2 Key findings and recommendations

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This chapter collates the key findings from each chapter and the resultant recommendations. Key findings and recommendations are arranged by chapter, resulting in a small amount of repetition. Not all chapters resulted in recommendations.

Key findings

Perspectives of perioperative anaphylaxis before NAP6

- 11,104 anaesthetists (77% crude response rate) from 341 (96%) hospitals responded.
- Most had immediate access to guidelines for anaphylaxis treatment (87%) and established referral pathways for investigation (82%), but a minority reported access to designated treatment packs (37%) or an anaphylaxis lead (35%).
- During their career, 76% of respondents had seen a case of perioperative anaphylaxis (1: 7.25 years of practice) and 4% reported a death (1: 311 years of practice), equivalent to 2.3% of events being fatal.
- Agents most frequently perceived to cause anaphylaxis were antibiotics, particularly penicillins, and neuromuscular blocking agents (NMBAs), notably rocuronium.
- Suxamethonium and penicillins were avoided by a higher proportion of respondents than events attributed to these drugs, while the converse was true for atracurium and teicoplanin.

The Activity Survey

As part of the NAP6 project we surveyed 356 National Health Service hospitals to determine anaesthetic activity in October 2016:

- Responses were received from 342 (96%) hospitals, and each reported an estimated 96% of their cases.
- The total annual anaesthetic workload is ≈3.13 million cases.
- Approximately 95% of elective work, 72% of emergency work and 87% of all work is performed on weekdays.
- Senior anaesthetists lead ≈90% of cases, and those with less than two years anaesthetic experience lead less than 1%.
- During weekends the urgency of work increases, the proportion of healthy patients reduces and the case mix changes.
- Senior involvement, including higher-risk cases at the weekend, remains high but falls through Saturday (89%) and Sunday (65%).
- Obstetric anaesthesia care is evenly distributed through the week and is associated with the lowest levels of senior anaesthetic involvement (69%), especially at weekends (45%).
- Senior involvement in emergency orthopaedic procedures is high during the week (93%) and at weekends (89%).
- We noted increases in the proportion of patients with obesity and in elective weekend working compared with data from 2013.
- Depth of anaesthesia monitoring has increased but neuromuscular monitoring has not, suggesting that current guidelines are not implemented.

The Allergen Survey

- Details of current UK drugs and allergen exposure were needed for interpretation of reports of perioperative anaphylaxis to the 6th National Audit Project (NAP6).
- We surveyed UK NHS hospitals for this purpose. Where relevant we compared these results with those of NAP5.
- From 342 (96%) hospitals we collected 15,942 forms: equating to an annual caseload for anaesthetists of 3,126,067, including 2,394,874 general anaesthetics (GAs).
- Propofol was the dominant induction agent (90.4%), and was used more often in caesarean section than in NAP5.
- Nitrous oxide use has fallen 30% since NAP5.
- Neuromuscular blocking agents were used in 47.2% of GAs. Suxamethonium use has fallen.
- Use of reversal agents is overall unchanged, but sugammadex use increased fourfold.
- Analgesics were used in 88% of cases: opioids 82.1%, paracetamol 56.1%, and non-steroidal anti-inflammatory drugs (NSAIDS) 28.3%. Local anaesthetics were used in 74.2% of cases and 68.9% of GAs.
- Anti-emetics were used in 73.1% of cases: during GA, ondansetron in 78.3% and dexamethasone in 60.4%.
- Overall antibiotic use was 57.2% of cases, with more than 3 million annual perioperative administrations: gentamicin (19.7% of uses), co-amoxiclav (17.0%), and cefuroxime (13.6%) were prominent.
- In 25% of teicoplanin or vancomycin uses, allergy history influenced drug choice.
- Chlorhexidine and iodine exposure were reported as 73.5% and 40.0% of cases respectively, and a latex-free environment in 21.2%.

- Blood products were used in ≈3% of cases, synthetic colloids in less than 2% (starch in only 1 in 600 cases), tranexamic acid in ≈6%.
- Exposure to bone cement, blue dyes and X-ray contrast were each reported in 2–3% of cases.
- This extensive national survey of anaesthetic practice provides detailed data on drug uses and allergen exposures in perioperative care. It is important for use as the denominator in the main NAP6 analysis and the data provide significant insights into many aspects of perioperative practice.

Clinical features

- Perioperative anaphylaxis is a clinical diagnosis, and presenting features may have many other causes that are more frequent than anaphylaxis. Despite this, early recognition and treatment of anaphylaxis during anaesthesia is essential for avoiding harm.
- In NAP6, of all perioperative anaphylaxis cases, 58% occurred in women. However, the proportion of women experiencing anaphylaxis was similar to the proportion of women undergoing anaesthesia and surgery.
- Hypotension was the presenting feature in 46% of anaphylaxis cases, and occurred during the episode in all cases.
- Hypotension was common in patients with coronary artery disease and those taking beta-blockers or ACE inhibitors. Outcomes in these patients were poor.
- Bronchospasm/high airway pressure was the presenting feature in 18% of cases and occurred in 49%.
- Bronchospasm/high airway pressure was a more common presenting feature in patients with asthma and in obese/morbidly obese patients than in those without these characteristics.
- Urticaria and flushing/non-urticaria rash were uncommon presenting features, even in patients with a past medical history of urticaria.
- Skin signs were uncommon in the more severe cases of anaphylaxis, sometimes only occurring after resuscitation.
- A reduced or absent capnograph trace was reported in only 30% of cases.
- An unrecordably low oximetry recording was associated with severe reactions, and especially with respiratory features, and led to prompt treatment by anaesthetists.
- A small number of patients presented with isolated cardiovascular or isolated respiratory features. Anaesthetists should bear this in mind in the early recognition of perioperative anaphylaxis.
- Anaphylaxis presented within 10 minutes of exposure to the culprit agent in 83% of cases. In less than 2% the presenting feature was delayed beyond 60 minutes.
- Anaphylaxis induced by neuromuscular blocking agents (NMBAs) occurred rapidly. Hypotension was a common presenting feature particularly with atracurium-induced anaphylaxis, whereas bronchospasm/high airway pressure was more common with suxamethonium-induced anaphylaxis.
- Antibiotic-induced anaphylaxis presented almost uniformly rapidly, and hypotension was the common presenting feature.
- Anaphylaxis caused by chlorhexidine and Patent Blue dye had a rather slower onset: hypotension was the commonest presenting feature and bronchospasm was not seen.

Immediate management and departmental organisation

- All patients were resuscitated by an anaesthetist of appropriate grade, and recognition of a critical event was prompt.
- The first clinical feature of anaphylaxis appeared in less than 5 minutes in 66% of cases, in less than 10 minutes in 83%, in less than 15 minutes in 88%, and after more than 30 minutes in 4.6%.
- Recognition of a critical event and of anaphylaxis was generally very prompt.
- There was delay in starting anaphylaxis-specific treatment in 25% of cases, illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis.
- Airway management was generally uncomplicated and without difficulty. A single front of neck airway was judged the only case of airway morbidity associated with anaphylaxis.
- When cardiac compressions were indicated there was delay starting them in more than half of cases.
- Vasopressin and glucagon were very rarely used.
- Fluid administration was frequently judged to be insufficient and was inappropriate in 19% of cases.
- The review panel judged management to be 'good' or 'good and poor' in 85% of cases.
- Careful examination of the role of antihistamines found no evidence of harm, and could not exclude evidence of benefit.
- 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.
- Six per cent of survivors underwent surgery between the index event and the patient being seen in clinic. This was uneventful in every case.

Deaths, cardiac arrest, profound hypotension and outcomes

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

- Most patients with severe perioperative anaphylaxis were well managed in terms of recognition of the event, recognition of anaphylaxis, and 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, and 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 CPR was uncommon in survivors of cardiac arrest during anaphylaxis (median 8 minutes) and universal in those who died (all >25 minutes).
- Following resuscitation from cardiac arrest, most patients required vasopressor infusions, but few stayed in 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 associated with cardiac arrest: presentation with a respiratory feature was less common.
- Hypotension was universal in cases of Grade 3–5 anaphylaxis.
- Hypoxia was an uncommon presenting feature, but 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 of 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, NMBAs were more commonly culprit agents, though strong conclusions cannot be drawn.

Investigations

- The average wait time before being seen in allergy clinic was 101 days (range 0–450 days). Only 39 (16%) were seen within the ideal six weeks; 23% breached the national UK 18-week target for first appointments, and 7% waited longer than six months.
- Waiting times for urgent referrals were not shorter than for non-urgent referrals.
- Regarding mast cell tryptases (MCTs):
  - At least three MCT samples were available in 67% of cases, two in 19% and one in 8%
  - Forty-five per cent of early samples met British Society for Allergy and Clinical Immunology (BSACI) guidance for 'immediate' sampling, and 76% met Australian and New Zealand College of Anaesthetists (ANZCA) guidelines
  - Earlier samples gave higher MCT levels, which rapidly fell within 30 minutes
  - Median first MCT levels rose with reaction grade, though this was less clear for peak levels
  - MCT level did not correlate with severity of clinical features
  - While median MCT values differed between trigger agents, the differences were not statistically significant
  - The Dynamic Tryptase algorithm [(baseline tryptase x 1.2) + 2 mcg/L] was found useful for detecting mediator release, especially when peak tryptase was within the reference range, and increased yield by 16%.
- Clinic investigations adhered fully to AAGBI guidance in 32% and to BSACI guidance in 17%. Most non-adherence was through failing to test for all potential culprits and poor communication.
- All potential culprit agents had been adequately investigated in only 27%.
- Ten per cent of assessments were 'good', 49% 'good and poor', and 41% 'poor'.
- Despite limitations of testing, in 88% of cases the same trigger was identified by the clinic and the panel.
- Seventy-four per cent of triggers were correctly predicted by the anaesthetist.
- NAP6 findings show that adherence to existing guidelines is poor, and confirm deficiencies in service availability, capacity, harmonisation of investigation, and reporting.
- The main areas for improvement are:
  - Improved access to services in a timely manner
  - Reduced waiting times to meet the ideal of 6–8 weeks post-reaction
  - Avoiding patients having to undergo non-urgent surgery without a completed allergy clinic assessment
  - Harmonisation of use of testing and imputability assessment
  - Improved communication of diagnosis and clear safe instructions for future safe anaesthesia, with involvement of anaesthetists in clinic activities to achieve this
  - All potential culprit agents should be tested by all relevant test modalities (SPT, IDT, sIgE and, where appropriate, challenge testing), as modalities are not always concordant
  - More data on the predictive values of different modes of testing using standardised methods are required for all triggers
  - Clarity and unambiguity of guideline recommendations is essential
  - Better standardised clinic reports should be developed to encourage reporting of all the relevant information to include, drugs identified, type of reaction, drugs to avoid, safe alternatives, tests used and results, to anaesthetists, general practitioners and patients.

Antibiotics

- Antibiotics were the main cause of perioperative anaphylaxis in the UK, being responsible for 46% of cases with identified culprit agents (ahead of NMBAs, the second leading cause, responsible for 33% of cases).
- The incidence of antibiotic anaphylaxis was 4.0 per 100,000 administrations.
- Teicoplanin (16.4 episodes per 100,000 administrations) and co-amoxiclav (8.7 per 100,000 administrations) had the highest incidences of reactions, and both were notably higher than all other antibiotics.
- Co-amoxiclav and teicoplanin accounted for 17.3% and 13.5% respectively of all cases of perioperative anaphylaxis, 23% and 18% of identified culprits, and together accounted for 89% of antibiotic-induced perioperative anaphylaxis.
- The most common first clinical feature was hypotension: in 42% of all antibiotic cases.
- The onset of anaphylaxis was within 5 minutes in 74% of cases, within 10 minutes in 92% and in all cases within 30 minutes.
- Administration of antibiotics several minutes before induction of anaesthesia would be likely to improve detection, may simplify treatment, and will help investigation when reactions occur.
- Several cases of anaphylaxis were related to antibiotic 'test doses'. Test doses were not administered in doses consistent with allergy-clinic challenge testing, and there was no evidence that a test dose reduced the severity of events when they occurred.
- Teicoplanin was frequently administered because of a history of penicillin allergy. With the knowledge that the attribution of penicillin allergy is unfounded in more than 90% of cases, effective de-labelling of penicillin allergy would decrease overall risk of anaphylaxis.
- Improvements in allergy-history taking and selective referral for investigation of antibiotic allergy may reduce antibiotic-induced perioperative anaphylaxis.
- Allergy clinics did not identify the antibiotic culprits in a quarter of all cases. This was mostly the result of incomplete investigations, including omission of appropriate skin tests and drug-provocation challenges. Allergy clinics may be underdiagnosing antibiotic allergy and potentially placing patients at risk of future reactions.
- In two thirds of cases, inappropriate advice on future avoidance was given by allergy clinics.

Neuromuscular blocking agents and reversal agents

- In the baseline survey, NMBAs were the drugs anaesthetists most commonly suspected to be triggers of anaphylactic reaction and were the drugs most commonly avoided because of risk of anaphylaxis.
- Sixty-four cases of Grade 3–5 NMBA-induced anaphylaxis were confirmed by the review panel: 33% of all cases with an identified culprit.
- In contrast to the majority of previously published studies, NMBAs were the second most common trigger agent, being 1.4-times less common than antibiotic-induced anaphylaxis.
- Suxamethonium was almost twice as likely to cause anaphylaxis as any other NMBA, with a rate of 11.1 per 100,000 administrations.
- The main non-depolarising NMBAs all have very similar incidences of anaphylaxis, meaning anaphylaxis risk should not be a major reason for choosing between them.
- Anaesthetists suspected NMBAs to be the cause of anaphylaxis 20–40% more often than was the case. This was most pronounced with atracurium.
- In 10% of cases of atracurium-induced anaphylaxis, the mechanism was non-allergic.
- Sugammadex was used during resuscitation of several cases of rocuronium-induced anaphylaxis, and in half of these cases no further resuscitation drugs were needed, but it is difficult to draw strong conclusions from this finding.
- Sugammadex was also used for management of non-rocuronium-induced anaphylaxis, with no clear evidence of benefit.
- A single case of sugammadex-induced anaphylaxis was identified by the review panel.
- There were no reported cases of anaphylaxis due to neostigmine.
- Investigation of NMBA-induced anaphylaxis had significant short comings. Use of the NAP6 NMBA minimum panel will help identify the culprit and safe alternatives especially for rapid sequence induction.

Chlorhexidine

- In NAP6 chlorhexidine accounted for almost 10% of all cases, and was the third most prevalent cause of anaphylaxis.
- The estimated incidence was 0.78 per 100,000 exposures.
- One case of chlorhexidine-induced anaphylaxis was fatal.
- The diagnosis was often not recognised, with anaesthetists suspecting that chlorhexidine was the culprit in approximately a quarter of the cases where it was confirmed to be.
- These included cases where a chlorhexidine-coated central venous line was not removed during anaphylaxis. This creates a risk of continued exposure to the trigger and an increasingly severe reaction.
- Three cases were potentially avoidable by better history-taking or by heeding a relevant history.
- Anaphylaxis from chlorhexidine was often delayed, but was more rapid and severe where chlorhexidine had direct access to the circulation.
- Bronchospasm was relatively infrequent as a presenting feature in chlorhexidine anaphylaxis.
- Perioperative anaphylaxis to chlorhexidine is an important healthcare risk due to its widespread presence in the healthcare setting, and it can be fatal.

- In fatal cases of perioperative anaphylaxis, a blood sample test for specific IgE for chlorhexidine may help in establishing the diagnosis.
- Testing for chlorhexidine was frequently omitted in allergy clinics. This should be done in all cases of perioperative anaphylaxis.
- Testing for chlorhexidine sensitisation is complex because a single test may be insufficient to exclude allergy.
- In cases of chlorhexidine allergy, tests against other allergens may also be positive, suggesting that more than one sensitisation is present; so when chlorhexidine is positive on testing all other relevant exposures should still be allergy tested.

Patent Blue dye

- Patent Blue dye was the fourth commonest cause of perioperative anaphylaxis reported to NAP6.
- Nine cases of Patent Blue dye anaphylaxis were identified. This equates to an incidence of 14.6/100,000 administrations (1:6,863). This is higher than suxamethonium and one of the highest in NAP6 (second only to teicoplanin).
- None of the cases were fatal, but profound hypotension was common and six patients required transfer to critical care.
- Hypotension, laryngeal oedema, urticaria and cyanosis were the initial presenting features, and hypotension was universal during the event. Three patients had no skin signs at any point.
- In contrast to most perioperative anaphylaxis, there was sometimes a delay between the dye being injected and the onset of anaphylaxis.
- Surgery was completed in seven of these patients and abandoned in two. Delayed cases may need urgent advice or assessment by an allergy clinic to avoid undue delay in cancer surgery.
- All cases had positive skin prick tests to Patent Blue dye in the allergy clinic, and in one case both positive skin prick and intradermal tests.
- There was good correlation between anaesthetist suspicion of Patent Blue anaphylaxis and confirmation by the allergy clinic and the NAP6 review panel.
- Assumptions that an anaphylactic event after administration of Patent Blue dye was caused by it led to failure to refer for investigation, or poor quality investigation in the allergy clinic.

Colloids and infrequent trigger agents

- Three cases of perioperative anaphylaxis were caused by gelatin or gelatin-containing intravenous fluids, giving an estimated incidence of 6.2 per 100,000 administrations, a risk rate similar to that of rocuronium.
- Ondansetron was the trigger agent in two cases.
- Each of the following triggers was identified in a single case:
  - Propofol
  - Aprotinin
  - Protamine.
- A single case of non-immunologically-mediated anaphylaxis to ibuprofen was reported.
- Two cases of anaphylaxis related to blood products (neither red cells) were reported.

Obstetric anaesthesia

- Severe perioperative anaphylaxis in obstetric patients is rare. We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey estimated 233,886 obstetric anaesthetics per year in the UK, giving an incidence of severe perioperative obstetric anaphylaxis of 3.4 per 100,000. This is significantly lower than the incidence in non-obstetric adult cases.
- Hospital Episode Statistics data for 2015-16 indicate 648,107 deliveries. This equates to an incidence of perioperative anaphylaxis of 1.2 per 100,000 maternities.
- There were no cases of anaphylaxis due to antibiotics and no cases related to latex.
- The majority of patients were awake at the time of the event. Complaints of 'feeling unwell' preceded onset of hypotension or other clinical signs.
- Recognition of a critical event was prompt, but recognition of anaphylaxis and starting anaphylaxis-specific treatment was slower than in non-obstetric cases. This probably illustrates the wide differential diagnosis of hypotension in the obstetric patient and the fact that anaphylaxis is low in the diagnostic triage.
- A consultant anaesthetist was involved in the management of all the cases.
- A specific anaphylaxis pack was used to assist management in only two cases.
- Adrenaline was administered notably less than in non-obstetric cases and phenylephrine was widely used. It was uncertain whether this was due to concerns about the impact of adrenaline on uteroplacental blood flow – which is unfounded – or because of the universal availability of phenylephrine in the obstetric setting.
- Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during neuraxial anaesthesia required tracheal intubation, and there were no cardiac arrests or maternal or neonatal deaths.

Paediatric anaesthesia

- Eleven cases of Grade 3–4 anaphylaxis in children were reported to NAP6.
- The incidence of perioperative anaphylaxis in children was 2.7 per 100,000. This is significantly lower than the incidence in adult cases.
- The commonest presentation was bronchospasm/high airway pressure.
- All cases of anaphylaxis were promptly recognised, and a consultant anaesthetist was involved in the management of all the cases.
- Treatment was started in the majority of cases within five minutes of the first clinical features.

- There were no cardiac arrests associated with any of the paediatric cases.
- There were no paediatric deaths reported.
- One patient and family reported anxiety about future potential procedures, and one child was reported as more withdrawn and angry after the event.
- Antibiotics and NMBAs are used about half as frequently in paediatric anaesthesia as in adult practice and this may partially explain the relative rates of anaphylaxis.
- In paediatric practice, when an NMBA was used this was atracurium in 57% of cases.
- Atracurium accounted for three of eleven episodes of anaphylaxis.
- There were no reports of teicoplanin-induced anaphylaxis, but its use is almost ten-fold lower than in adults.
- Allergy clinic testing was generally rather poor, being frequently incomplete and with advice given to patients/families being inadequate. Some patients were left at risk of future anaphylaxis as a result.

Critical care

- Critical care was not a prominent source of reports of anaphylaxis but was a common location for their management.
- Two thirds of patients who were admitted required brief Level 3 care and half required catecholamine infusions.
- No patient required an increase in level of care after their admission.
- No recrudescence of anaphylaxis while in critical care was reported.
- Length of stay was generally short, with rapid establishment of a good outcome.
- More than 95% of patients survived to hospital discharge.
- This suggests highly effective use of resources.

The independent sector

- The care of a substantial proportion of patients undergoing surgery and anaesthesia in independent hospitals is funded by the NHS.
- Only 13% of the 304 independent hospitals contacted by NAP6 agreed to take part. The reasons cited by those unable to take part included the difficulties associated with communicating with the large number of consultant anaesthetists with practising privileges, and the lack of an 'anaesthetic department'.
- The NHS and other organisations funding the care of patients in independent sector hospitals should work with regulators and inspectors to ensure that all independent hospitals are included in national audits and registries.
- As very few independent sector hospitals reported to NAP6, the data are unlikely to be representative of the sector, so we excluded the data from formal numerical analysis.
- We are unable to comment on the frequency of perioperative anaphylaxis in independent hospitals, nor on the adequacy of its management or investigation.
- Those cases that were reported to NAP6 showed that life-threatening perioperative anaphylaxis may occur in independent hospitals.
- Solo anaesthetists, isolated locations, the lack of critical care facilities, the potential need to transfer patients to another hospital and the lack of integrated allergy clinics all present unique challenges to those managing these events in independent sector hospitals.

Reporting and learning

- Reporting of life-threatening perioperative anaphylaxis to local reporting systems (and thence to the National Reporting and Learning System – NRLS) occurs in 70% of cases, usually by the index anaesthetist.
- Reporting to the UK regulatory system (Medicines and Healthcare products Regulatory Agency – MHRA) is poor, occurring in fewer than one quarter of cases.
- The potential value of reports to the MHRA from a general public health perspective is much greater than local reporting.
- Current reporting levels and processes mean that data held by the MHRA is unlikely to be representative of the prevalence of perioperative anaphylaxis and that data on suspected trigger agents are highly likely to be inaccurate.
- Steps are needed to improve the ease of reporting and to remove barriers to this.
- It is likely that a lack of feedback from the NRLS and MHRA hinders reporting.
- Combining relevant data from the NRLS and MHRA (while avoiding double-reporting of cases) may have considerable benefit.

Recommendations

Immediate management and departmental organisation

National

1. There is a pressing need for investment in and expansion of specialised perioperative allergy clinic services to ensure prompt investigation of urgent cases and that no patient with suspected perioperative anaphylaxis has non-urgent surgery without a timely allergy clinic assessment. This applies to both adult and paediatric services.
2. Relevant standard-setting and examining organisations should ensure that the detection, management and referral for investigation of perioperative anaphylaxis is a core-curriculum content for anaesthetists and intensivists.

3. Allergy history-taking should be included in core curricula for medical and nursing training. Nurses in pre-operative assessment clinics require particular skills and training.

Institutional

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

Individual

15. All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.
16. Adrenaline is the primary treatment of anaphylaxis and should be administered immediately if anaphylaxis is suspected. In the perioperative setting this will usually be IV.
17. Where a critical perioperative hypotensive event occurs, and perioperative anaphylaxis is one of several differential diagnoses, treatment for anaphylaxis should start promptly as there is little to be lost and much to be gained.
18. If IV access is not immediately available intramuscular or intraosseous routes should be used promptly, until IV access is established.
19. A rapid IV crystalloid (not colloid) fluid challenge of 20 ml/kg should be given immediately. This should be repeated several times if necessary.
20. During anaphylaxis with a systolic blood pressure <50 mmHg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with adrenaline and liberal IV fluid administration.
21. If an IV colloid is being administered at the time of the anaphylactic event, it should be discontinued, and the IV administration set replaced.
22. Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory.
23. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1 mg should be considered, repeated as necessary.
24. When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one.
25. A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis.
26. Chlorphenamine may be given as part of the resuscitation process, but NAP6 found no evidence of either benefit or harm. It may reduce angioedema and urticaria.
27. Blood samples for mast cell tryptase (MCT) should be taken in accordance with national guidelines:
    - 1st sample as soon as the patient is stable
    - 2nd sample as close to 1-2 hours as possible after the event
    - 3rd (baseline) at least 24 hours after the event.
28. All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event: ie. the consultant anaesthetising or supervising the case.
29. Where a trainee refers a patient to an allergy clinic the contact details of a consultant anaesthetist should be included in the referral.

30. If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice, as well as making a written referral.
31. Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules (see Chapter 11 Appendix C).

Research

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

A patient's experience of perioperative anaphylaxis

Institutional

35. Consent should always be informed. Therefore, patients should be informed of the risk of anaphylaxis preoperatively. Patient information leaflets may be suitable as part of this process.
36. Following a perioperative anaphylactic event, and before discharge from hospital, the patient should be provided with a letter from their anaesthetist. The NAP6 template patient letter is in Chapter 11, Appendix B. This letter should be used in addition to the discharge summary, and a copy should be sent directly to the patient's GP.
37. The practice of NHS drug allergy clinics should be standardised so that patients and commissioners can expect a consistent service. BSACI (British Society for Allergy and Clinical Immunology) guidelines should be followed. Regulators and inspectors should pay heed to this too.

Research

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

Clinical features

Institutional

39. All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.

Individual

40. Perioperative anaphylaxis can present with a single clinical feature, in particular isolated hypotension. Anaesthetists should exercise a high index of suspicion in recognising perioperative anaphylaxis and commence treatment promptly.
41. In patients with asthma, the occurrence of bronchospasm or high airway pressures should not automatically be attributed to acute asthma, as, in these patients this may be the presenting feature of life-threatening anaphylaxis.
42. As anaphylaxis may be delayed, particularly with some oral drugs, referrals to allergy clinics should include details of all agents that the patient has been exposed to within at least the previous 120 minutes.
43. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1 mg should be considered, repeated as necessary.

Research

44. Further studies are required to clarify the role of a fall in end-tidal carbon dioxide concentration in the early recognition and management of severe perioperative anaphylactic reactions.
45. The role of glucagon and vasopressin in refractory anaphylaxis (particularly in high risk groups such as the elderly, and those taking beta blockers or ACE inhibitors) needs further investigation.

Deaths, cardiac arrest, profound hypotension and outcomes

Severe perioperative anaphylaxis here refers to perioperative anaphylaxis requiring CPR or with profound hypotension such as systolic blood pressure <50 mmHg.

46. In patients who experience perioperative anaphylaxis with a high risk of adverse outcome (elderly, obese, ASA of or above 3, patients taking beta-blockers or ACE inhibitors, or prolonged CPR), anaesthetists should be prepared to escalate treatment early.
47. 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.
48. During perioperative anaphylaxis in patients taking beta-blockers, early administration of IV glucagon 1 mg, repeated as necessary, should be considered.
49. Administration of IV vasopressin 2 units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory.
50. The need for a vasopressor infusion should be anticipated after severe perioperative anaphylaxis.
51. Non-essential surgery should not be started after severe perioperative anaphylaxis.
52. Where severe perioperative anaphylaxis occurs during non-essential surgery the operation should be curtailed unless there is an overriding reason to continue.
53. Patients with severe anaphylaxis should be admitted to critical care.

54. 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.
55. All cases of severe perioperative anaphylaxis, including fatalities, should be discussed with an allergy clinic at the first available opportunity.

Investigation

National

56. There is a pressing need for investment in and expansion of specialised perioperative allergy clinic services to ensure prompt investigation of urgent cases and to ensure that no patient with suspected perioperative anaphylaxis has non-urgent surgery without a timely allergy clinic assessment. This applies to both adult and paediatric services.
57. Consideration should be given at a national level to reconfiguring paediatric services for investigation of perioperative anaphylaxis to address the current shortfall in provision. In view of the small number of cases involved collaboration with local hub services should be explored.

Institutional

58. Patients should be given appropriate information after investigation of perioperative anaphylaxis in an allergy clinic. This information should also be sent to their GP and entered in their medical record. Recommended content is shown in the NAP6 template allergy clinic patient letter (Appendix B Chapter 11).
59. Specialist perioperative allergy clinics should adopt a multidisciplinary-team approach, including where practical having an anaesthetist with a special interest, in the allergy clinic. Where this is not practical cases should be discussed with an anaesthetist before the patient attends the clinic.
60. Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the event and a full list of the patient's medication and drugs administered prior to the event. A standardised form (eg. the NAP6 or AAGBI pro-forma) should accompany the referral.
61. Outcomes of urgent investigations by allergy clinics should be communicated urgently and directly to the referring anaesthetist, ideally by phone and in writing.
62. Allergy clinics should provide standardised clinic reports to encourage better communication to anaesthetists, GPs and patients. Recommended content is in the NAP6 recommended allergy clinic letter (Chapter 11).

Individual

63. All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event, ie. the consultant anaesthetising or supervising the case.
64. The anaesthetist referring the patient for investigation of perioperative anaphylaxis should explain the importance of attending the clinic, and allay any fears the patient may have to improve uptake of allergy clinic appointments.
65. Blood samples for mast cell tryptase (MCT) should be taken in accordance with national guidelines:
    - 1st sample as soon as the patient is stable
    - 2nd sample as close to 1–2 hours after the event as possible
    - 3rd (baseline) at least 24 hours after the event.
66. Where the baseline sample is not collected prior to attending the allergy clinic it should be collected at the clinic.
67. If the MCT is elevated more than 24 hours after the event, the possibility of a mast cell disorder should be considered.
68. A dynamic rise and fall in mast cell tryptase should be used to detect mediator release.
69. Where peak mast cell tryptase level is less than the upper limit of the reference range (ie, the 99th centile limit of 14 mcg/L) a dynamic rise and fall in tryptase level may still be useful to diagnose anaphylaxis.
70. When investigating suspected perioperative anaphylaxis, chlorhexidine and latex should be tested.
71. More than one test for chlorhexidine is necessary to exclude allergy.
72. When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitisation.
73. All potential culprit agents to which the patient has been exposed should be tested. The clinic should make a critical appraisal of the imputability of each potential trigger in making a diagnosis.
74. Avoidance advice should be specific and not excessive, as this may lead to harmful consequences. When no culprit agent is identified, further investigations should be carried out rather than giving 'blanket advice' on avoidance of multiple drugs.
75. All skin testing should be at concentrations validated to be below the non-specific histamine-releasing/irritant concentrations (as published and verified locally).
76. Allergy clinics should adhere to published guidelines on the investigation of suspected NMBA anaphylaxis. When NMBA allergy is diagnosed the clinic should identify a safe alternative, including for rapid sequence induction (ie, establishing whether either suxamethonium or rocuronium is safe). The NAP6 minimum panel is suitable for this.
77. The possibility of reaction to more than one agent should be considered.
78. Specific IgE bloods tests should be used for agents for which they are available, as no modality is 100% sensitive or specific.

79. Where allergy testing has been performed less than four weeks after the event, retesting after an interval should be considered, to exclude false negatives and identify multiple sensitisations.
80. Broad advice to avoid beta-lactam should be discouraged, and patients should be further investigated to clarify the specific drug(s) to avoid and to identify safe alternatives.
81. Allergy clinics should advise patients to keep a copy of their drug allergy clinic letter with them at all times, and to use this to inform clinicians of their allergy, particularly when attending hospital appointments or before future surgery.

Research

82. As none of the test modalities is wholly reliable, there needs to be research to establish an appropriate form of challenge testing for chlorhexidine.
83. More data on the predictive values of different modes of testing using standardised methods are required for all triggers.
84. There is a need for further research and consensus on the logical interpretation of positive tests where mast cell tryptase level is not raised, and negative tests where mast cell tryptase level is raised, as current guidance is lacking.
85. Studies are needed to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.

Antibiotics

Institutional

86. Patients with reported allergy to a beta-lactam antibiotic and at least one other class of antibiotics should be referred for specialist allergy investigation before elective surgery, in line with National Institute for Health and Care Excellence guidelines CG183 (NICE 2014).
87. If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed.
88. Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

Individual

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

Neuromuscular blocking agents and reversal agents

Institutional

94. Allergy clinics should adhere to published guidelines on the investigation of suspected NMBA anaphylaxis. When NMBA allergy is diagnosed the clinic should identify a safe alternative, including for rapid sequence induction (ie, establishing whether either suxamethonium or rocuronium is safe). The NAP6 NMBA minimum panel is suitable for this.

Individual

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

Research

96. Further research on population sensitisation by pholcodine is needed. If a causal association is confirmed, withdrawal of pholcodine-containing medicines from the UK market should be formally considered.
97. There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium-induced anaphylaxis specifically. Clinical trials would provide valuable evidence.

Chlorhexidine

National

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

Institutional

99. Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy.
100. Investigation of suspected perioperative anaphylaxis should include chlorhexidine.
101. More than one test for chlorhexidine is necessary to exclude allergy.
102. When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitisation.

Individual

103. Chlorhexidine allergy should be included in the allergy history taken by anaesthetists, nurses and other healthcare professionals.

104. Clinical teams should be aware of 'hidden chlorhexidine' such as in urethral gels and coated central venous catheters, and should consider this as a potential culprit if perioperative anaphylaxis occurs.
105. When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one.

Patent Blue dye

Individual

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

Obstetric anaesthesia

Institutional

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

Individual

110. An allergy history should be taken even when there is extreme urgency to deliver the baby.
111. Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients.
112. Anaphylaxis in obstetric patients should be managed following the same principles as in non-obstetric patients. Adrenaline should not be withheld for fear of a detrimental effect on placental perfusion.
113. Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase levels should be measured.
114. Anaesthetists should be aware that hypotension due to anaphylaxis can be exacerbated by neuraxial blockade and or aortocaval compression.

Paediatric anaesthesia

National

115. Consideration should be given at a national level to reconfiguring paediatric services for investigation of perioperative anaphylaxis in order to address a current shortfall in provision. In view of the small number of cases involved, collaboration with local hub services should be explored.

Institutional

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

Critical Care

Institutional

119. Patients with severe anaphylaxis should be admitted to critical care.

The independent sector

National

120. The results and recommendations of NAP6 are relevant to independent sector hospitals and should be disseminated to independent sector hospitals, their governance leads and anaesthetists working there.
121. For reasons of patient safety and quality assurance, commissioners of services in independent sector hospitals, and both regulators and inspectors, should ensure that these hospitals, and the patients undergoing care in them, are included in national audits and registries.

Institutional

122. Independent sector organisations should work to improve engagement with national audits and registries that focus on quality and safety of patient care.
123. Independent sector hospitals should have the same levels of preparedness for managing life-threatening perioperative anaphylaxis as NHS hospitals. This includes, but is not limited to, an anaphylaxis lead, a resuscitation team, anaesthetic anaphylaxis treatment and investigation packs in all theatres, appropriate training of all theatre staff, immediate availability of first line anaphylaxis drugs (adrenaline and corticosteroids), prompt availability of second line drugs (glucagon and vasopressin), standard operating procedures for management of anaphylaxis, escalation to provision of intensive care before transfer, ongoing care and transfer to another hospital where necessary, and referral for specialist investigation.
124. Independent sector hospitals should have systems to ensure safety-relevant matters can be discussed, disseminated and acted on by all anaesthetists who work there. Collaborative working between anaesthetists in independent sector hospitals should be encouraged to increase governance and safety. An 'independent department of anaesthesia' is one solution to this, and this may provide benefits equivalent to those of departments of anaesthesia in the NHS.

Individual

125. Anaesthetists working in independent sector organisations should be trained and prepared to manage life-threatening anaphylaxis.
126. Anaesthetists working in independent sector organisations should participate in national audits and registries.

127. Anaesthetists working in independent sector organisations should be trained in and prepared to transfer a critically ill patient to another hospital for further care. Where they do not possess these skills, another clinician with these competences should be enrolled in the patient's care.

Reporting and learning

National

128. MHRA should improve communication with clinicians; for example, providing an annual report which includes perioperative anaphylaxis.

Institutional

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

Individual

132. The departmental lead should be informed of the case.
133. The MHRA case identifier should be included in the referral to the allergy clinic.
134. All cases of Grades 3–5 perioperative anaphylaxis should be presented and discussed at local Morbidity and Mortality meetings for purposes of education and familiarisation.