaphylaxis can be exacerbated by neuraxial block and/or aortocaval compression.

Paediatric

Institutional

85. Protocols and anaesthetic anaphylaxis treatment and investigation packs appropriate for children should be immediately available wherever paediatric anaesthesia is administered.
86. All anaesthetists administering anaesthesia to children should be trained in the management of paediatric anaphylaxis.
87. The preparation of drugs for management of paediatric anaphylaxis may be prone to error in the emergency setting. Paediatric anaesthetists should consider rehearsal of drills locally or in a simulation setting.

Critical care

Institutional

88. Patients with severe anaphylaxis should be admitted to critical care (HDU/ICU).

Handling editor: H.C. Hemmings Jr

Supplementary material

Supplementary material A

Anaesthetic anaphylaxis treatment pack: contents

Supplementary material B

Anaesthetic anaphylaxis investigation packs

1. Checklist
2. Template letter to give to the patient
3. Template letter to send to the GP
4. Referral form to be sent to the allergy clinic

Supplementary material C

Departmental Lead for Perioperative Anaphylaxis; roles and responsibilities

A

ANAESTHETIC ANAPHYLAXIS TREATMENT PACK

Suggested contents

- Adrenaline pre-filled syringe x2 (1mg/10ml = 100mcg/ml).
Each syringe = 20 doses of 50mcg, 10 doses of 100mcg, 1 dose of 1mg (cardiac arrest)
- Hydrocortisone 100mg x2.
- Details of where to find glucagon (for patients on beta blockers) and vasopressin (for protracted hypotension) (<10 minutes away)
Details of doses: glucagon 1-2mg repeated as at 5 minute intervals,
vasopressin 2 units repeated as needed, consider infusion.
- Anaphylaxis management algorithms (adult and paediatric) e.g.

RC(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 - Initial 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 - initial 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

B

ANAESTHETIC ANAPHYLAXIS INVESTIGATION PACK CHECKLIST

This pack contains:

1. Instructions on taking three timed blood samples for Mast Cell Tryptase
2. Template letter to give to the patient
3. Urgent surgery management plan
4. Template letter to send 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 24h 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.
 - o 1st sample as soon as the patient is stable. (Ideally <30 mins)
 - o 2nd sample as close to 1 -2 hours as possible after the event. (No more than 6 h)
 - o 3rd (baseline) at least 24 hours after the event.
- Phone your local lab (usually Immunology) when you have taken the second 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 **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.

LETTER TO THE PATIENT FOLLOWING PERIOPERATIVE ANAPHYLAXIS

[Hospital HEADER]

Date

Patient's name

Address

MRN

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:

.....

It normally takes a few weeks to receive an allergy clinic appointment.

- *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)

.....

I will write to your GP with this information.

Yours sincerely,

Consultant Anaesthetist

Contact phone

number.....

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)

Suspected cause of the reaction

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 :
3 :
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

C

NAP6 Suggested roles for **ANAESTHETIC DEPARTMENT ANAPHYLAXIS LEAD**

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)
- Co-ordinate, with primary care, appropriate follow-up of patients who have experienced perioperative anaphylaxis, usually in an out-patient setting, to identify physical or psychological adverse sequelae. 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 and
 - anaesthesia anaphylaxis investigation packs.
- Ensure that cases are presented at departmental meetings and that learning points are acted-upon and audited if appropriate.