6 Anaesthesia, surgery and life-threatening allergic reactions - Summary of main findings

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This chapter describes summary findings from NAP6 in two parts.

Part A: Epidemiology and clinical features of perioperative anaphylaxis

Key findings

- The 6th National Audit Project on perioperative anaphylaxis collected and reviewed 266 reports of Grade 3–5 anaphylaxis over one year from all National Health Service hospitals.
- Estimated incidence of perioperative anaphylaxis is ≈1:10,000 anaesthetics. Case exclusion due to reporting delays or incomplete data means true incidence may be 70% higher.
- The distribution of 199 identified culprit agents was antibiotics 47%, neuromuscular blocking agents (NMBA) 33%, chlorhexidine 9%, and Patent Blue dye 4.5%.
- Teicoplanin comprised 12% of antibiotic exposures, but caused 38% of antibiotic-induced anaphylaxis.
- Suxamethonium-induced anaphylaxis, mainly presenting with bronchospasm, was twice as likely as with other NMBAs.
- Atracurium-anaphylaxis mainly presented with hypotension. Non-depolarising NMBAs had similar incidences to each other.
- There were no reports of latex-induced anaphylaxis.
- Commonest presenting features were hypotension (46%), bronchospasm (particularly in patients with morbid obesity and asthma) (18%), tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%), and reduced/absent capnography trace (2.3%).
- All patients were hypotensive during the episode.
- Onset was rapid for NMBAs and antibiotics but delayed with chlorhexidine and Patent Blue dye.
- There were ten deaths and 40 cardiac arrests.
- The review panel judged that cardiac compressions should be started in adults with systolic blood pressure <50 mmHg.
- Pulseless electrical activity was the usual type of cardiac arrest, often with bradycardia.
- Poor outcomes were associated with increased age, ASA grade, obesity, beta-blocker, and/or ACE inhibitor medication.
- Seventy per cent of cases were reported to the hospital incident reporting system and only 24% to the Medicines and Healthcare products Regulatory Agency via the Yellow Card Scheme.

Anaphylaxis is defined as a severe, life-threatening generalised or systemic hypersensitivity reaction (Johansson 2001). Most anaphylactic reactions are allergic. Severity is commonly graded 1-5, though multiple grading systems exist. Mild reactions (Grades 1 and 2) do not constitute anaphylaxis. NAP6 investigated Grades 3, 4 and 5 (fatal) reactions occurring in the perioperative period.

Estimates of the incidence of perioperative anaphylaxis vary between 1:6,000 to 1:20,000 anaesthetics (Hepner 2003). In a large French study, the estimated incidence of IgE-mediated perioperative hypersensitivity (Grades 1-4) was 1:10,000 anaesthetics (Mertes 2011a).

Perioperative anaphylaxis may vary over time and between different patient populations. Most studies have identified neuromuscular blocking agents (NMBAs) as the commonest cause. In a French study, latex was the second-commonest cause of anaphylaxis: unlike in a more recent UK study (Low 2016).

The majority of previous reports have included all grades of perioperative hypersensitivity and all report similar patterns of clinical features (Table 1). In a small number of cases, there may be single organ-system involvement, and cutaneous features predominate in mild, non-IgE-mediated perioperative hypersensitivity (Mertes 2011a, Low 2016). Most studies agree that the clinical features of severe anaphylaxis are very similar regardless of whether allergic or non-allergic in nature.

It is important to understand how severe anaphylaxis presents, as there is a wide differential diagnosis, no bedside tests, and prompt, specific treatment is essential (Krøigaard 2007, Harper 2009, Kolawle 2017).

There are few large prospective studies of perioperative anaphylaxis, with most looking retrospectively at cases that have been referred to allergy clinics for investigation. In addition, few studies have focused solely on severe (Grade 3-5) perioperative anaphylaxis or investigated relationships between presenting features and co-morbidities/concomitant medication. Individual trigger agents may elicit disparate patterns of presentation, including onset time, cardiovascular or respiratory system preponderance, and outcomes may also differ.

It is known that onset of anaphylaxis to chlorhexidine, latex and Patent Blue dye can be delayed (Harper 2009, Parkes 2009, Egner 2017a, Mertes 2008).

Methods

Methods are discussed in detail in Chapter 5, Methods. Denominator data were derived from the NAP6 Activity Survey (Chapter 8) and Allergen Survey (Chapter 9).

Results

We identified 266 cases of Grade 3-5 anaphylaxis meeting our inclusion criteria. A further 261 cases were excluded due to failure to provide information on allergy clinic investigation, lack of detail or being uninterpretable, as described in Chapter 5, Methods.

The Activity Survey (Chapter 8) estimated that 3,126,067 anaesthetics are delivered in the UK each year, giving a calculated incidence of perioperative anaphylaxis of 1 : 11,752 (95% Confidence interval 10,422 - 13,303).

In 148 cases the culprit was identified as 'definite' and in 44 cases as 'probable' (including seven cases where two probable culprits were identified), giving a total of 199 identified culprit agents in 192 cases. In 15 cases the culprit was designated 'possible' and in 57 cases the culprit could not be identified. The most common cause of perioperative anaphylaxis was antibiotics, followed by NMBAs, chlorhexidine and Patent Blue dye (Table 1).

The incidences of the for most prevalent groups of drugs or agents were:

- *Antibiotics:*
  92/2,469,754 = 1 in 26,845 (95% CI 1 in 21,889 – 1 in 33,301)
- *NMBAs:*
  64/1,220,465 = 1 in 19,070 (95% CI 1 in 14,934 – 1 in 24,762)
- *Chlorhexidine:*
  18/2,298,567 = 1 in 127,698 (95% CI 1 in 80,800 – 1 in >150,000)
- *Patent Blue dye:*
  9/61,768 = 1 in 6,863 (95% CI 1 in 3,616 – 1 in 15,009).

Fifty-eight per cent of the anaphylactic events occurred in the operating theatre, of which 3% were before induction of anaesthesia, 81% after induction and before surgery, 13% during surgery, and 3% after surgery.

Clinical features

The first clinical feature was hypotension (in 46%), bronchospasm/high airway pressure (18%), tachycardia (9.8%), cyanosis/oxygen desaturation (4.7%), bradycardia (3%) and reduced or absent capnography trace (2.3%) (Figure 1). Three patients (1.2%) presented with cardiac arrest.

Bronchospasm was the presenting feature more frequently in morbidly obese compared with other patients (Figure 2) and in (mainly well-controlled) asthmatic patients (34%) compared with non-asthmatic patients (15%).

Presentation was similar regardless of whether the mechanism was allergic or non-allergic. In approximately 1 in 20 cases an awake patient's report of feeling unwell was the harbinger of anaphylaxis (Figure 1). Fifteen (5.6%) patients presented with isolated cardiovascular features and four (1.5%) with isolated respiratory features.

Table 1. The 199 identified culprit agents in 192 cases of anaphylaxis in NAP6

Agents by class			
	Definite	Probable	Total
Antibiotics	67	27	94
NMBAs	49	16	65
Chlorhexidine	14	4	18
Patent Blue	8	1	9
Others	10	3	13
All	148	51	199
Antibiotics			
Co-amoxiclav	38	8	46
Teicoplanin	21	15	36
Cefuroxime	2	2	4
Gentamicin	1	2	3
Flucloxacillin	2	0	2
Piperacilin & tazobactam	1	0	1
Vancomycin	1	0	1
Metronidizole	1	0	1
NMBAs			
Rocuronium	21	6	27
Atracurium	14	9	23
Suxamethonium	13	1	14
Mivacurium	1	0	1
Antiseptics and dyes			
Chlorhexidine	14	4	18
Patent Blue dye	8	1	9
Other agents			
Gelatin	3	0	3
Blood products	2	0	2
Ondansetron	1	1	2
Sugammadex	1	0	1
Ibuprofen	1	0	1
Propofol	1	0	1
Protamine	1	0	1
Aprotinin	0	1	1
Heparin	0	1	1

Figure 1. First clinical feature (%) in allergic anaphylaxis and all patients with Grade 3-5 perioperative anaphylaxis

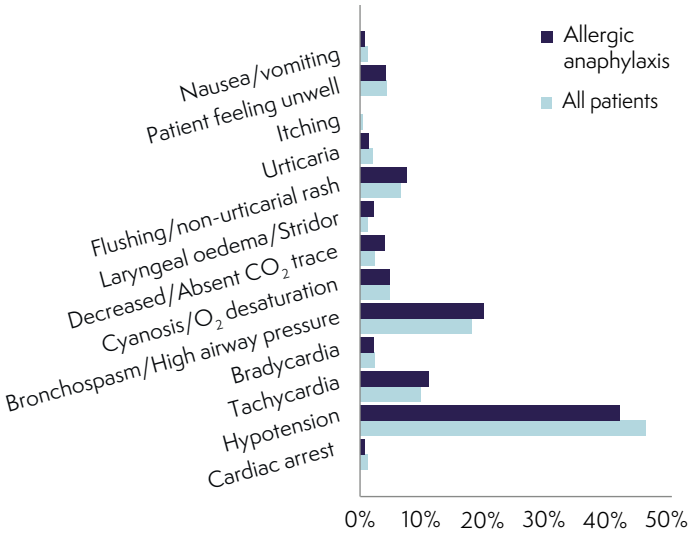
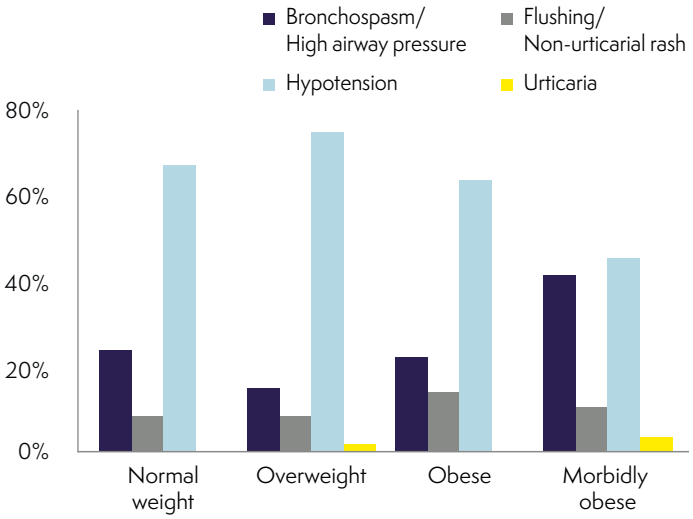
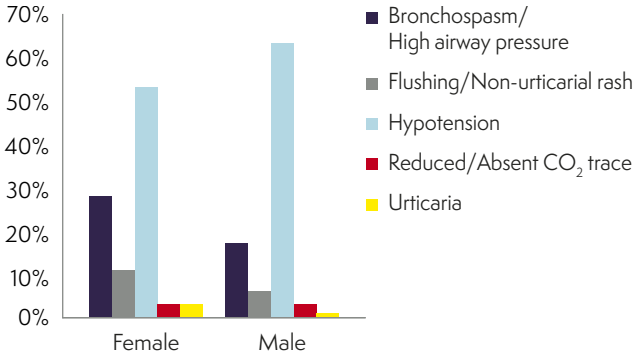


Figure 2. Presenting features and body habitus in Grade 3-5 perioperative anaphylaxis



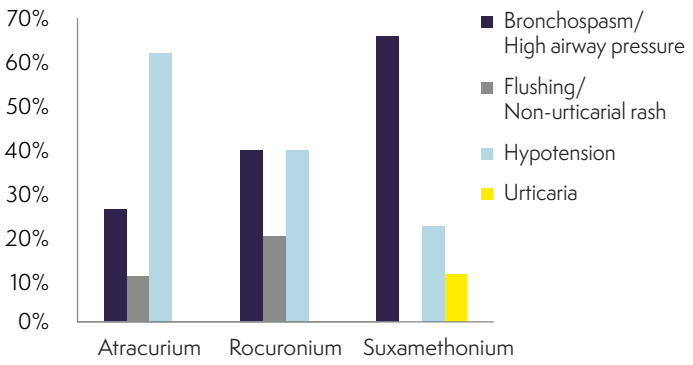
Hypotension as the presenting feature was proportionately more common in men than women, perhaps related to coronary artery disease (23.7% vs 8.4%), beta-blockers (26.7% vs 11.2%) and ACE in hibitor (ACEI) medication (21.2% vs 15.2%). Bronchospasm was more common in women: more women had asthma (25% vs 15.5%) (Figure 3).

Figure 3. Presenting features of Grade 3-5 perioperative anaphylaxis in female and male patients



There was a marked difference between NMBAs: bronchospasm was the most common presentation when suxamethonium was the trigger and hypotension with atracurium (Figure 4).

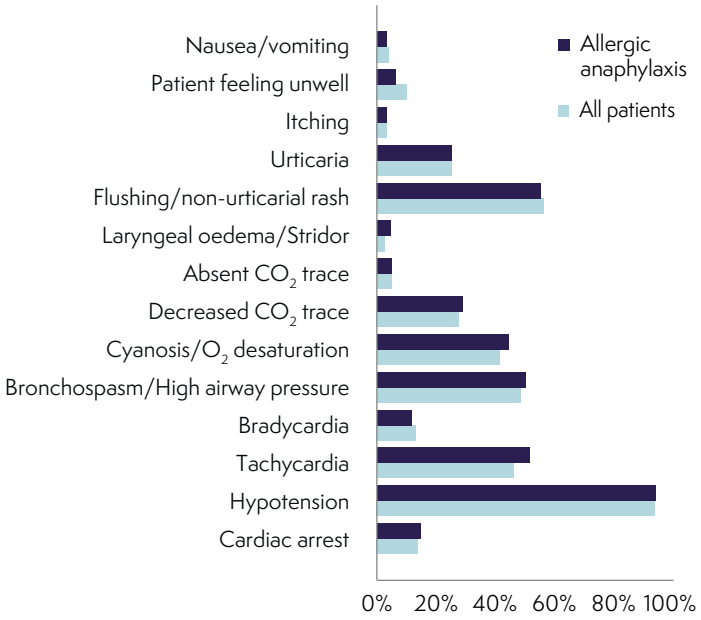
Figure 4. Presenting features of Grade 3-5 neuromuscular blocking agent-induced anaphylaxis



Considering clinical features present at any time during the anaphylactic episode, hypotension was universal. Rash, seldom a presenting feature, developed in 56.4% of cases, bronchospasm/high airway pressure in 48.5%, tachycardia in 46.2%, cyanosis/oxygen desaturation in 41.4% and a reduced/ absent capnograph trace in 32.7%. Bronchospasm at any time was also seen in a higher proportion of patients with asthma (59%) than others (46%). Again, this clinical pattern was very similar in the subgroup of allergic anaphylaxis patients (Figure 5).

Two notable features were almost absent. Rash was an uncommon presenting feature, and was notably rare at any time in the most serious of cases. Airway problems were also rarely seen. A single patient required a front of neck airway to manage laryngeal oedema but there were no other presentations or significant clinical features of airway difficulty.

Figure 5. Clinical feature (%) present at any time during Grade 3-5 perioperative anaphylaxis: allergic anaphylaxis and all patients



Considering all cases, onset time was <5 min in 66.2%; <10 min in 82.7%; <15 min in 87.6% and <30 min in 94.7%. Onset times for individual agents are discussed below.

Fatalities, cardiac arrests, and profound hypotension

Ten patients died, either directly (eight) or indirectly (two), due to anaphylaxis, equating to an incidence of perioperative death from anaphylaxis of 1 in 313,000 and a per case mortality rate of 1 in 26.6 cases. All fatalities were aged >46 years and half aged >66. Two were ASA 2, six ASA 3, and two ASA 4. In the Activity Survey (Chapter 8) 25% of patients were aged >66 years, 77% were ASA 1-2 and <2% ASA 4-5.

Only one patient was of normal weight – four were overweight, one was obese and four morbidly obese. In the Activity Survey (Chapter 8) 21% of all patients were obese or morbidly obese. None of the patients who died had a history of atopy or asthma. Five had coronary artery disease, most of whom were undergoing

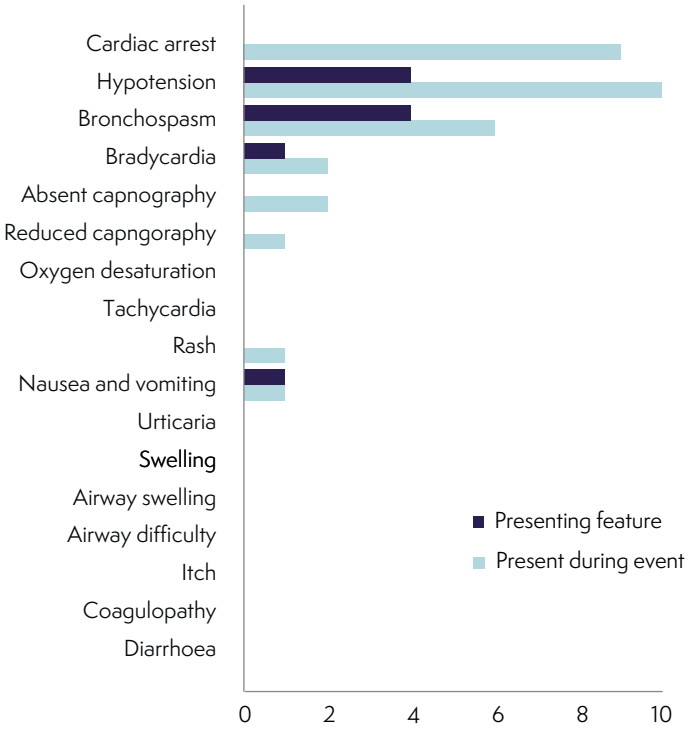
non-cardiac surgery. Six were taking beta-blockers and six ACE inhibitors; three were taking both and one patient neither drug. Among the 266 reports of life-threatening anaphylaxis 14.7% had evidence of coronary artery disease, 17.4% were taking beta-blockers and 17.1% were taking ACE inhibitors (Table 2).

Table 2. Comparison of patients who survived or died after perioperative anaphylaxis

	Died after anaphylaxis n=10	Survived anaphylaxis n=256
Aged >66 yrs	40%	31%
Obese or morbidly obese	50%	36%
Coronary artery disease	50%	13%
Taking beta-blocker	60%	15%
Taking ACE inhibitor	60%	21%
Asthma	0%	21%

Three patients were undergoing cardiac surgery. The surgical procedure was abandoned in nine cases and proceeded in one. Cardiac arrest was pulseless electrical activity (PEA) in all fatal cases, none preceded by significant arrhythmias, though there was bradycardia in two. The clinical features (presenting, and at any time during the episode) of the ten fatal cases are shown in Figure 6. Management of these cases is described in the second section of this chapter.

Figure 6. Clinical features of ten fatal cases of perioperative anaphylaxis (presenting, and at any time)



Forty (15%) patients, all of whom were adults, experienced cardiac arrest, including nine of the patients who died. Thirty-one (77.5%) survived. Most (81%) events occurred after induction of anaesthesia and before surgery. A consultant was involved in all resuscitations. No particular trigger agents were associated with a higher risk of cardiac arrest. However, survivors of cardiac arrest were younger, fitter and had less co-morbidity than patients who died (Table 3).

Table 3. Characteristics of patients who died, compared to those who survived cardiac arrest, experienced profound hypotension or did not experience profound hypotension. CAD = coronary artery disease, ACEI = angiotensin converting enzyme inhibitor

	Deaths (n=10)	Non-fatal cardiac arrest (n=31)	BP <50 mmHg without cardiac arrest or death (n=79)	All others (n=135)
Patient characteristics				
Age >66	50%	35%	33%	34%
ASA ≥3	80%	13%	33%	27%
Obesity	50%	31%	34%	43%
CAD	55%	8%	15%	14%
Beta-blocker	60%	7%	14%	19%
ACEI	60%	32%	9%	17%
Asthma	0%	14%	19%	24%

The presenting features are shown in Figure 7. Hypotension and bronchospasm/raised airway pressure were prominent, and rash notably uncommon. Reduced or absent capnograph trace was not recorded as a presenting feature in any cases. Bradycardia was more common than tachycardia. Cardiovascular presenting features occurred in 25 cases, respiratory in eleven, and others in four. Of all cardiac arrests, 34 were PEA, four VF/VT and two asystole. Only six patients developed an arrhythmia prior to cardiac arrest: four of them bradycardia and two ventricular tachycardia. There were no reports of atrial fibrillation or supraventricular tachycardia.

Figure 7. Clinical features of 37 non-fatal cardiac arrests from perioperative anaphylaxis (presenting, and at any time)

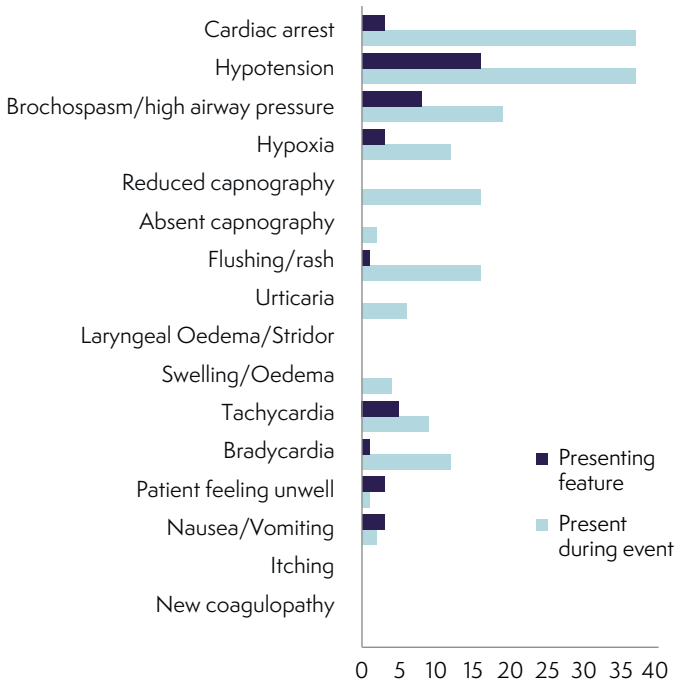


Table 4. Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6
*Annual usage identified from the Allergen Survey (Chapter 9)

	Culprits identified by the review panel	Proportion of antibiotic usage*	Patients receiving the drug per annum*	Anaphylaxis rate per 100,000 administrations	Relative rates (cefuroxime=1)
Co-amoxiclav	46	29.8%	532,580	8.7	9.2
Teicoplanin	36	12.3%	219,621	16.4	17.4
Cefuroxime	4	23.7%	424,143	0.94	1.0
Gentamicin	3	34.5%	616,899	0.49	0.5
Flucloxacillin	2	11.9%	211,973	0.94	1.0
Piperacillin-tazobactam	1	1.6%	28,237	3.5	3.7
Vancomycin	1	1.0%	17,648	5.7	6.1
Metronidazole	1	15.2%	272,173	0.37	0.4
Total (all antibiotic administrations)	94 culprits (92 cases)	100%	2,323,274	4.0	4.2

Harm, as a result of anaphylaxis was judged to occur in 10 (32%) of 31 survivors. Reported sequelae included new anxiety, a change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of post-traumatic stress disorder, myocardial damage, heart failure, and new renal impairment.

In adult patients, the lowest blood pressure recorded in the first hour after the event was 'unrecordable' in 56 (21%) cases, <50 mmHg in 58 (22%) cases, and 51-59 mmHg in 53 (20%) cases.

Antibiotics

Ninety-two cases of antibiotic-induced anaphylaxis were identified (including 94 Definite or Probable antibiotic culprits) – 48% of all cases with identified culprits. The majority were caused by co-amoxiclav or teicoplanin, which between them accounted for 89% of identified antibiotic culprits. The overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100,000 exposures. The highest incidence was seen with teicoplanin (16.4 per 100,000 exposures) then co-amoxiclav (8.7 per 100,000 exposures). The relative anaphylaxis rate using cefuroxime as an index was 17.4 for teicoplanin and 9.2 for co-amoxiclav (Table 4).

The onset of anaphylaxis was within 5 minutes in 74% of cases; 18% between 6-10 minutes; 5% between 11-15 minutes, 2% between 16-30 minutes. None was delayed >30 minutes.

Of the 36 patients who reacted to teicoplanin, 20 (56%) stated preoperatively that they were allergic to penicillin. Of the 36 reactions 16 were Grade 3, 18 Grade 4, and two Grade 5. Ten developed moderate and two died. Among the 20 who probably received teicoplanin because of a history of allergy, two reactions were Grade 4 and one Grade 5, six developed moderate harm and one died. The NAP6 Allergen Survey (Chapter 9) demonstrated that the choice of antibiotic was influenced by preoperative allergy history in a quarter of patients who received teicoplanin or vancomycin.

In less than 1% of cases, communication failure led to an antibiotic being administered despite a relevant positive allergy history. Two cases were judged preventable by better allergy history communication.

Eighteen antibiotic related reactions related to test doses: in ten cases the patient reacted to the test dose itself (52.6%), which ranged from 5–30% of the therapeutic dose, and the other eight patients reacted to the full dose, which was given within one minute of the test dose in all but one case (given within 10 minutes). There was no evidence that administration of a 'test dose' of antibiotic reduced the severity of an ensuing reaction. On the contrary, in cases of anaphylaxis caused by an antibiotic where a test dose had been given, a slightly greater proportion of severe reactions (Grade 4 and 5) was seen than if no test dose had been given (58% vs 51%). Of the ten deaths, four were judged to be due to an antibiotic.

Neuromuscular blocking agents and reversal agents

Sixty-five cases of anaphylaxis were triggered by NMBAs, 25% of all cases and 32% of cases leading to death or cardiac arrest. Ninety-five per cent of NMBA-induced reactions presented within 5 minutes.

The culprit NMBAs were rocuronium (42% of cases), atracurium (35%), suxamethonium (22%) and mivacurium (1.5%). There were no cases of anaphylaxis due to vecuronium, pancuronium or cisatracurium, though these only account for 4.4% of all NMBA use (Chapter 9). The review panel identified non-allergic anaphylaxis to atracurium in three cases, and to mivacurium in a single case.

Incidence per 100,000 exposures is a more meaningful metric than occurrence rate. The overall incidence of reported NMBA-induced anaphylaxis was 5.3 per 100,000 exposures. The highest incidence was seen with suxamethonium (11.1 per 100,000 exposures), while all others were similar to each other. Suxamethonium was twice as likely to cause anaphylaxis as any other NMBA (Table 5).

In 71% of cases where the anaesthetist suspected an NMBA, the culprit was confirmed by the panel and in 14.3% an alternative culprit was identified. The ratio of suspected/confirmed cases was 1.4 for atracurium, 1.3 for rocuronium and 1.1 for suxamethonium (Table 5).

Previous exposure to pholcodine was recorded in only two patients, both of whom had NMBA-induced anaphylaxis (rocuronium and suxamethonium), but no conclusions can be drawn due to very limited recording of pholcodine exposure.

Table 5. NMBAs confirmed as causative agents by the panel, absolute and relative risks
*Data from the NAP6 Allergen Survey (Chapter 9)

	Cases suspected by anaesthetist	Cases confirmed by review panel	Proportion of UK NMBA usage*	Patients receiving the drug per annum*	Anaphylaxis rate/100,000 administrations	Relative risk of anaphylaxis (atracurium=1)
Atracurium	32	23	49.1%	554,543	4.15	1
Rocuronium	34	27	40.6%	459,047	5.88	1.42
Suxamethonium	16	14	11.2%	126,086	11.1	2.67
Mivacurium	0	1	2.7%	30,786	3.25	0.78
Vecuronium	0	0	2.2%	24,315	-	-
Cisatracurium	0	0	1.6%	18,629	-	-
Pancuronium	0	0	0.6%	7,059	-	-

No episodes were due to neostigmine. The anaesthetist suspected that sugammadex was the suspected trigger agent in two cases, and one of these was confirmed by the review panel.

Chlorhexidine

There were 18 cases of chlorhexidine-induced anaphylaxis, representing 9% of culprits. The Allergen Survey (Chapter 9) identified 2,298,567 exposures to chlorhexidine by at least one route annually (73.5% of all cases). Based on NAP6 data, the incidence of anaphylaxis to chlorhexidine is 0.78 per 100,000 exposures, probably an over-estimate as almost all patients are exposed to chlorhexidine during anaesthesia and surgery.

Despite reporting chlorhexidine allergy prior to the event, one patient was exposed resulting in anaphylaxis. One patient reported a prior reaction during anaesthesia that was not investigated, and reacted to chlorhexidine when exposed. One patient experienced a subsequent reaction to chlorhexidine despite confirmation of allergy to chlorhexidine following investigation of the index NAP6 event. There was one fatal reaction. Eight reactions were Grade 4 and nine were Grade 3. Consistent with published data, most cases were in males (16/18). Ten were ASA Grade 2 and eight ASA Grade 3. Urology (6), cardiac (3) and orthopaedic (3) surgery accounted for the majority of cases.

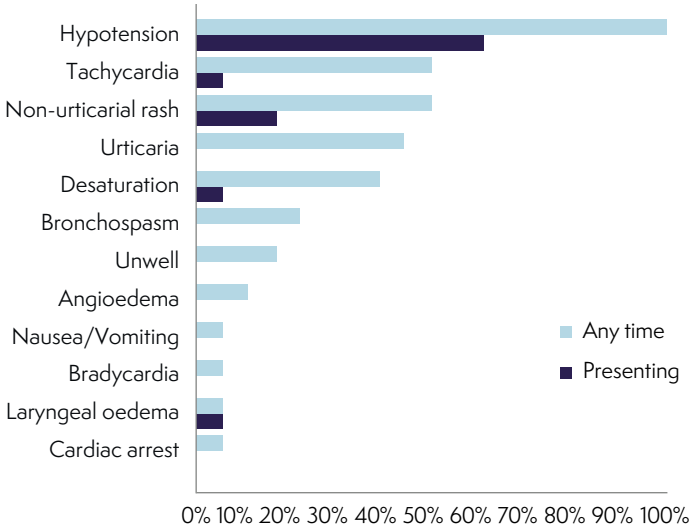
The anaesthetist suspected chlorhexidine in only five (28%) cases. Reactions to cutaneous chlorhexidine were mostly slower than other agents and of lower grade. There was quicker onset and greater severity in patients with exposure via a coated central venous catheter (mostly onset <5 minutes of exposure and Grade 4 events) than those with only topical surgical site exposure (mostly onset at 1 hour and Grade 3 events).

Approximately two thirds of cases presented with hypotension and none presented with bronchospasm (Figure 8).

Patent Blue dye

We identified nine (3.4%) cases of Patent Blue dye-induced anaphylaxis, five Grade 3 and four Grade 4. Based on an estimated 61,768 annual exposures (Chapter 9), the incidence of anaphylaxis to Patent Blue was 14.6 per 100,000 administrations (higher than suxamethonium). All patients were female, and eight were scheduled for breast cancer surgery, which was abandoned in two cases.

Figure 8. Presenting clinical features and those occurring at any time during chlohexidine-induced perioperative anaphylaxis



Onset was slower than other trigger agents, with only two cases <5 minutes; four presented after >15 minutes, including two after >60 minutes. Hypotension was the commonest presentation: all patients became significantly hypotensive, and in three cases systolic blood pressure fell below 50 mmHg. Four patients desaturated to <90%. Cutaneous features were present in six patients.

All cases were resuscitated successfully and no long-term physical sequelae were reported.

Miscellaneous trigger agents

We identified three cases of anaphylaxis to succinylated gelatin solutions and two to blood products. Ondansetron, propofol, aprotinin, protamine and ibuprofen were responsible for a very small number of cases. The Allergen Survey (Chapter 9) estimated that 48,203 UK patients are exposed to gelatin-based IV fluids during anaesthesia each year, giving an approximate incidence of 6.2 per 100,000 administrations, a rate similar to rocuronium.

Reporting

As reporting is a positive action, it was inferred that this did not take place where the information was not provided. Nine per cent of cases were reported to the Medicines and Healthcare products

Regulatory Agency (MHRA) by the anaesthetist, 8.3% by the Local Coordinators, 3% by the allergy clinic and 2.6% by others, including Critical Care. Only three deaths and nine of 31 who survived cardiac arrest (29% combined) were reported to the MHRA.

Reporting to the trust's critical reporting incident system was performed in 70.3% of cases (including eight of ten deaths and 24 (77%) of 31 cardiac arrest survivors). Of these 187 cases, 160 were reported by an anaesthetist, six by the nursing team and five by the surgical team.

Discussion

The overall incidence of perioperative anaphylaxis was estimated to be 1 in 10,000 anaesthetics. This is likely to be an under-estimate: we received 541 reports over a one-year period; 412 had Part A and Part B completed, and only 266 NHS cases met the inclusion criteria, were interpretable and were Grade 3–5 anaphylaxis. Inability to interpret reports was predominantly due to lack of information, usually as a result of uncertainty about the comprehensiveness of allergy-clinic testing. Of the reviewed cases, only 17 were not anaphylaxis or were Grade 2, suggesting that the true incidence could be up to 70% higher than our estimate (ie. 1 in 7,000). Previous estimates are similar, but the majority included perioperative hypersensitivity of all grades: despite including only Grades 3 to 5, our estimated incidence is at least as high. It is possible that the incidence of perioperative anaphylaxis is rising, perhaps as a result of increasing antibiotic sensitisation in the population, and it is notable that antibiotics have overtaken NMBAs as the most frequent trigger agent. Irrespective of absolute incidences, because of our methodology we believe our results accurately represent the relative incidence with different trigger agents.

Presenting features

Perioperative anaphylaxis has several unusual if not unique elements. Firstly, the vast majority of triggers are administered intravenously, therefore having the potential for the most rapid and severe reactions. Secondly, multiple drugs are administered almost concurrently. These routinely alter normal physiology such that hypotension, arrhythmia, bronchospasm and even rash may be more commonly due to causes other than anaphylaxis. Lastly, the events occur in the immediate presence of a trained 'resuscitationist' who may be able to identify and manage the event more promptly than in many other settings.

Variation in presenting clinical features between different patient groups, with different drugs and with different severity of reactions are all notable and add to the available literature. It is worth noting that hypotension was universal. Bronchospasm was less common but was more often seen in the obese and those with pre-existing asthma. Rash was rarely present – although sometimes missed with the patient hidden under drapes – and was particularly uncommon in the most severe cases, often only occurring when blood pressure and presumably perfusion had been restored. Bradycardia was relatively common, again in the more severe events, and arrhythmias were rare. Airway complications were almost absent.

Fatalities

Our data suggest that perioperative anaphylaxis was more likely to be fatal in patients who were older, of a higher ASA class and significantly obese. Unlike anaphylaxis in the community (Pumphrey 2000), we found no evidence of asthma as a risk factor for fatal perioperative anaphylaxis, but coronary artery disease and administration of beta-blockers and/or ACEI were prominent. Patients died despite prolonged attempts at resuscitation, with most aspects of care being rated as 'good' (described in detail in the second part of this chapter).

Cardiac arrest and survivors

Most patients who survived cardiac arrest were younger and fitter than those who died. Again, prescription of ACEI was prominent in those who developed cardiac arrest. A considerable majority were PEA, and the absence of tachyarrythmias either as a primary event or secondary to adrenaline administration is notable.

Profound hypotension

A group of patients who had profound hypotension, without being designated as 'in cardiac arrest', was identified during review as an apparently high-risk cohort with some poor outcomes. There was discussion regarding the point at which cardiac compressions should be started and, after seeking wide expert advice, we decided this should be 50 mmHg, so any patient with a lowest systolic blood pressure <50 mmHg was designated as requiring CPR, and therefore Grade 4, and where cardiac compressions were not started this was judged to have been an omission. This is a newly identified group and perhaps a contentious one. Their management and outcomes are discussed in the second part of this chapter.

Antibiotics

In contrast to many published series (Mertes 2011a, Harboe 2005, Leysen 2013), antibiotics, not NMBAs, were the most common cause of perioperative anaphylaxis. The high frequency of teicoplanin-induced anaphylaxis is noteworthy and is likely to represent an upward trend. Our findings demonstrate that administration of teicoplanin is closely related to patient-reported penicillin allergy, the most commonly reported drug allergy in the community with up to 10% of the population labelled as allergic. It is likely that the majority are mislabelled, and that at least 90% could be de-labelled if an adequate description of the original reaction could be obtained or the patient investigated in an allergy clinic (NICE 2014).

Considerably more than half of all patients received an antibiotic, which in almost all cases was administered after induction of anaesthesia. In three quarters, signs of anaphylaxis were identified in <5 minutes, and almost all in <10 minutes. Anaphylaxis-induced hypotension is likely to be exacerbated by general or neuraxial anaesthesia. There is a strong argument for antibiotics to be administered several minutes before induction of anaesthesia. There are several potential benefits: first, lack of allergy can be confirmed with the patient immediately before administration, second, the severity of physiological derangement due to

anaphylaxis may be lessened, and third, investigation of anaphylaxis is considerably simplified if fewer drugs have been administered.

It is likely that some of the anaphylactic reactions to antibiotics could have been avoided. Perversely, this is particularly likely to be the case in patents reported to be allergic to penicillin who were then given teicoplanin, which we have shown has a 17-fold higher risk of anaphylaxis than flucloxacillin (or cefuroxime). If it were possible to identify the >90% of patients who report that they have penicillin allergy, but who in fact do not, then avoidance of second-line antibiotics would be likely to lessen overall risk of perioperative anaphylaxis significantly. It is noteworthy that second-line antibiotics are more expensive and are associated with increased duration of treatment, hospital stay and antibiotic resistance (Macy 2014, Sade 2003, Solensky 2014). It is currently impractical for all putative penicillin allergy to be investigated in allergy clinics preoperatively, and the process is significantly complex. However, with the ever-increasing importance of antibiotic stewardship, avoidance of a spurious label of 'penicillin-allergic' is an area ripe for research.

Thirteen patients with anaphylaxis due to co-amoxiclav and four of those with anaphylaxis due to teicoplanin had received an IV 'test dose' of between 5%-30% of the therapeutic dose. It cannot reasonably be expected that a single test dose will eliminate the risk of anaphylaxis. In the allergy clinic the starting dose for drug challenge (which starts only after negative skin testing) will vary depending on: the severity of the index reaction, the dose that is believed to have caused it, the patient's concurrent co-morbidities, whether the challenge is oral or intravenous, and the drug itself. With some high-risk drug challenges this can be as low as 10^{-3} of the therapeutic dose increasing in 2-10 fold increments. Indeed, NAP6 provides evidence that anaphylaxis occurring after a test dose is no less severe than after a full dose. A third of UK anaesthetists routinely administer a test dose when administering an IV antibiotic (Kemp 2017), despite guidelines from the AAGBI advising against their use (Harper 2009) and we find no evidence to support the practice.

NMBA and reversal agents

In previous studies NMBAs were reported to be responsible for 40-66% of all cases of perioperative anaphylaxis (Leysen 2013, Mertes 2003).

Sensitisation to NMBAs may occur during anaesthesia but the majority of patients do not give a history of previous exposure (Baldo 2009), and environmental exposure to the quaternary ammonium epitope has been implicated in generating NMBA allergy (Didier 1987). In addition, pholcodine-containing cough medicines may cause sensitisation to NMBAs (Johansson 2010) and NMBA-sensitisation has declined in Norway since withdrawal of pholcodine cough medicine (de Pater 2017).

Non-allergic anaphylaxis may occur with atracurium and mivacurium. Recent evidence implicates specific receptors on the surface of mast cells (McNeil 2014). Variation in receptor expression may explain why these drugs cause dramatic non-IgE-mediated mediator release in some individuals.

No previous study has undertaken parallel investigation of incidence and NMBA exposure. Studies relying on sales of drug ampoules to estimate the number of patient-exposures may not estimate the denominator accurately. Ampoule sales of suxamethonium probably overestimate usage as a result of waste. To avoid these pitfalls, NAP6 surveyed the number of patients receiving NMBAs during the same year as the case reporting phase.

NMBAs accounted for approximately one third fewer cases of anaphylaxis than antibiotics, but carry at least as high a risk as antibiotics per administration, with the exception of teicoplanin. The lower occurrence rate of NMBA-induced anaphylaxis observed is due to ≈2.5 million administrations of antibiotics to surgical patients per year compared to ≈1.2 million administrations of NMBAs. Suxamethonium is well known to carry a greater risk of anaphylaxis than other NMBAs. Our data confirm this. The risk of suxamethonium-induced anaphylaxis was approximately twice that of all other NMBAs.

Sadleir and colleagues have suggested that rocuronium is associated with a relatively higher risk of anaphylaxis than vecuronium (Sadleir 2013). In that study, the incidence of suxamethonium-anaphylaxis could not be accurately estimated because of lack of denominator data. Vecuronium is used only rarely in the UK (Chapter 9). Although our data cannot be definitive regarding the relative incidence of atracurium and rocuronium-induced anaphylaxis, we identified no major difference in their observed incidences. The difficulties inherent in interpreting the reported incidences of uncommon anaphylactic events are described by Laake and colleagues (Laake 2001). In particular, marginal under-reporting has a disproportionately large effect on calculated incidence. Anaesthetists tended to overestimate the number of cases caused by NMBAs, perhaps as a result of their well-known allergenic potential.

We are unable to comment on the possible influence of pholcodine consumption on the incidence of NMBA-anaphylaxis. This information was not recorded in two thirds of reports: only 18% of allergy clinics routinely ask for this information (Egner 2017b).

A single case of sugammadex-induced anaphylaxis was reported. Onset was delayed, and anaphylaxis should be considered among other differential diagnoses if a patient deteriorates in the recovery room. Sugammadex was used as treatment for anaphylaxis and this is discussed in the second part of the chapter.

Chlorhexidine

Perioperative chlorhexidine exposure may occur via topical skin disinfection, chlorhexidine-coated central venous catheters (CVC) and the use of chlorhexidine-containing lubricating gels (Parkes 2009). It may not be immediately obvious that these products contain chlorhexidine, which has been called "the hidden allergen" (Ebo 2004).

There are geographical differences in the incidence of chlorhexidine-induced perioperative anaphylaxis; 7.7% of cases in the United Kingdom (Krishna 2014) and 9.3% in Denmark

(Opstrup 2014), but it is a rare allergen in France (Mertes 2016). The cause for the variation is not clear but may be related to under-recognition and differences in practice (eg. more use of povidone-iodine and lower use of chlorhexidine-coated catheters). As exposure to chlorhexidine is highly likely in any surgical setting, several centres routinely test all patients referred with perioperative anaphylaxis for chlorhexidine allergy. In countries adopting this practice chlorhexidine allergy is commonly identified (Krishna 2014, Opstrup 2014).

Sensitisation to chlorhexidine can occur in healthcare or the community as chlorhexidine-containing products are found in both environments (Garvey 2007, Nakonecha 2014). The true prevalence of chlorhexidine allergy remains unknown. During a ten year period up to 2004 only 50 cases of IgE-mediated reactions were reported in the medical literature. More recently, 104 cases were reported from four UK specialist centres covering only 2009-2013 (Egner 2017a).

Chlorhexidine is not yet considered among the 'mainstream' causes of perioperative anaphylaxis, despite evidence to the contrary. This is reflected by lost opportunities during perioperative history taking, and the low suspicion rate we observed. In previous studies, up to 80% of patients diagnosed with chlorhexidine allergy reported possible chlorhexidine allergy that could have been identified prior to their adverse reaction (Nakonecha 2014, Garvey 2001).

Despite an alert relating to chlorhexidine-containing medical products and devices being issued nationally by MHRA in 2012 (MHRA 2012), it appears that many clinical staff are unaware of which products contain this antiseptic and the risks of anaphylaxis.

It is unsurprising that reactions are more rapid and severe when a CVC is the source of the chlorhexidine and the allergen is delivered directly to the circulation. Removing the CVC is central to treating the reaction under these circumstances.

Patent blue

Patent Blue dye is found as a food dye (E131), approved for use in the UK but not in the USA, Australasia, Japan, and several other countries. It structurally resembles other triarylmethane dyes widely-used in manufacturing. During surgery it may be injected into the tissues and taken up by the lymphatic system enabling sentinel lymph nodes to be seen directly. Sensitisation is likely to be due to environmental exposure to the dye or a cross-reacting epitope.

The reported estimated incidence of allergic reactions, which are commonly mild, varies between 150 to 1,000 per 100,000 administrations (Mertes 2008, Barthelmes 2010, Brenet 2013, Hunting 2001). Reactions are frequently delayed, at 30-60 minutes, possibly due to slow absorption from subcutaneous tissues and lymphatics (Brenet 2013).

As Patent Blue dye interferes with pulse oximetry (causing spuriously-low readings) this has the potential to delay recognition of the onset of anaphylaxis. While two studies examining this effect reported mean reductions in digital oxygen saturation (SpO_2) of <2% (Mertes 2008, Ishyama 2015), in some individuals considerably greater falls in oximetry values may be observed (Takahashi 2013, Murakami 2003).

In NAP6 reactions to Patent Blue dye were relatively common, were severe and required significant resuscitation. Cutaneous signs were absent in a third of patients and absence of rash should not dominate the differential diagnosis. As hypoxaemia is common after perioperative anaphylaxis, any fall in oxygen saturation should be assumed to be real until blood gas analysis has ruled this out.

Miscellaneous agents

The very small number of cases of reactions to blood products (and none to red blood cells) is notable. The Activity Survey (Chapter 8) estimated approximately 84,000 perioperative administrations of blood products. The relative infrequency of these is perhaps attributable to the success of the serious hazards of transfusion (SHOT) haemovigillance scheme https://www.shotuk.org/.

Ondansetron is administered during an estimated 77% of general anaesthetics and 66% of all cases involving anaesthetist delivered care (Chapter 9, Allergen Survey). Two reports of ondansetron-induced anaphylaxis indicates its extreme rarity. However, these reactions may be severe: two cases of fatal anaphylaxis attributed to ondansetron have been reported (Ouni 2017).

We observed a single case of propofol allergy. Propofol is an extremely uncommon cause of anaphylaxis. Our survey data indicate that well over two-million patients in the UK are exposed to this induction agent perioperatively each year (Chapter 9). Twenty-four IgE-mediated cases were reported in a French eight-year study (Mertes 2011a), and two cases were recorded in a UK seven-year single-clinic study (Low 2016). Asserhøj and colleagues suggested that propofol-induced anaphylaxis may occur in some patients via a non-IgE-mediated mechanism (Asserhøj 2016). Skin testing is negative in this situation, and controlled provocation testing with IV propofol would be necessary to confirm the diagnosis, a procedure that is not generally available. The same publication dispelled the notion that propofol is contraindicated in adults who are allergic to egg, soya or peanut, but some uncertainty still exists in children who have experienced anaphylaxis to egg (Harper 2016). A diagnosis of hypersensitivity to propofol has serious implications for the patient, given the ubiquity of this induction agent and therefore merits full investigation.

We recorded one case of anaphylaxis to protamine in a patient with diabetes. It has been suggested that patients who have been exposed to Neutral Protamine Hagedorn insulin, which contains protamine, are more likely to experience protamine-induced anaphylaxis (Stewart 1984). Fish allergy has been implicated as a risk factor for protamine-anaphylaxis, as protamine is traditionally extracted from the sperm of fish. It is possible that the drug will be increasingly synthesised by recombinant biotechnology. Sensitisation to the fish-derived product may be unlikely to result in anaphylaxis when a patient is exposed to the recombinant formulation.

Anaphylaxis due to non-steroidal anti-inflammatory drugs (NSAIDs) has been comprehensively reviewed by Kowalski and colleagues (Kowalski 2013). There is a wide spectrum of severity and pathogenesis. Reactions are commonly non-immunologically mediated and there may be cross-reactivity to drugs sharing COX-1 enzyme inhibition. An eight-year national study in France identified only three immunologically-mediated perioperative hypersensitivity reactions to NSAIDs (Mertes 2011a).

Reporting

Reporting rates are disappointingly-low. All NAP6 cases were at least Grade 3, representing a life-threatening incident, yet almost a third were not reported to the hospital's critical incident reporting system, reducing the likelihood of lessons being learned where applicable. Only a quarter of cases were reported to the MHRA, despite AAGBI guidance, irrespective of severity of the outcome. Local Coordinators were responsible for many of the reports to MHRA, and it is unlikely that these would have been reported either by the index anaesthetist or the allergy clinic. Our data imply that pharmacovigilance is not being supported adequately and, further, mean that data reported back to anaesthetists and allergy clinics by the MHRA is likely to be unreliable. Factors contributing to poor reporting rates have been discussed by Mahajan (Mahajan 2010).

Conclusions

We believe this is the largest study of life-threatening perioperative anaphylaxis that incorporates contemporaneous real-life data on exposure to potential allergens, permitting calculation of accurate relative-incidence rates. We highlight antibiotic allergy as an increasing problem, particularly teicoplanin, and suggest that optimising preoperative allergy history could reduce the number of perioperative anaphylactic reactions. We hope our data have finally dispelled any notion that test doses might prevent or ameliorate anaphylaxis. An awake patient is able to report early symptoms of evolving anaphylaxis, and our data support administering antibiotics before induction of anaesthesia if practicable. Early recognition is key to successful treatment, and our results show that initial presentation can be varied, likely to be bronchospasm if suxamethonium is the trigger agent, and may be delayed, particularly with Patent Blue dye and some exposures to chlorhexidine, the 'hidden allergen'. We point to the ways in which patient factors, eg. ASA grade, obesity, beta-blockers and ACEI influence clinical features of perioperative anaphylaxis, a dimension previously under-reported. We do not believe that the risk of anaphylaxis should be a determining factor in the choice of non-depolarising NMBAs. We urge anaesthetists to report cases through the MHRA Yellow Card Scheme so that pharmacovigilance can be better supported in the future. In the next section of this chapter we describe clinical management and outcomes.

Part B: Management of, and outcomes after perioperative anaphylaxis

Key findings

- All patients were resuscitated by anaesthetists of appropriate seniority.
- A management guideline was immediately available in 86% of cases.
- Immediate management was judged 'good' in 46% and 'poor' in 15% of cases.
- Recognition of and treatment of anaphylaxis were judged prompt in 97.3% and 83.4% of cases, respectively.
- Adrenaline was administered IV in 76% of cases, IM in 14% and both in 6%.
- No adrenaline was administered in 11% of cases.
- The majority received other vasopressors (metaraminol, phenylephrine) before adrenaline.
- An IV infusion of adrenaline or noradrenaline was administered in 30.7% and 18.9% of cases respectively.
- Two patients received vasopressin and one glucagon.
- Steroids and antihistamines were generally administered early.
- Careful examination of the role of antihistamines found no clear evidence of harm or benefit.
- Sugammadex was given to treat anaphylaxis in 7.1% of cases.
- IV fluid administration was inadequate in 19% of cases.
- Cardiac arrests (15% of cases) were promptly treated; mean duration of cardiac compressions was 14 minutes, but cardiac compressions were performed in only 50% of patients with unrecordable blood pressure.
- The surgical procedure was postponed or abandoned in two thirds, and urgent surgery was delayed in 10% of all cases.
- More than half of patients required admission to critical care: 70% for level 3 care and most of these patients required catecholamine infusions after admission.
- Adverse sequelae were reported in a third of cases, including new anxiety, change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of post-traumatic stress disorder, myocardial damage, heart failure and new renal impairment.
- Ten deaths (3.8%) were attributable to anaphylaxis, a per case mortality rate of 1 in 26.6 cases.
- Six per cent of survivors underwent surgery (all uneventfully) between the index event and the patient being seen in the allergy clinic.

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 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 not visible under surgical drapes or delayed, especially in more severe cases. Hypotension is usually the first sign of perioperative anaphylaxis (see earlier section of this chapter). 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.

Similarly, bronchospasm, which not uncommonly accompanies general anaesthesia especially in asthmatic patients, is the first clinical feature in 18% of cases of perioperative anaphylaxis (see earlier in chapter), and anaphylaxis may not be the first differential diagnosis.

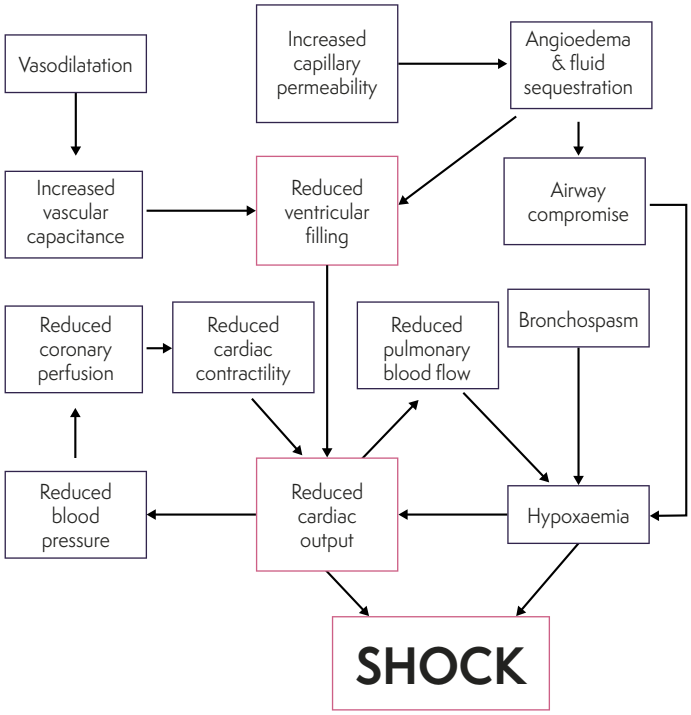
It is generally agreed that adrenaline is the mainstay of management, and it is recommended in all published guidelines (Harper 2009, Marakian 2009, Krøigaard 2007, NICE 2014, Simons 2011, NICE 2011, RCUK 2016, Kolawole 2017). Having both alpha and beta agonist properties, adrenaline has compelling theoretical advantages in the treatment of anaphylaxis by ameliorating many of the pathophysiological processes (Figure 1).

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 2011).

McLean-Tooke concluded that adrenaline is not contraindicated in patients with coronary artery disease as continuing anaphylaxis is likely to further reduce coronary artery perfusion (McLean-Tooke 2003). However, excessive dose or over-rapid IV administration can cause arrhythmias. Intravenous (IV) adrenaline is more likely than intramuscular (IM) 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 (RCUK 2016). The AAGBI guidelines recommend an initial IV dose of 50 mcg, repeated as necessary (Harper 2009). The 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).

Metaraminol is a second-line treatment in the AAGBI guidelines (Harper 2009), but is widely available in anaesthesia settings. Several case reports describe survival after use of IV vasopressin

Figure 1. Physiological mechanisms responsible for anaphylactic shock



2-15 units (antidiuretic hormone) in the management of intractable perioperative anaphylaxis (Schummer 2008, Bensghir 2013, Meng 2008, Hussain 2008), and this drug is included in the ANZAAG guidelines (Kolawole 2017). The benefit of adrenaline is likely to be reduced in the presence of beta blockade. There are single case reports of glucagon use in beta-blocked patients leading to rapid resolution of hypotension (Zaloga 1986, Javeed 1996). European guidelines (Mertes 2011b) and ANZAAG guidelines (Kolawole 2017) recommend glucagon 1-2 mg every 5 minutes 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 (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). Hydrocortisone is recommended in published guidelines. Dexamethasone 7.5 mg has an equivalent glucocorticoid effect to hydrocortisone 200 mg.

The use of antihistamines in relatively minor out-of-hospital allergic reactions benefits urticaria and pruritus. A Cochrane review of H1 anti-histamines 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). We aimed to establish whether administration of chlorphenamine, the most commonly used antihistamine, influenced outcome.

Several case reports may be considered supportive of administration of sugammadex during rocuronium-induced anaphylaxis (McDonnell 2011, Kawano 2012, Barthel 2012). The hypothesis that encapsulating the antigen may halt the clinical features of anaphylaxis is unproven, despite in vitro and clinical studies (Clarke 2012). Platt *et al* reported sugammadex administration during immediate management of suspected rocuronium-induced anaphylaxis, in 13 cases, of which five were not rocuronium-induced (Platt 2015). 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. We sought to determine to what extent sugammadex has been incorporated into current management of perioperative anaphylaxis.

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); there is consensus for rapid IV infusion of crystalloid fluids. Recent guidelines emphasise the need to give rapid, repeated IV fluid challenges while monitoring the response: ANZAAG guidelines (Kolawole 2017) recommend giving repeated boluses of 20 ml/kg. There is a paucity of information concerning IV fluid management in 'real-life' management of perioperative anaphylaxis, but we support these recommendations.

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

Methods

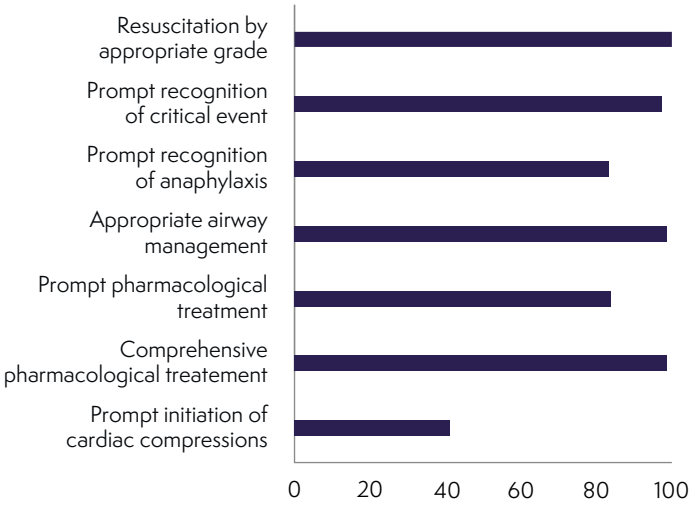
Methods are discussed in detail in Chapter 5, Methods. At panel review the quality of immediate management was assessed and classified, including factors such as timeliness, accuracy and completeness. In doing this we also referred to current guidelines of the AAGBI (Harper 2009) and the Resuscitation Council of the United Kingdom (RCUK) on management of perioperative anaphylaxis (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 a full panel review of 184 cases (see Chapter 5, Methods).

Results

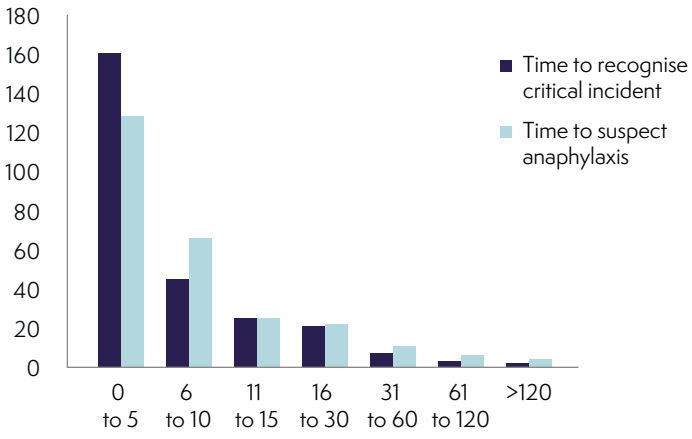
Resuscitation was performed by an anaesthetist of appropriate grade in all cases. The review panel considered that overall management was 'good' in 46% cases, 'good and poor' in 39%, and 'poor' in 15% (Figure 2).

Figure 2. Quality of management of perioperative anaphylaxis by anaesthetists (% of cases)



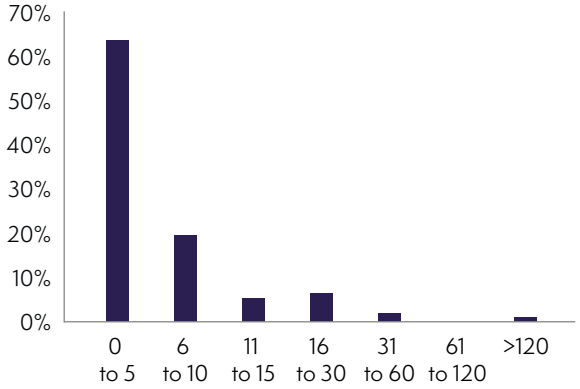
Recognition of a critical incident and suspicion of anaphylaxis was within five minutes in 60% and 49% of cases, respectively. By 10 minutes, the corresponding figures were 78% and 74%. Recognition of anaphylaxis and treatment were judged prompt in 97.3% and 83.4% of cases respectively (Figure 3).

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



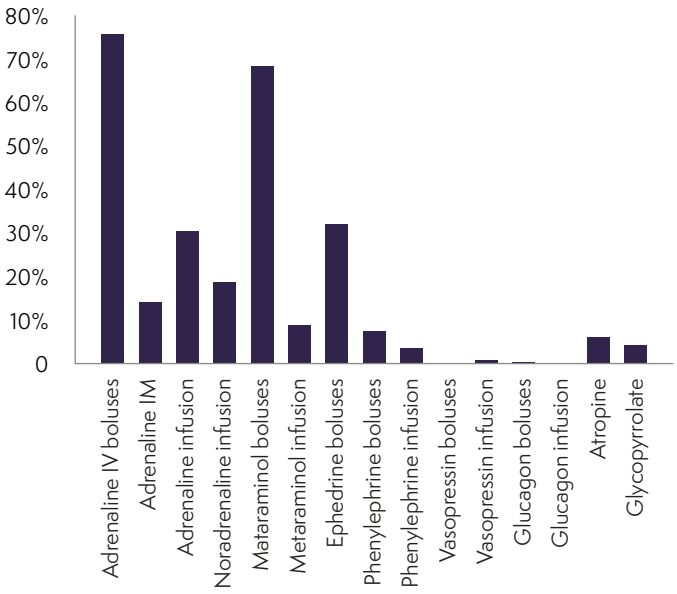
Specific treatment for anaphylaxis following the first clinical feature was started in <5 minutes in 64% of cases and <10 minutes in 83%. (Figure 4). Reported reasons for delay included confounding differential diagnoses such as pulmonary embolism, tension pneumothorax, gas embolism during abdominal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

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



Pharmacological treatment was judged prompt and comprehensive in 83.9% and 98.8% of cases respectively. The vasoactive drugs administered are shown in Figure 5. Adrenaline was administered in 82.3% of cases, as IV boluses in 75.9%, and was more likely to be given as severity increased. The median total dose was 0.2 mg, 0.5 mg and 4 mg in severity Grades 3, 4 and 5 respectively. There was wide variation in the number of IV doses, ranging from one to thirty (median three doses). Recognition of anaphylaxis was delayed in approximately one third of cases. The IM route was used in 14.1% of cases. Sixteen patients (6%) received both IV and IM adrenaline.

Figure 5. Vasoactive drugs administered during initial management of perioperative anaphylaxis (% of cases)



An IV infusion of adrenaline was used in 30.7% of cases, preceded by bolus doses in all except a single case. Adrenaline was judged not to have been given when indicated in 19.4% of cases – either not administered (11%) or given late (8.4%).

Metaraminol boluses were administered in 68.7% of patients, of whom 73.6% also received adrenaline. Phenylephrine was administered by IV bolus in 7.8% of cases, and an infusion in 3.5%. Most cases were obstetric. An IV infusion of noradrenaline was administered in 18.9% 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 adrenaline.

Bradycardia was present in 13.2% of all cases, a third in association with cardiac arrest, and was treated with glycopyrronium in 4.3% and atropine in 6.2%. Tachyarrythmia was rare, being treated once with amiodarone, which was also used during the management of four cases of cardiac arrest.

IV hydrocortisone was administered in 82.9% of cases (1–4 doses, median dose 200 mg) and dexamethasone (administered after the event) in 16.1% of cases (median dose 6 mg). In 8.7% of cases both drugs were administered. Two patients received methylprednisolone. It should be noted that dexamethasone was also given before the event in 19.2% of cases. Thirty-four patients (12.8%) did not receive a steroid, including four fatalities.

Intravenous chlorphenamine was administered in 73.6% (median 10 mg, 5-40 mg) (Table 1) and intravenous ranitidine in 5.3% of cases. Nine (3%) patients received both drugs. We performed further analysis using a logistic regression model to elucidate benefit or harm associated with chlorphenamine. Variables included; initial resuscitation drugs, (adrenaline bolus, corticosteroids, metaraminol, ephedrine and chlorphenamine); patient factors (age group intervals excluding children and over 75 years 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/death) as defined in Chapter 5. In spite of the univariate analysis, in the logitistic regression analysis 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.

Table 1. 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
Chlorphenamine		
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%

Sugammadex

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

IV fluids

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

Ninety-eight per cent of patients received IV crystalloids in the first hour after the reaction, 86% during the subsequent 2 hours and 69% during hours 3-5. 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.

Airway

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 difficulty and complications were uncommon. 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 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 due to airway swelling.

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 the 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; local or trust guidelines accounted for 3.8% of cases. In 44 (18.6%) 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 ten cases, and all resuscitations followed a guideline and were managed by a consultant. Nine patients had a cardiac arrest and resuscitation was prompt, prolonged and extensive. CPR took place for a median 39 minutes and in all cases for >25 minutes. Resuscitation included extra-corporeal-membrane oxygenation in one case, and immediate cardiac catheterisation to explore or manage an acute coronary syndrome in two cases. Adrenaline was administered IV in all cases, including an infusion in five cases. A median of 5 doses (5 mg) adrenaline was administered (range 2-13 mg). No patient received IM or intraosseous adrenaline. Ephedrine, metaraminol, glycopyrronium and atropine were used early in resuscitation. Five patients received noradrenaline, one vasopressin and one glucagon, administered at 65 minutes after the reaction. Approximately half of cases received chlorphenamine and hydrocortisone. Sugammadex was not used. Fluid resuscitation volumes were relatively modest 1-4.5L (median 1.5L) in the first hour, and in the first five hours 1-9.5L, (median 1.5L); only one patient received >4L in total. Five patients did not survive initial resuscitation, while five did, of whom one died soon after. Of the four remaining patients, all were admitted to critical care and all survived at least one 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 in Chapter 14, Investigation. 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, 1 uncertain). Inadequate fluid administration was a recurrent theme.

Cardiac arrests

Cardiac arrest was reported in 40 (15%) patients – in 27% of these within 5 minutes of trigger administration, though in others preceded by prolonged hypotension. Nine of these patients died and 31 survived. All these patients received cardiac compressions; the mean duration was 14 minutes (range 1 to 60 minutes). The need for cardiac compressions was generally prolonged in those who died (see above section) but brief in those who survived (median 8 minutes, IQR 2-8 minutes in survivors). The event was generally promptly recognised and treated. Delays in managing anaphylaxis were due to slow diagnosis or uncertain diagnosis (one case each) and loss of IV access (one case). Quality of resuscitation is summarised in Table 2. On average five doses of IV adrenaline were administered (mean 5 mg, range 0-12 mg). Half of survivors received an adrenaline infusion after initial resuscitation. Second-line drugs included noradrenaline (to 15 patients), vasopressin (to two), glucagon (to one), intralipid (to one) and sugammadex (to one). Chlorphenamine and steroid were given to approximately 75% of patients during resuscitation. Fluid volumes were modest – median volume 1.75L (range 0-4.5L) during the first hour and 3.25L (range 0-9.5L) during the first five hours. Panel judgements on quality of care are included in Table 2.

Profound hypotension

CPR was initiated in 28 (50%) of those with an unrecordable blood pressure, in five (9%) with systolic blood pressure <50 mmHg and in two (3.8%) with lowest blood pressure of 50-59 mmHg. The panel, after taking external expert advice, used a threshold of <50 mmHg as the point at which CPR was indicated in adult patients. Deakin *et al.* demonstrated using invasive blood pressure measurement that systolic blood pressure <50 mmHg was associated with pulselessness with a 90% positive predictive value (Deakin 2000). When non-invasive blood pressure monitoring is used this will underestimate hypotension (Lehman 2013). So, when the lowest blood pressure was <50 mmHg CPR was deemed indicated. There were 114 (42.9%) such cases. Overall prompt CPR (when the blood pressure was <50 mmHg or unrecordable) was reported in 23% of cases. Pharmacological treatment was judged inadequate in 21% and adrenaline administration was judged inadequate in 17%. Fluid administration was judged inadequate in 24%. 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 comprised 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, comprising IV gelatin, administration of a second dose of protamine and two instances of retained chlorhexidine-coated central venous line.

Continuation of surgery

In approximately one third of cases the procedure was unchanged but, in more than half the 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.

Table 2. Quality of resuscitation and outcomes in adult patients who died, compared to those who survived cardiac arrest, or experienced profound hypotension or did not experience profound hypotension

	Deaths (n=10)	Non-fatal cardiac arrest (n=31)	sBP <50 mmHg without 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%
Adrenaline administered as needed	90%	100%	76%	77%
Prompt CPR 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%
Critical care for vasopressors (% of all cases)	n/a	67%	32%	23%
Time on Critical care (median, all cases)	n/a	2	0	1
Unplanned hospital length of stay	n/a	2	1	1

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.

Outcomes (cases of all severity)

The severity of physical harm (see Table 3 in Chapter 5 for definitions) identified by the review panel was none in 8% of cases, low in 51%, moderate in 34%, severe/death in 4%, and uncertain in 3%. Concomitant beta-adrenergic blocking drugs were associated with greater severity – 60% of fatalities were taking a beta-blocker compared with 18% of all cases.

We asked about physical and psychological sequelae after the event. Data was 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, and in three cases this extended to symptoms of post-traumatic stress disorder. Ten patients reported problems with mood, memory or coordination. There were twelve 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 (28.6%), 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

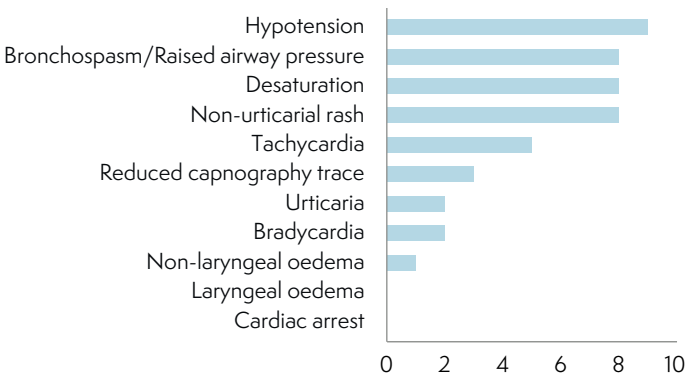
We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey (Chapter 8) estimated that 233,886 obstetric anaesthetics are administered per annum in the UK, giving an incidence of severe obstetric perioperative anaphylaxis of 3.4 per 100,000, which is significantly lower than in adult non-obstetric cases. 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 or maternal or neonatal deaths. All patients developed hypotension, which was 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 adrenaline, and three both. 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 'good' and in one 'good and poor'. Identified culprits were chlorhexidine, atracurium, 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 under 16 years 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 2.73 per 100,000 paediatric anaesthetics which is significantly lower than in adult cases. 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 and/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 five minutes, whereas hypotension was generally slower in onset. A decrease in end-tidal carbon dioxide levels 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 among the paediatric cases. 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.

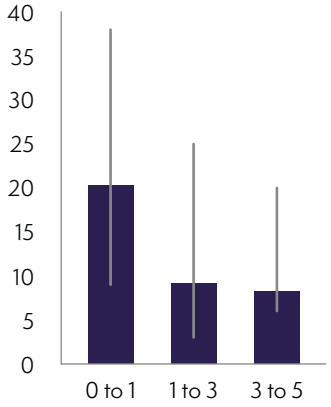
Figure 6. Number of children exhibiting clinical features at any time during the anaphylactic episode



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 adrenaline 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 five minutes in six of the seven cases where bronchospasm and/or high airway pressures were the presenting features. When hypotension or tachycardia were the presenting features, specific treatment tended to be started later. Adrenaline was administered in ten cases, either IV or IM, 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, glycopyrrolate, sugammadex or magnesium sulphate. Ten patients received IV crystalloid, one IV gelatin, and one no IV fluid. The volume of IV crystalloid administered during the first five hours is shown in Figure 7.

Figure 7. Volume of IV crystalloid (ml/kg) administered to children during the first five hours after an anaphylactic event (median, range)



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.

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 MHRA, and two patients were issued with a hazard alert by the anaesthetist.

Eight cases had at least one mast cell tryptase sample taken 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; suxamethonium, 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, in eight cases fully reviewed, was judged as good in one, good and poor in three and poor in four.

Concordance

Concordance between triggers suspected by the anaesthetist and identified by the panel is discussed in greater detail in Chapter 14.

Among cases with an identified trigger, overall concordance was 75% between the anaesthetist and the panel. However, anaesthetists were likely to over-identify NMBAs 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 following 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 26.6%, written in 19.8%, both in 39.2% 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.

Discussion

Immediate management: all cases

It is reassuring that resuscitation involved a consultant or other career grade anaesthetist in all cases. The majority (88.7%) of UK patients are anaesthetised by consultant or career grade anaesthetists (Chapter 8), nevertheless, anaesthetists in training 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 multi-factorial and included insufficient IV fluids, non-administration or late administration of adrenaline, delays in recognising anaphylaxis and starting specific treatment, and lack of cardiac compressions where the BP was <50 mmHg or unrecordable.

An apparent reluctance to give adrenaline has been previously reported (Garvey 2011). We suggest that four factors operate. First, anaphylaxis is very uncommon: an anaesthetist will see perioperative anaphylaxis on average only once every 7.25 years (Kemp 2017). Second, when faced with hypotension, it has been the anaesthetist's previous experience that repeated doses of the 'usual' vasopressors will eventually restore the blood pressure, encouraging a 'more of the same' approach. An analogous behaviour is the 'task fixation' sometimes observed when managing a difficult intubation. Third is the phenomenon of crisis-denial and the realisation that giving adrenaline will affirm that a crisis exists. Fourth, unless the anaesthetist has a critical care background, administration of adrenaline may be outside their previous experience. It is also possible that the anaesthetist may have, unfounded, concerns that adrenaline is contraindicated in patients with coronary artery disease or in obstetric patients. In addition

to immediate availability of management guidelines, overcoming these barriers to adrenaline administration requires frequent practice drills and, ideally, simulator training (Johnston 2017). Reluctance to administer large volumes of IV fluids was also observed, particularly in patients with cardiac disease, perhaps through misplaced fears of causing fluid overload and precipitating heart failure.

Vasopressin is recommended for intractable hypotension in several guidelines (Krøigaard 2007, Kolawole 2017), but was administered in only two cases despite the presence of persistent hypotension, evidenced by the administration of noradrenaline infusion in almost 1 in 5 cases. Several cardiac arrests were preceded by prolonged hypotension. It is to be noted that earlier guidelines omitted this drug (Harper 2009), and it likely that awareness 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.

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 that chlorphenamine administration was associated with decreased probability of 'no harm' and increased probability of 'moderate/severe' harm. However, the confidence intervals were wide and Fisher's 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, ie. we were unable to demonstrate causality. The review panel considered that chlorphenamine should continue to be recommended, though mainly to reduce angioedema/urticaria.

Our data do not support efficacy of sugammadex in rocuronium-induced anaphylaxis. Of seven proven cases, four needed no further pharmacological treatment after sugammadex was given, but three required further vasopressor and or bronchodilator therapy.

Patients with profound hypotension had less good quality of care than any other patient group. They were more likely to have delayed diagnosis and administration of adrenaline, and CPR was a rarity: significant numbers of patients came to harm. Early recognition of these patients as at high risk of harm, early management with adrenaline, fluids and CPR provides an opportunity to improve outcomes.

Treatment and referral to allergy clinics might be improved by provision of specific Anaesthetic anaphylaxis treatment packs and Anaesthetic anaphylaxis investigation packs. These are described in Chapter 11.

The majority of patients in our cohort required transfer to critical care, mostly for Level 3 care; half of the 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 were of the view 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 (Sadleir 2018) demonstrated that patients with Grade 3 anaphylaxis whose surgery continued (42.2%) did not require more intraoperative adrenaline 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 rise as a surrogate for severity, but NAP6 data demonstrated no relationship between acute mast cell tryptase levels and indices of clinical severity (Chapter 14, Investigation). In Sadleir's study, surgery was continued in a small proportion of cases of Grade 4 anaphylaxis.

The potential risks of patients undergoing surgery without adequate precautions before they have attended an allergy clinic are underlined by a case in which an NMBA was the suspected culprit but chlorhexidine was demonstrated to be the cause on allergy testing. In most circumstances urgent surgery can be performed before allergy clinic assessment by applying some simple, cautious rules: we have developed a management plan (see Chapter 11) for patients in whom surgery is needed before a clinic diagnosis has been obtained.

Gibbison *et al* demonstrated that perioperative anaphylaxis accounts for a third of all cases of anaphylaxis admitted to critical care units (Gibbison 2012); a similar proportion to that admitted from the emergency departments following community anaphylaxis. Our data, comprising 144 admissions over a one year period, are compatible with Gibbison's. Almost two thirds of patients admitted to critical care required continuing inotropic support, but only 5% needed continuing bronchodilator therapy; we believe this is a novel finding. Notably, there were no cases of so-called biphasic anaphylaxis (recrudescence).

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

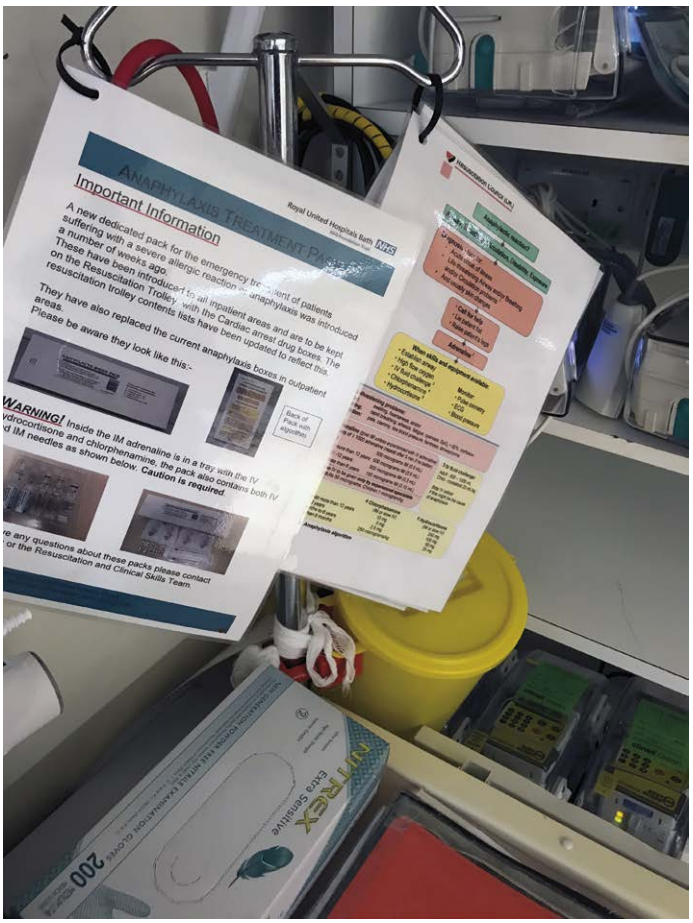
Obstetric cases

Anaphylaxis during pregnancy is very uncommon (≈1.6–3.0 per 100,000 maternities (Lennox 2014, Mulla 2010, Bunch 2016)). The predominant use of neuraxial techniques probably limits exposure to many of the trigger agents associated with general anaesthesia. Previous studies have highlighted latex and suxamethonium as culprits (Hepner 2013). The incidence during caesarean section was reported as 2.1 per 100,000, with antibiotics important triggers. Perioperative obstetric anaphylaxis is complicated by the need to ensure the safety of both patients and of the potential impact of both maternal hypotension and adrenaline administered to the mother on uteroplacental haemodynamics. The literature is generally reassuring, with good maternal and neonatal outcomes, but it is notable that maternal outcomes may be less good when anaphylaxis occurs during caesarean delivery and neonatal outcomes worse when maternal anaphylaxis develops during

labour. The placenta is metabolically active and metabolises histamine and other endogenous mediators (Baraka 1980), potentially protecting the fetus from mediator-related morbidity.

The overlapping clinical features of anaphylaxis with other acute obstetric morbidities can hinder the diagnosis of anaphylaxis, particularly during the onset or in the presence of neuraxial block. In the absence of vasopressor-prophylaxis, hypotension occurs in two-thirds of patients during spinal anaesthesia. However other conditions such as aortacaval compression, haemorrhage and, much more rarely, amniotic fluid or thromboembolic embolus can lead to severe hypotension.

Phenylephrine was the most commonly used vasopressor. Phenylephrine infusions are recommended to prevent and treat hypotension associated with spinal anaesthesia (Kinsella 2017) and are therefore immediately available and familiar to the anaesthetist working on the labour ward. In the presence of spinal anaesthesia, hypotension from other causes can be exacerbated and require large doses of vasopressor to treat effectively. Adrenaline is recommended for the management of anaphylaxis and although there might be theoretical concerns about its potential effect on the uteroplacental circulation, particularly when used to treat anaphylaxis before delivery, this effect is short lived (Hood 1986) and any transient effect on uteroplacental circulation is likely to be less than the impact of maternal hypotension. Thus, adrenaline should be first-line treatment in obstetric patients.



Laminates may guide actions during resuscitation

Paediatric cases

Perioperative anaphylaxis is uncommon in children and reported incidences vary considerably (Murat 1993, Mertes 2011a, Habre 2017). Latex and NMBAs have historically been prominent triggers and antibiotics less commonly cited. This is probably influenced by differences both in procedures commonly undergone by children and in anaesthetic technique.

The low incidence of paediatric perioperative anaphylaxis may have several causes. Latex exposure has reduced significantly in recent years, and it is also likely that children are both less sensitised before anaesthesia and less exposed than adults to allergens during the perioperative period. NAP6 indicates that NMBAs and antibiotics were used in 24.7% and 26.4% of paediatric general anaesthetics, compared to 47% and 57% in adults (Chapter 21). The Allergen Survey (Chapter 9) also showed that 14% of children received only sevoflurane, a low anaphylaxis-risk anaesthetic, for induction and maintenance.

Unlike in adult patients, bronchospasm and/or high airway pressures were the most common presenting features in children. Bradycardia was also more common in children compared with adults (18% vs 12.6%). Cardiopulmonary resuscitation was not performed in any paediatric case: four children's systolic blood pressure was <50 mmHg, but expert opinion did not favour setting a blood pressure 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 suxamethonium appear to be proportionate to the number of exposures. Atracurium was the most-used NMBA in children (57%) by a large margin, followed by rocuronium (5.2%) and suxamethonium (2.6%). Paediatric cases are increasingly intubated without an NMBA (Sneyd 2010).

There were no cases of latex-induced anaphylaxis, which may reflect its declining presence in the workplace (Newsom 1997) as well as an increased awareness that latex is a potential hazard following historical paediatric case reports (Kelly 1994).

Conclusions

We are not aware of other studies which 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, either 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 Appendix D.

In Chapter 2 and in each detailed chapter we list a series of recommendations intended to improve care. 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 (Cook 2011, Cook 2016)) the many recommendations we have made will be largely implemented. Others may 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 potentially life-threatening events. This will have the potential to make inroads into preventing avoidable anaphylaxis and improving the quality of care patients receive when it occurs and afterwards, both by anaesthetists and in allergy clinics.

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