12 Deaths, cardiac arrests, profound hypotension and outcomes

Tim Cook

Key findings

Severe perioperative anaphylaxis here refers to perioperative anaphylaxis requiring CPR or with profound hypotension (eg. <50 mmHg).

- Most patients with severe perioperative anaphylaxis were well managed in terms of recognition of the event, recognition of anaphylaxis, prompt administration of adrenaline and CPR when indicated.
- Patients who died from anaphylaxis were more likely to be older, obese and co-morbid than those who survived.
- Patients who died from anaphylaxis were more likely to have coronary artery disease and to be taking beta-blockers than those who survived.
- Patients who experienced a cardiac arrest during perioperative anaphylaxis were more likely to be taking ACE inhibitors than those who did not.
- Patients who died or experienced cardiac arrest from perioperative anaphylaxis were not more likely to have asthma than those who did not.
- Patients with a very low blood pressure (<50 mmHg) but who did not have a cardiac arrest were managed less well than other patients in terms of speed of treatment, administration of adrenaline and CPR when indicated. This was reflected in panel judgement of quality of care. The majority of these patients came to harm.
- Cardiac arrest types were: PEA 34 (often preceded by bradycardia), VF/VT four (all preceded by tachycardia) and asystole two. No other arrhythmias preceded cardiac arrest.
- Prolonged cardiopulmonary resuscitation (CPR) was uncommon in survivors of cardiac arrest during anaphylaxis (median 8 minutes) and universal in those who died (all >25 minutes).
- Following resuscitation, most patients required vasopressor infusions, but few stayed on critical care for more than two days.
- Hypotension and bronchospasm were the prominent presenting features in fatal cases of anaphylaxis.
- The presenting feature was cardiovascular in the majority of cases of anaphylaxis with cardiac arrest, with pure respiratory less common.
- Hypotension was universal in cases of Grade 3–5 anaphylaxis.
- Hypoxia was an uncommon presenting feature but was common in the hour after resuscitation.
- Rash, urticaria and oedema were uncommon during anaphylaxis with cardiac arrest, and sometimes only appeared after resuscitation.
- Neither airway swelling nor airway difficulty were seen in any cases of anaphylaxis with cardiac arrest.
- Fluids administration was generally modest and was judged inadequate in 1 in 5 severe anaphylaxis cases.
- Surgery was abandoned in the vast majority of cases where cardiac arrest occurred.
- In patients who had a cardiac arrest and especially those who died, neuromuscular blocking agents (NMBAs) were more commonly the culprit agents, though strong conclusions cannot be drawn.

What we already know

Fatal anaphylaxis remains a rare event. Death often occurs within one hour of exposure to the culprit agent (Low 2006, Pumphrey 2000b, Shen 2009). Epidemiology and risk factors for fatal reactions are likely to vary for sting, food and drug anaphylaxis. Drug anaphylaxis is rising worldwide (Liew 2009, Jerschow 2014, Turner 2015, Mullins 2016), but extracting data that differentiate between community and hospital-based events can be challenging.

Risk factors for severe anaphylaxis vary depending on allergen and location. For instance, asthma is a risk factor for severe food anaphylaxis (Smith 2015); increasing age and/or cardiovascular disease are risk factors for near-fatal and fatal drug-induced anaphylaxis (Motosue 2017, Liew 2009, Jerschow 2014, Turner 2015, Turner 2017).

There are (surprisingly) little robust data about mortality from perioperative anaphylaxis, and this is generally retrospective and historical to the extent that results may no longer be applicable. It is also likely that severity of perioperative anaphylaxis and mortality will vary in different countries for a variety of reasons, including drug choices, patient characteristics and quality of rescuscitative and critical care services.

A figure of ≈4% is quoted in a number of references regarding the mortality rate of perioperative anaphylaxis (Levy 2011, Mertes 2003, Sampson 2005, Light 2006). Gibbs writing in 2013 noted that many reviews report the same figure and quote the same sources – which may in fact may lack accuracy (Gibbs 2013).

Gibbs and colleagues (Gibbs 2013) reported no anaphylaxis deaths in a retrospective review of 45 anaesthesia-related deaths in Western Australia between 2000-2009. Inclusion criteria included death within 48 hours of anaesthesia and 'all deaths due to a complication of an anaesthetic'. The authors estimated an anaphylaxis rate of ~1:11,000 and 264 cases of anaesthesia-related anaphylaxis in the same time period, giving a mortality rate of 0% and a 95% upper confidence limit of 1.4%.

While there are several case series of post mortem examinations after fatal anaphylaxis, out of hospital anaphylaxis due to orally ingested food or drugs may present with a greater proponderence of 'asthma-like' symptoms and respiratory arrests than drug-induced anaphylaxis, in which shock and cardiac arrest is more prevalent (Pumphrey 2000a). This is probably exacerbated when the drug is delivered intravenously.

Post mortem signs are likely to vary according to the mode of death and hence the mode of anaphylaxis: indeed, there may be very few signs (Da Broi 2011, Kobek 2014). Several series are reported but all include anaphylaxis cases of any source (eg. food, oral drugs, intravenous drugs). Post mortem findings are generally described as non-specific but also include pulmonary congestion, pharyngeal and laryngeal swelling, pulmonary mucus plugging, petechial haemorrhages and cerebral hypoxia (Low 2006, Shen 2009, Pumphrey 2000b). In one series there were no specific findings in 41% of post mortem examinations (Pumphrey 2000b).

When anaphylaxis is less severe, it may cause cardiac arrest. Pumphrey reported the median time to respiratory or cardiac arrest was 30 min for foods, 15 min for venom and 5 min for drug reactions (Pumphrey 2000b). Sadleir recently reported 39 patients requiring cardiopulmonary resuscitation for pulseless electrical activity (PEA) or asystolic cardiac arrest without any deaths (Sadleir 2017).

Gouel-Cheron and colleagues recently reported that an end-tidal carbon dioxide value less than 2.6 kPa may be a useful indicator of a severe anaphylactic reaction (Gouel-Cheron 2017). This has not been examined in other settings, but NAP6 provides an opportunity to examine this.

Sadleir recently reported on the impact on patients of continuing with surgery after the development of anaphylaxis (Sadleir *et al*., 2017). The observational study included 167 Grade 3 and 4 cases. In Grade 3 cases, after successful resuscitation and, where resuscitation could be re-instituted if required, continuing with surgery was not associated with poorer outcomes. In Grade 4 events, all cases except one were abandoned where this was practical, but there was a significant complication rate irrespective of whether surgery was abandoned or continued. 'Major sequelae' occurred in 4.7% of Grade 3 cases and 12.8% of Grade 4 cases. The observational nature of this study means that factors that influenced the decision to continue or abandon may have been missed.

Numerical analysis

Deaths

Incidence

Ten patients died directly (eight) or indirectly/delayed (two) following anaphylaxis during the NAP6 data collection period. This equates to an incidence of perioperative death from anaphylaxis of 1 in 239,000 general anaesthetics and 1 in 313,000 anaesthetic interventions. Of all cases of life-threatening (Grade 3+) anaphylaxis, 3.8% (1 in 26.6) died.

One other patient experienced Grade 4 anaphylaxis to an antibiotic and died of an apparently unreladed cardiovascular event at least a week later. That case is not considered further.

Patient characteristics

All reported deaths occurred in NHS hospitals. Six were female and four male. All were white British except one patient from the Indian subcontinent. All patients were aged more than 46 years: two 46–55 years, three 56–65 years, three 66–75, and two 76–85 years. Two patients were ASA Grade 2, six ASA 3 and two ASA 4. In the Activity Survey (Chapter 8) almost half of patients were aged less than 45 years and only 25% aged more than 65% years, 77% were ASA 1–2 and less than 2% ASA 4–5. This suggests that fatal cases of anaphylaxis were more likely in patients who were older and of a higher ASA grade.

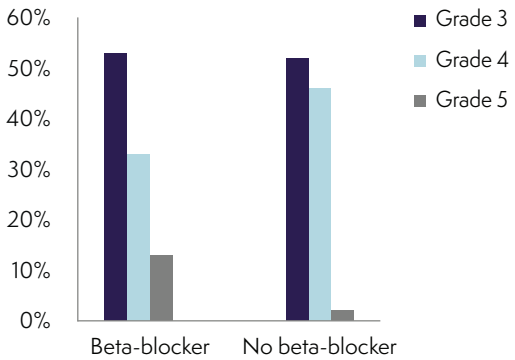
Obesity or morbidly obesity is present in 21% of the surgical population (Chapter 8 Activity Survey), 37% of the NAP6 cohort and 50% of those who died. Only one patient (who had a delayed death) was of normal weight; four were overweight, one obese and four morbidly obese. This raises the possibility that perioperative anaphylaxis is more likely to be fatal if patients are significantly obese.

A morbidly obese ASA 3 patient had anaphylaxis at induction of anaesthesia. There was a PEA arrest from which the patient was resuscitated after prolonged CPR. The patient developed multi-organ failure while on crtitical care. Co-morbidities meant the patient was unlikely to survive and life-sustaining treatment was withdrawn after a prolonged period of time.

An elderly co-morbid patient experienced severe anaphylaxis, requiring CPR, and was resuscitated. The patient was admitted to critical care for ventilation and vasopressor support. During a long hospital stay the patient had more than one admission to ICU and life-sustaining treatment was eventually withdrawn.

No patients 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 only one patient neither drug. Amongst 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. There therefore appears to be a higher proportion of patients with cardiac disease and taking beta-blocker medication who suffered a Grade 5 reaction (Figure 1).

Figure 1. Grade of reaction (%) in patients taking beta-blockers or not



Characteristics of patients who survived or died after perioperative anaphylaxis are compared in Table 1.

Table 1. 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%

No fatal anaphylaxis was associated with an incomplete drug history, drug error or cross-reactions. No patient had had a known previous reaction, either investigated or not investigated.

All patients underwent general anaesthesia, two with additional regional anaesthesia techniques. Half of procedures were elective and half expedited or urgent, proportionately more than in the Activity Survey (Chapter 8) (35% urgent or expedited).

All patients were initially cared for by a consultant (eight) or a career grade doctor (two): in these latter two cases a consultant assisted during resuscitation. All events occurred between Tuesday and Friday: none at the weekend.

In one fatality (in a morbidly obese patient) intravenous (IV) access was lost during resuscitation requiring intraosseous (IO) administration of drugs.

Three (30%) patients were undergoing cardiac surgery (<1% of cases in the Activity Survey), three general surgery, and the other four a mixture of surgeries. Eight events occurred before surgery and one during surgery, six in the anaesthetic room, three in the operating room with one not specified. The surgical procedure was abandoned in nine cases and proceeded in one where it had already started.

Drugs used during induction were similar in distribution to those used in the Activity Survey, as was exposure to chlorhexidine (60% vs 73%) and distribution of NMBAs used (rocuronium and atracurium predominant). Six patents received antibiotics, compared to 57% in the Activity Survey.

A patient received only a small dose of fentanyl and a dose of antibiotic before any other agents. The patient complained of nausea and vomiting before becoming hypotensive. The patient had a rapid and severe anaphylactic reaction resulting in cardiac arrest and death. Although no immunology investigations were performed except a single mast cell tryptase level, the culprit agent was relatively easy to identify, due to the small number of drugs administered before the onset of symptoms.

Causitive agents

The causative agents are shown in Table 2. The culprit was identified by the review panel in nine cases at the definite or probable level. In the final case rocuronium and amoxicillin were both judged possible triggers as a result of which (see Chapter 5, Methods) causation could not be confirmed. In all cases the anaesthetist's suspected agent was confirmed as the most likely agent by the panel.

Table 2. Culprit agents in cases of fatal anaphylaxis in NAP6

	Agent	Certainty of culprit
NMBAs 4	Rocuronium 3	1 definite, 2 probable
	Suxamethonium 1	1 definite
Antibiotics 3	Teicoplanin 2	2 probable
	Co-amoxiclav 1	1 definite
Other 2	Geloplasma 1	1 definite
	Chorhexidine 1	1 probable
Uncertain 1	-	Rocuronium and amoxicillin both possible

A patient had central neuraxial anaesthesia and general anaesthesia. Hypotension required significant vasopressor use. A gelatin-containing IV fluid was administered. Severe hypotension and cardiac arrest occurred. Subsequent testing confirmed anaphylaxis to the IV gelatin.

Clinical features

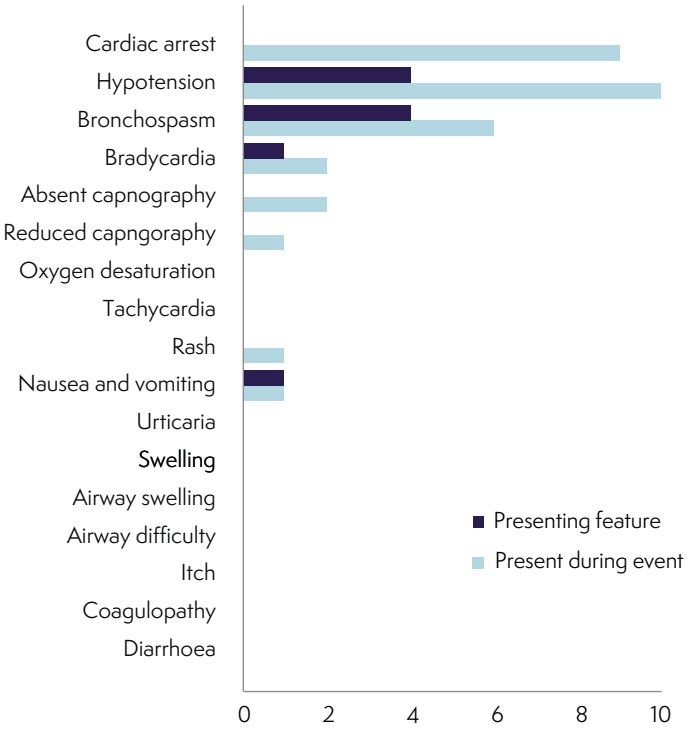
Onset was judged to be within 5 minutes of administration of the trigger agent in seven cases and within 10 minutes in three. A critical event was recognised within 5 minutes in eight cases and within 10 minutes in all cases. Anaphylaxis was suspected rapidly in nine cases but in one case it was not considered for up to an hour, because of potential confounding diagnoses.

The presenting feature was bronchospasm in four cases (and 18% of all NAP6 cases), hypotension in four (and 46% of all NAP6 cases), bradycardia in one and nausea/vomiting in one (Figure 2).

All cases had hypotension, six had bronchospasm, four bradycardia (two in patients not on beta-blockers), three a reduced or absent capnography trace, two oxygen desaturation and one each of tachycardia, rash, and nausea and vomiting. Seven patients became hypoxic in the hour after the event. There were no cases of urticaria, swelling, stridor, diarrhoea, itch or coagulopathy (Figure 2).

There were no reports of airway swelling. One patient was intubated and one re-intubated. There were no reports of airway difficulty. The panel judged airway management to be appropriate in all cases.

Figure 2. Clinical features at presentation and during ten fatal anaphylaxis events



Nine of ten patients experienced cardiac arrest at the time of the event, and the final patient was established on cardiopulmonary bypass as part of resuscitation. There were no significant arrhythmias preceding the nine cardiac arrests. Cardiac arrest was preceeded by prolonged hypotension in four cases and by prolonged hypoxia (and hypotension) in one. Cardiac arrest occurred within 5 minutes of administration of the suspected culprit drug in seven cases and within 10 minutes in all cases where it occured. Cardiac arrest was PEA in all cases, in two preceded by bradycardia.

Immediate management was prompt in all but one case. Assistance by other healthcare staff was sought in four cases. All resuscitation followed a guideline – either the AAGBI anaphylaxis or Advanced Life Support guidelines (seven from a laminate, one from an anaphylaxis pack and two from memory). Assistance was effective in all nine cases where this was recorded.

Adrenaline was administered IV in all cases, including an infusion in five cases. A median of five doses and 5 mg adrenaline was administered (range 2–13 mg). No patient received intramuscular (IM) adrenaline. Ephedrine, metaraminol, glycopyrrolate and atropine were used early in resuscitation and other notable drugs included noradrenaline infusions in five cases, vasopressin infusion in one case and glucagon in one case. In this last case glucagon was administered more than an hour after the event occurred. Approximately half of cases received chlorphenamine and hydrocortisone. Sugammadex was not used.

> A patient due for cardiac surgery had a cardiac arrest as a result of anaphylaxis. Resuscitation included almost an hour of CPR, ECMO, cardiac catheterisation and placement of cardiac stents.

Resuscitation was prolonged and extensive. It was started promptly in all cases except one where this was uncertain. Cardiopulmonary resuscitation (CPR) took place for a median 39 minutes, and in all cases, except one of the delayed deaths, was required for more than 25 minutes. Resuscitation included extra corporeal membrane oxygenation (ECMO) in one case and immediate cardiac catheterisation to explore or manage a potential acute coronary syndrome in two cases.

Fluids administered during resuscitation were predominantly crystalloids but included: crystalloids in all cases, a gelatin in two cases, and blood and blood products in one case each. 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), with only one patient receiving more than 4L in total.

Five patients did not survive initial resuscitation, while five did, one of whom died soon after. Of the four remaining patients, all were admitted to ICU and all survived at least one week, but all deaths occurred in less than 30 days. Four patients had multiple organ falure prior to death.

At least one mast cell tryptase (MCT) sample was sent in all cases (3 samples in three cases, 2 samples in two and 1 sample in five). A dynamic change in MCT was identifiable in five cases. The first (and peak) levels had a median of 198 mcg/L, (range 11.6–300 mcg/L). No samples for specific IgE were taken. No patient was referred to or discussed with an allergy clinic. The review panel, with limited data available, judged four cases to be allergic anaphylaxis, five to be unspecified anaphylaxis and one was classified as uncertain.

Three cases were reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and eight through the trust reporting systems.

Overall care by the anaesthetic team was judged 'good' in six cases and 'good and poor' in four. Inadequate fluid administration was a recurrent theme. Good elements of care were: appropriately senior resuscitator (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).

No reports of post-mortem examinations were provided.

Cardiac arrest and profound hypotension

Profound hypotension

Amongst 255 adult patients reported to NAP6, hypotension was universal in the hour after the event started. In 190 (74%) cases the lowest recorded blood pressure was ≤60 mmHg.

Amongst all 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. CPR was initiated in 28 (50%) of those with an unrecordable blood pressure, in five (9%) with blood pressure <50 mmHg, and in two (3.8%) with lowest blood pressure 50–59 mmHg.

The panel, after taking external expert advice, used a cut-off of 50 mmHg as the point at which CPR was indicated in adult patients. So, when a lowest blood pressure was <50 mmHg and CPR was not started, this was deemed to be suboptimal care. Of 114 cases with lowest blood pressure of <50 mmHg or unrecordable, 78 were reviewed in full. CPR was initiated in 33 (29%) and this was judged prompt in 26 (79% of cases in which CPR was started). Overall, prompt CPR (when the blood pressure was <50 mmHg) was reported in 23% of cases. This was the sole deviation from Resuscitation Council (UK) guidelines in only 12 cases.

In this same group of patients, all 78 were judged to have been resuscitated by an anaesthetist of an appropriate grade. Airway management was deemed appropriate in 69/71 (97%) of evaluable cases. Pharmacological treatment was judged not prompt in 14/68 (21%) of evaluable cases. In 13/78 (17%) cases adrenaline administration was judged to be inadequate. Fluid administration was deemed adequate in 54 (71%) of 78 evaluable cases and inadequate in 18 (24%). In 55/78 of fully reviewed cases there was an opportunity to abandon the cases: this was done in 51 (93%) and not done in four (7%) cases. Of these four patients one developed post-traumatic stress disorder, but the others had no sequelae. Overall quality of initial management of this group of patients with profound hypotension was judged as 'good' in 22 (28%), 'good and poor' in 37 (47%) and 'poor' in 19 (24%).

Amongst these 114 patients with blood pressure <50 mmHg or unrecordable, 90 culprit drugs (65 at the definite and 25 at the probable level) were identified in 87 patients. Culprit agents were 42 antibiotics, 31 NMBAs, 8 chlorhexidine, 5 Patent Blue dye and 4 others – a similar distribution to cases without profound hypotension.

Patient characteristics, quality of care, outcomes and causative agents for patients who died, survived cardiac arrest, had profound hypotension without cardiac arrest and others are summarised in Tables 3, 4 and 5.

Table 3. Characteristics of patients who died, compared to those who survived cardiac arrest, or 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%

Table 4. Quality of resuscitation and outcomes in 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)	BP <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				
Median severity of harm	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

Table 5. Distribution of culprit agents in 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)	BP <50 mmHg without cardiac arrest or death (n=79)	All others (n=135)
Patient characteristics				
Antibiotic	33%	58%	40%	48%
NMBA	44%	38%	27%	29%
Chlorhexidine	11%	4%	9%	10%
Patent Blue	0%	0%	6%	5%
Other	11%	0%	3%	7%

Cardiac arrest

Forty (15%) patients, all of whom were adults, were deemed to have experienced a cardiac arrest, including nine of the patients who died. Thirty-one (77.5%) survived. Survivors of cardiac arrest were younger, fitter and less co-morbid than patients who died (Table 3).

Patients were female in 26 cases (65% in this cohort vs 59% in Activity Survey Chapter 8), obese in 22 (55% vs 49%), British or Irish white in 34 of 36 reporting ethnicity (95% vs 87%), aged over 65 years in 15 of 39 reporting age (38% vs 28%), and ASA 3–5 in 12 of 39 reporting ASA class (31% vs 21%). Patients' admissions were as an emergency in three of 37 reporting this information (8% vs 24%) and surgery was urgent or emergency in three of 39 (8% vs 14%). Ten per cent were undergoing cardiac surgery.

Five patients had asthma (12.5% vs 21% of all NAP6 cases), seven of 34 had coronary artery disease (21% vs 15%), seven of 37 were taking beta-blockers (19% vs 18%) and 14 of 37 were taking ACE inhibitors (38% vs 17%).

The event occurred after induction of anaesthesia and before surgery in 26 (81%) of 32 cases where this was reported, during surgery in four, before induction in one and after surgery in one. The location of the event was equally distributed between anaesthetic room and operating theatre. Most events (95%) occured during a weekday. A senior specialist registrar was responsible for one patient while all others were cared for by trained anaesthetists, and a consultant was involved in all resuscitations.

Drug administration did not differ dramatically in this cohort compared with either the Allergen Survey (Chapter 9) or other NAP6 cases (propofol 92%, opioid 95%, antibiotics 60% – commonest antibiotics coamoxiclav and teicoplanin, 16% with a test dose, local anaesthesia 38%). Modest differences occurred in NMBA use (78% of cardiac arrests vs 67% of all NAP6 cases) and in the use of rocuronium (47.5% of cardiac arrests vs 30% of all cases in NAP6).

The presenting features are shown in Figure 3 – hypotension (16 (40%) cases) and bronchospasm/raised airway pressure (8 (20%) cases) were prominent, and rash uncommon (1 case). Bradycardia was more common that tachycardia. Cardiovascular presenting features occurred in 25 (62.5%) cases, respiratory in 11 (27.5%) and others in four.

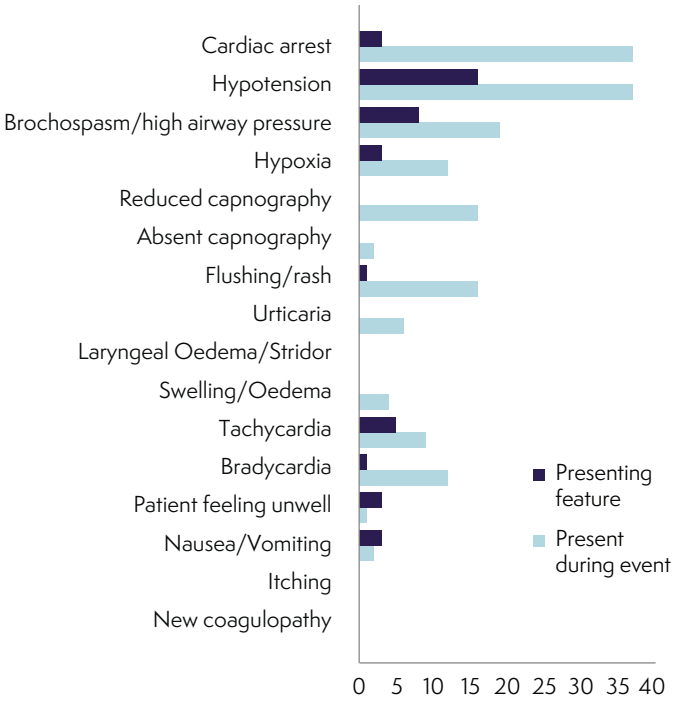
Only six patients developed an arrhythmia prior to cardiac arrest: four bradycardia and two ventricular tachycardia (VT). There were no reports of atrial fibrillation or supraventricular tachycardia.

Types of arrest were PEA (including profound bradycardia) in 34 cases (85%), VF/VT in four (10%) and asystole in two (5%). Of those nine patients who died and had a cardiac arrest at the time of the anaphylactic episode all were PEA, two with profound bradycardia. In all cases where the cardiac arrest was VF/pulseless VT, the presenting feature of the anaphylactic event was tachycardia. None of these patients were elderly or had known coronary artery disease. Fifteen of 40 cardiac arrests were preceded by prolonged

hypotension and two by hypoxia. In four (10%) of cardiac arrests initial treatment of anaphylaxis was delayed, in one case by loss of venous access in a morbidly obese patient.

Clinical features, presenting and during the event, are shown in Figure 3. Hypotension was universal and bradycardia occurred in twelve (30%) cases, slightly more often than tachycardia, which occurred in nine (22.5%) cases. Rash occurred in 16 (40%) patients and oedema in only four, with several comments that cutaneous features did not occur until blood pressure was restored. Reduced and absent capnography traces were seen in 16 and two cases respectively.

Figure 3. Clinical features of 37 cardiac arrests from perioperative anaphylaxis



Hypoxia in the hour after the event was common (75%), and was more common than in patients who did not arrest (40%).

Neither airway swelling nor airway difficulty were seen in any case. Seven patients were intubated during the event (all without difficulty), two patients were managed with a supraglottic airway throughout, and two had a supraglottic airway changed to a tracheal tube. No difficulty was reported, and there were no cases requiring a front of neck airway.

The event was recognised as a clinical emergency in less than 5 minutes in 82% of cases, and as anaphylaxis in less than 5 minutes in 69%, in less than 10 minutes in 90%; in only one case did the diagnosis of anaphylaxis take more than 60 minutes. Delay in managing anaphylaxis in three (7.5%) cases was due to slow diagnosis or uncertain diagnosis (one case each) and loss of IV access (one case).

Assistance was called in 30 cases. The theatre team contributed in all cases: fully in 37 cases and partially in three. An anaphylaxis or cardiac arrest algorithm was used in 35 (88%) cases. A laminate (17 cases), memory (11 cases) or smartphone (four cases) were the common sources.

On average five doses of IV adrenaline were administered (mean 5 mg, range 0–13 mg). Half of survivors received an adrenaline infusion after initial resuscitation. Adrenaline was administered IM once and IO once. Amongst other drugs metaraminol (given early) was administered to 20 patients, ephedrine (early) to eleven, noradrenaline to 15, vasopressin to two, glucagon to one, intralipid to two and sugammadex to one. Chlorphenamine and steroid were given to approximately 75% of patients during resuscitation.

A median volume of 1.75L (range 0–4.5L) fluid was administered during the first hour, and 3.25L (range 0–9.5L) during the first five hours. Seven patients received an IV gelatin during resuscitation and none a starch.

CPR was often only briefly required: median 8 minutes (interquartile range 2–8 minutes) in survivors, but prolonged in many fatal cases (see above).

Quality of resuscitation is summarised in Table 4.

The surgical procedure was usually abandoned. In 28 cases surgery was abandoned before starting, in three after starting and in two the procedure was modified. In six cases the procedure was not abandoned or modified: in three it was already complete, in two it was completed (one patient survived surgery but had a delayed death) and in one case there were no details provided.

Most (91%) of survivors were transferred to critical care: 90% as Level 3 patients and 10% as Level 2 (none of whom required an increase in level of care). While in critical care vasopressors were required for 61% of survivors and bronchodilators in 6%. Typically, patients spent one day as a Level 3 patient and one as a Level 2 patient, and then were discharged. The longest length of unplanned stay was nine days in critical care (two patients) and 17 days in hospital.

There were no episodes of recrudescence of anaphylaxis.

Harm, as a result of the anaphylactic event, was judged to occur in 10 (32%) of 31 survivors. Details of sequelae were only reported in a minority of patients. Eleven of 14 reported new anxiety (three severe, five moderate, four mild) and five of 16 reported a change in mood (one severe, two moderate, two mild). Other sequelae were impaired memory (3 of 16), impaired coordination (2 of 17), impaired mobility (1 of 16) and symptoms of post-traumatic stress disorder (3 of 12). Myocardial damage (2 of 16), heart failure (2 of 16) and new renal impairment (3 of 19) were reported. One patient had new shortness of breath. None reported evidence of stroke. It was not clear in those who did not report outcomes whether there were no sequelae or these were simply not reported.

Nine (29%) of 31 survivors were reported to the MHRA and 24 (77%) through local reporting processes. All but one patient were referred to an allergy clinic. Two patients underwent further anaesthesia before this appointment, both without further anaphylaxis.

Table 6. Sequelae reported as a consequence of anaphylaxis in 266 patients: reported before clinic referral/at the time of clinic investigation

	Altered mood	Altered memory	Altered coordination	Altered mobility	Anxiety	Features of post-traumatic stress disorder	Myocardial infarction	Cardiac failure	Cerebro-vascular event	Acute kidney injury	ANY
Mild	7/7	4/4	1/0	2/2	43/20	1/1	2/3	3/3	0/0	4/1	67/41
Moderate	7/5	1/2	1/2	1/1	11/13	6/2	1/0	0/1	0^/0*	1/1	29/27
Severe	1/0	0/0	0/0	0/1	5/3	0/0	1/0	0/0	0/0*	1/1	8/5
All	15/12	5/6	2/2	3/4	59/36	7/3	4/3	3/4	0/0*	6/3	104/73

*^One pre-existing CVE is not included. *One CVE occurring weeks later is not included.*

A healthy patient underwent minor elective surgery. Grade 4 anaphylaxis developed after induction and administration of antibiotics. The first presenting feature was desaturation, and a PEA cardiac arrest developed requiring several minutes of CPR and administration of multiple doses of adrenaline. After resuscitation, surgery was completed and the patient was transferred to ICU requiring a vasopressor infusion. The patent was in critical care for one day and was discharged home soon afterwards. Allergy testing confirmed allergic anaphylaxis to the antibiotic. The patient did not have physical sequelae but developed a significant change in mood and severe anxiety about future anaesthesia, with some features of post-traumatic stress disorder.

Outcomes: all patients

We asked about physical and psychological sequelae after the event. Data were recorded poorly, so any estimates must be judged as minima. Sequelae were reported by 65 patients when Part A was completed before allergy clinic referral and by 40 patients when Part B was completed at the time of allergy clinic investigation (a mean 101 days later), suggesting some improvements over time. Complications recorded in Part A included 104 sequelae (67 mild, 29 moderate and eight severe) and in Part B 73 sequelae (41 mild, 27 moderate and five severe) (Table 6).

Anxiety about future anaesthetics was the most commonly reported consequence, accounting for more than half of longer term consequences, in three cases this extended to symptoms of post-traumatic stress disorder. Ten patients reported problems with mood, memory or coordination. There were thirteen reports of myocardial infarction, acute kidney injury or new shortness of breath. Two strokes that occurred several weeks or months after the anaphylactic event were not judged related to it.

Data on length of stay was available for most (78%) of patients reported to NAP6. In spite of the life-threatening nature of all the perioperative anaphylaxis reviewed in NAP6 one quarter of all patients had a normal outcome and length of stay was not extended. Thirty-seven per cent had their length of stay increased by one day and 38% by more than this.

Table 7. Additional length of stay (LOS) and degree of harm in survivors of life-threatening anaphylaxis

Extended LOS due to anaphylaxis	Number (%)	Level of harm	None/ mild	Moderate	Severe
Reported in 199 (78%)	-	Reported in 127 (64%)	-	-	-
0 day	49 (25%)	30	24 (80%)	6 (20%)	0 (0%)
1 day	75 (38%)	48	33 (69%)	15 (31%)	0 (0%)
>1 day	75 (38%)	49	24 (49%)	24 (49%)	1 (2%)

Discussion

This chapter is lengthy and has reported the details of patients who died or nearly died in some detail. We judge that the findings of NAP6 add considerably to the existing literature in this area.

We report a 3.8% fatality rate after Grade 3–5 perioperative anaphylaxis. A retrospective report from Western Australia reported no deaths between 2000 and 2009 from 264 'perioperative anaphylaxis cases' – a mortality rate of 0% with the upper limit of the 95% confidence interval being 1.4% (Gibbs 2013). In the Australian series of 264 cases, 175 (66%) were IgE mediated with the other third of cases being of lower severity. Almost half of all cases were Grade 1–2, only 8% required CPR, surgery was abandoned in only 34%, and only 38% were admitted to critical care post-operatively. It is therefore arguable that not all of these cases would meet strict definitions of anaphylaxis which includes only Grade 3–4 cases, and it is likely that the severity of reactions is less than in the NAP6 cohort. In Gibbs' paper there is limited patient data provided, but median age was 45 years and patients were therefore also somewhat younger than the NAP6 cohort.

Reported mortaliy rates are dependent on a number of factors, including:

- The definition of perioperative anaphylaxis used
- The grades of anaphylaxis included
- The patient case mix
- The causative agents
- The methodology of the study.

Many series include milder grades of hypersensitivity than NAP6, which only included life-threatening anaphylaxis (Grade 3-5). Other series, that only review cases referred to allergy clinics, or only review deaths within a certain timeframe after anaesthesia, will be likely to miss many fatalities. In NAP6, using a prospective methodology and without such time limits, we believe that we have captured all deaths from suspected perioperative anaphylaxis.

It is notable that those patients who died were older, more co-morbid, more obese and more likely to be taking beta-blockers and ACE inhibitors than both survivors of cardiac arrest and others who did not develop cardiac arrest. Reitter previously reported cardiovascular disease, obesity and use of beta-blockers as risk factors for fatal anaphylaxis from NMBAs (Reitter 2014). The events were rapid and severe, with most fatal cardiac arrests occurring within five minutes of drug administration, consistent with previous data (Pumphrey 2000). Resuctitation was performed by senior clinicians, followed guidelines and was prolonged with evidence of considerable efforts being made to save patients' lives. Of those who died almost half reached critical care and these patients generally died of multi-organ failure at least a week later, often with the decision to withdraw treatment being influenced by the patient's poor general pre-morbid condition.

Our data showed that a higher percentage of patients on beta-blocker medication died during the anaphylactic episode. Glucagon was used in only one of these patients. Beta-blockers are known to be associated with increased risk of fatal anaphylaxis (Brown 2004, Simons 2011, Reitter 2014). This in part is attributed to reduced efficacy of adrenaline secondary to beta receptor blockade, and expert recommendation is to consider use of glucagon in patients on concurrent beta-blocker medication. This was rarely done in NAP6.

A significant proportion of patients who died did not receive steroids or chlorphenamine during resuscitation. Focus on resuscitation from cardiac arrest may have distracted from following anaphylaxis guidelines. We do not know what impact this omission may or may not have had on outcomes.

Amongst the clinical features of fatal anaphylaxis or anaphylaxis leading to cardiac arrest, rash, oedema and urticaria were uncommon. Airway swelling was absent. Rash and swelling sometimes presented only after resuscitation and an effective circulation had been re-established. This finding presumably relates to the very profound low cardiac output state seen in severe anaphylaxis, and has been noted before (Krøigaard 2007) but may not be widely appreciated. It is important because the lack of a rash or swelling may hamper early diagnosis of anaphylaxis, and later swelling may necessitate both careful assessment of the airway and liberal fluid administration – which was absent in many cases in NAP6.

Few cases of fatal anaphylaxis or cardiac arrest were associated with reports of reduced or absent capnogram, and this was seen overall in 30% of cases in NAP6. While a recent report suggested that a low capnography value may be of use in diagnosing severe anaphylaxis (Gouel-Cheron 2017), NAP6 has not confirmed this. There are several possible reasons for this discrepancy, including failure to detect changes and prompt resuscitation – this is discussed further in Chapter 10, Clinical features.

Cardiac arrest was recorded in 15% of patients reported to NAP6. Management of patients with cardiac arrest was generally led by a senior clinician, was prompt, and followed established guidelines. Almost 80% of patients survived, and those that did survive came to little harm. Delayed treatment of anaphylaxis may have contributed to the development of cardiac arrest in four cases, of which delayed diagnosis may have been responsible in three patients. This should not be interpreted as criticism of the anaesthetist: delayed diagnosis is unavoidable in many cases of perioperative anaphylaxis. In some cases cardiac arrest was initially thought to have had a primary cardiac cause until anaphylaxis was considered, and in co-morbid elderly patients making the diagnosis in these circumstances can be difficult.

Cardiac surgery was the setting for 30% of fatal anaphylaxis and 10% of anaphylaxis associated with cardiac arrest. As cardiac surgery accounts for less than 1% of all surgical workload, it is over-represented, and this may indicate a high risk for anaphylaxis or poor outcomes for those who develop it in this setting – where diagnosis may be particularly hard, as a primary cardiac cause for deterioration is so much more likely.

Cardiac arrest was PEA in the vast majority of cases, and preceding arrhythmias were very infrequent. No adrenaline-induced tachyarrythmias were reported, and this suggests that the benefit of administering adrenaline IV in life-threatening anaphylaxis far outweighs any risk, including in elderly patients and those with cardiac disease. Cardiac arrest was generally preceded by hypotension, and in many cases occurred within five minutes of drug administration. While most anaesthetists were prompt in responding to the critical incident and in administering anaphylaxis-specific medication, these data emphasise the need to give adrenaline as soon as possible (intravenously in an anaesthetic context) and to administer liberal fluids. Overall fluid administration in NAP6 was often inadequate, and volumes administered in patients with profound hypotension were not markedly larger than in patients with milder reactions.

Survivors of cardiac arrest were notably younger and fitter than those who died, and were resuscitated with only short periods of CPR. In contrast older age and co-morbidity, especially coupled with a need for prolonged CPR after perioperative anaphylaxis, may be signs of likely poor outcome.

Early in the review process it became apparent that patients with profound hypotension were not receiving CPR. The review panel sought expert external opinion concerning the threshold blood pressure below which cardiac compressions should be started. There was consensus that, in adults, systolic blood pressure below 50 mmHg is an indication for initiating cardiac compressions, unless there are contraindications. Deakin and Low demonstrated that this threshold results in a 90% positive predictive value for absent carotid, radial and femoral pulses, even with invasive arterial monitoring (Deakin 2000). Non-invasive blood pressure monitoring, likely to be in use in most cases, will overestimate systolic blood pressure during hypotension (Lehman 2013). The review panel attributed Grade 4 severity to these patients. As a result, 85 of the 216 cases (39%) reported as Grade 3 by the anaesthetist were designated Grade 4 by the review panel.

This group of patients with profound hypotension but without clear cardiac arrest were the group for whom management was least good. As most cardiac arrests in NAP6 were PEA, there is likely to be a continuum of increasing low flow states from severe hypotension to cardiac arrest. Despite equally rapid recognition of a critical incident and diagnosis of anaphylaxis in this group, delayed treatment and delayed adrenaline administration was common, delayed CPR was almost ubiquitous, and treatment was only judged good in 1 in 12 cases. It is likely that our declaration that all patients with a blood pressure less than 50 mmHg require CPR will be controversial, but we welcome the debate. This group of patients could have been managed better and sequelae may have been prevented.

The decision whether to continue with or abandon a procedure when anaphylaxis occurs can be a difficult one. In the vast majority of cases in NAP6 where there was cardiac arrest or profound hypotension, the procedure was abandoned when this was feasible. With the majority of patents in this setting requiring management in critical care and more than half an infusion of vasopressors, there seems little rationale to continue except in the setting of life-saving surgery. This is discussed further in Chapter 11, Immediate management and departmental organisation.

Survival from life-threatening anaphylaxis can always be considered a success, but our evidence suggests this is a crude outcome measure. There was evidence of good-quality extensive care for the majority of patients, including those who died. Typically, patients spent one day as a Level 3 patient and one as a Level 2 patient and then were discharged. However, we have identified a significant burden of sequelae and harm consequent on these events. This has included death, multi-organ failure, cardiac and kidney injury, and a significant psychological burden on survivors. It is highly likely that our data represent minimum levels of harm. A particular finding has been anxiety about future anaesthesia, and it is not clear what services are in place to identify or manage this. These findings are likely novel, and merit further exploration in future studies.

Mast cell tryptase levels were available for all patients who died from anaphylaxis, and this helped considerably in confirming the diagnosis. The vast majority of patients with the most profound perioperative anaphylaxis were referred for specialist allergy clinic investigation. However, none of the patients who died appeared to be referred or discussed. The diagnosis of anaphylaxis may be assisted by mast cell tryptase levels taken acutely, post mortem (Pumphrey 2000, Low 2006) or from pre-event samples to act as a baseline (See Chapter 14, Investigation). Blood tests to identify specific IgE antibodies to potential culprits may also have value. Early discussion with a specialist allergy clinic may therefore be useful.

Culprit agents for severe and fatal perioperative anaphylaxis were generally consistent with those identified elsewhere in NAP6. However, NMBAs (especially rocuronium) appeared somewhat more frequently in cases of anaphylaxis leading to death or cardiac arrest than in other groups. The numbers are too small for statistical analysis or robust conclusions, but it is a notable finding.

Only one patient who died was reported to have undergone a post mortem examination and details were not provided. With the current limited data on post mortem findings after fatal perioperative anaphylaxis, learning from such examinations has the potential for increasing our knowledge-base and perhaps facilitating post mortem diagnosis in unexplained deaths in the future. Post mortem examination should therefore be encouraged.

Reporting of these incidents to the MHRA was limited – even for cases resulting in cardiac arrest or death. Without significantly improved reporting, the data held by the MHRA is unlikely to be accurate or particularly useful in determining risks and trends. This is discussed in detail in Chapter 24, Reporting and learning.

Recommendations

(Severe perioperative anaphylaxis here refers to perioperative anaphylaxis requiring CPR or with profound hypotension (eg. systolic blood pressure <50 mmHg)).

- In patients who experience perioperative anaphylaxis with a high risk of adverse outcome (elderly, obese, ASA >=3, patients taking beta-blockers or ACE inhibitors, or prolonged CPR), anaesthetists should be prepared to escalate treatment early
- During anaphylaxis with a systolic blood pressure of less than 50 mmHg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with adrenaline and liberal IV fluid administration
- During perioperative anaphylaxis in patients taking beta-blockers, early administration of IV glucagon 1 mg, repeated as necessary, should be considered
- Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory
- The need for a vasopressor infusion should be anticipated after severe perioperative anaphylaxis
- Non-essential surgery should not be started after severe perioperative anaphylaxis
- Where severe perioperative anaphylaxis occurs during non-essential surgery the operation should be curtailed unless there is an overriding reason to continue
- Patients with severe anaphylaxis should be admitted to critical care
- While it is not possible to be definitive about how long a patient should be observed after Grade 3–4 perioperative anaphylaxis, it would seem imprudent for them to be discharged on the same day as the event
- All cases of severe perioperative anaphylaxis, including fatalities, should be discussed with an allergy clinic at the first available opportunity.

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Transfer to critical care after perioperative anaphylaxis is the norm