Anaesthesia, Surgery and Life-Threatening Allergic Reactions

Report and findings of the
Royal College of Anaesthetists'
**6th National Audit Project:
Perioperative Anaphylaxis**

MAY 2018

EDITORS
Professor Tim Cook
Professor Nigel Harper

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List of standard abbreviations

AAGBI — Association of Anaesthetists of Great Britain and Ireland

ASA — American Society of Anesthesiologists Physical status grade

ACE — angiotensin converting enzyme

ACEI — angiotensin converting enzyme inhibitor

BP — blood pressure

BSACI — British Society for Allergy and Clinical Immunology

CAD — coronary artery disease

DCC — direct clinical care

GA — general anaesthetic

IDT — intradermal test

IgE — immunoglobulin E

IM — intramuscular

IO — intraosseous

IV — intravenous

MCT — Mast cell tryptase

MHRA — Medicines & Healthcare products Regulatory Agency

NICE — National Institute for Health and Care Excellence

NMBA — Neuromuscular blocking agent

RCoA — Royal College of Anaesthetists

RCUK — Resuscitation Council of the United Kingdom

RSI — Rapid sequence induction

SPA — supporting professional activity

SPT — skin prick test

VF — ventricular fibrillation

VT — ventricular tachycardia

Notes on publications and referencing

PATIENTS

25 YEARS
RC°A
Royal College of Anaesthetists
1992–2017

TRAINING

25 YEARS
RC°A
Royal College of Anaesthetists
1992–2017

STANDARDS

The Royal College of Anaesthetists

35 Red Lion Square

RC°A
Royal College of Anaesthetists

Churchill House

Faculty of Pain Medicine
Faculty of Intensive Care Medicine
British Pain Society
Intensive Care Society

WARNING
CLOSED CIRCUIT TELEVISION

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Foreword

Liam Brennan

It is my great pleasure to introduce this report on *Anaesthesia, Surgery and Life-Threatening Allergic Reactions*, which summarises the work of The Royal College of Anaesthetists' 6th National Audit Project (NAP6): Perioperative Anaphylaxis. The publication of a NAP report is always a watershed moment for anaesthesia both in the UK and internationally and the way we think about rare but serious complications in our specialty.

NAP6, like each of its predecessors, provides reassurance for anaesthetists on those areas where our practise is successful, but also identifies areas where there is room for improvement, and questions our preconceived ideas about managing these challenging clinical scenarios. Like many anaesthetists, I have my own experiences of managing patients with anaphylaxis and I particularly recommend to you the vignettes that illustrate the profound and long-lasting effects on those affected by this life-threatening condition.

The College is indebted to the legion of NAP Local Coordinators who reported each case of perioperative anaphylaxis in their hospitals across the year of data collection and coordinated the Baseline and Activity Surveys. The Local Coordinators are the backbone of every NAP and the involvement of 100 per cent of eligible NHS hospitals is a testament to their commitment. Every anaesthetist and allergist who completed a NAP6 survey is to be commended; the openness and engagement shown by the clinical community with each NAP is immensely gratifying, and in the case of NAP6 a great credit to both specialties. I am also pleased to note that NAP6 is the first National Audit Project to engage with the independent healthcare sector.

I extend my gratitude to Professor Nigel Harper, Clinical Lead for the project, and the anaesthetists, allergists, immunologists and lay representatives of the multidisciplinary NAP6 steering panel. The commitment of this group in designing the audit and analysing the hundreds of reported cases should not be underestimated. You shall read more from them in the following chapters. Thanks must also go to the RCoA's Research Department whose dedication to this project, in particular that of Ms Laura Farmer, ensured that everything remained on track.

Finally, my sincere thanks go to Professor Tim Cook, for whom the publication of the NAP6 report is the culmination of a long association with the National Audit Projects dating back over more than a decade. Tim will shortly be stepping down from his role as the RCoA's Director of the NAP programme and the whole College and wider specialty of anaesthesia are indebted to him for his tireless leadership and the improvements in clinical practice that the NAPs have delivered.

It is these changes in clinical practice that form the legacy of each National Audit Project. Despite the long processes of data collection and analysis, the 'knowledge mobilisation' following each NAP is often its most challenging component. How do we, as a healthcare community, respond to and take forward its points of learning? How will you, personally, rise to the challenge an incorporate the lessons learnt into your clinical practice? I strongly encourage all clinicians reading this document to join me in working to implement the recommendations made in this report – improvements to ensure we deliver the best possible care for patients with perioperative anaphylaxis.

Dr Liam Brennan
President, Royal College of Anaesthetists

@RCoANews

1   Introduction

Nigel Harper   Tim Cook

In this introduction we aim to describe why NAP6, the 6th National Audit Project of the Royal College of Anaesthetists (RCoA), was undertaken, and to point towards ways in which we hope this report will enhance quality of care and improve patient experience. We guide you briefly through the various chapters and hope to whet your appetite to read on at least the next chapter (Key Findings and Recommendations) and perhaps even the entire report.

The process of learning starts with listening, and in Chapter 3 a survivor of perioperative anaphylaxis describes her experience, the shock of unexpected events, and aspects of her care.

This theme is continued in Chapter 4, in which lay members of the NAP6 panel set out a patient-centred response to the findings of this report and make recommendations for improving the patient experience.

More than three million anaesthetics are delivered to patients in NHS hospitals each year and, thankfully, the vast majority are uneventful. Minor, expected effects of anaesthesia on cardiovascular and respiratory function are easily recognised and can be treated promptly and effectively.

Occasionally much more dramatic changes in vital signs are seen, and, in extreme cases, the episode presents as a critical event. There are several well-recognised causes of such episodes during anaesthesia, for example, surgical haemorrhage, acute asthma, an acute coronary event, collapse of a lung, or embolism of a blood clot. The preoperative health status of the patient, such as asthma or coronary artery disease, often points to the cause. This information facilitates prompt diagnosis and enables the anaesthetist to target immediate management.

In contrast, perioperative anaphylaxis is a completely unexpected critical event presenting suddenly and without warning, and may occur in patients with no chronic health problems. In severe cases, extremely low blood pressure, impaired circulation, and difficult ventilation of the lungs combine to starve the tissues of oxygen, and shock ensues. In extreme cases, there is rapid progression to cardiopulmonary arrest, which may be fatal despite prolonged attempts to resuscitate the patient. Clinical features during the episode of more than 250 cases of life-threatening perioperative anaphylaxis are presented and discussed in Chapter 10.

It is not surprising that it may take a few minutes for the anaesthetist to exclude other, more common, causes before the diagnosis of anaphylaxis becomes evident and specific treatment is started. We have made allowance for this sequence of events when assessing the promptness of treatment and the quality of immediate management in the cases reported to NAP6.

What is anaphylaxis?

The accepted definition of anaphylaxis is "a severe life-threatening generalised or systemic hypersensitivity reaction" (Johansson 2001). 'Hypersensitivity' is an umbrella term describing reproducible symptoms that occur in response to a defined stimulus, such as a wasp sting or a particular food or drug, in a quantity that is tolerated by most people. Hypersensitivity, and therefore anaphylaxis, is usually allergic but this is not always the case, for example, in some reactions to non-steroidal anti-inflammatory drugs.

The severity-grading of hypersensitivity reactions depends on signs and symptoms. Minor or moderate reactions (Grade 1 and Grade 2) are correctly termed 'hypersensitivity', and should not be called 'anaphylaxis' as only Grade 3, 4 and 5 hypersensitivity can correctly be termed anaphylaxis. Grade 1 is characterised by cutaneous features such as rash, itch or peripheral swelling; Grade 2 by mild hypotension or wheeze (usually not requiring treatment), with or without Grade 1 features. In Grade 3, these features are severe, and may include airway swelling. Grade 4 fulfils the requirements for initiating cardiopulmonary resuscitation, and Grade 5 is a fatal reaction. We considered including Grade 1 and Grade 2 hypersensitivity in NAP6, but concluded at an early stage that the increased number of reports would be unmanageable. In addition, we felt that learning opportunities were more likely to occur in cases of life-threatening perioperative hypersensitivity.

The majority of anaphylactic reactions occur in the community, but more than a third of all patients admitted to intensive care with severe anaphylaxis come from operating theatres (Gibbison 2012). In relation to anaesthesia, anaphylaxis can occur in the preoperative ward in response to premedication drugs, in the operating theatre, and in the recovery room. The term 'perioperative' in relation to NAP6 includes all these sites, as well as interventions requiring anaesthesia care in critical care units, emergency departments, and anywhere else in the hospital that anaesthetist-delivered care is provided.

What triggers anaphylaxis during anaesthesia and surgery?

Patients are exposed to a large number of potential trigger agents during surgery and other invasive procedures. An average of eight drugs are administered during a general anaesthetic, but the number can be as high as 20 (Chapter 9, Allergen Survey). In addition to induction and maintenance agents, most patients receive an analgesic drug, an antibiotic for surgical prophylaxis, and at least one anti-emetic. Almost half receive a neuromuscular blocking agent (NMBA). The majority of patients are exposed to chlorhexidine and many are exposed to latex. Other potential trigger agents include radiological contrast and other dyes, intravenous colloid fluids, drugs that affect blood coagulation, and local anaesthetic drugs. Exposure to many of these potentially allergenic agents is not confined to general anaesthesia, and we included patients undergoing procedures with spinal, epidural or local anaesthesia under the care of an anaesthetist, as well as monitored anaesthesia care.

Why do some patients experience perioperative anaphylaxis and not others?

Most anaphylaxis is allergic and, characteristically, the patient's immune system has been sensitised to the same substance during a previous uneventful exposure. Sometimes it is only necessary for the patient to have been exposed to a critical small part of the molecular structure of the trigger agent – the epitope or 'antigenic determinant'.

The majority of patients who experience NMBA-induced anaphylaxis have not had previous exposure, but have been sensitised to a particular epitope which is found in many everyday products. A similar process occurs with Patent Blue dye which may be injected into the tissues to show up lymph nodes during breast surgery. Unfortunately, neither previous uneventful anaesthesia nor the absence of a previous anaesthetic guarantee that perioperative anaphylaxis will not occur.

How is perioperative anaphylaxis treated?

We wished to know how perioperative anaphylaxis is managed in the UK, and whether published guidelines are being followed. Our findings are described in Chapter 11, Immediate management and departmental organisation.

Adrenaline is the mainstay of the treatment of anaphylaxis, and is recommended in all published guidelines. Anaesthetists are very familiar with the range of drugs used routinely to support the blood pressure and relieve bronchospasm, but administration of adrenaline may be outside their 'comfort zone', and an apparent reluctance to administer adrenaline has been described in Denmark (Garvey 2011). We discuss this phenomenon in Chapter 11. Liberal quantities of intravenous fluids are required to restore circulating blood volume and cardiac filling, but there is little published information on the volumes of fluid used in practice.

What did we do in NAP6?

In order to understand perioperative anaphylaxis, we adopted an inclusive approach, with anaesthetists, allergists, clinical immunologists, patient group representatives, and other relevant parties working together, both in the steering group and in the case-review panel. We set up a network of Local Coordinators, one based in every UK NHS hospital, who managed the study locally. We then used this network to collect detailed, anonymised case reports for a one-year period via a secure web-based registry. Each submitted case remained entirely anonymous and was subjected to a series of structured reviews by a multidisciplinary panel to extract the quantitative and qualitative learning on which this report is based. The project methods are discussed in full in Chapter 5.

There were multiple components to NAP6. The first component was a baseline survey of anaesthetists' experiences and perceptions of perioperative anaphylaxis, including the decisions anaesthetists make to avoid anaphylaxis (Chapter 7). In the second part we captured details of waiting times, investigation pathways, and adherence to published guidelines in a survey of specialist allergy clinics investigating suspected perioperative anaphylaxis (Chapter 13). An anaesthetic Activity Survey (Chapter 8) characterised anaesthesia service provision, surgical specialty case-load, and working patterns. This is useful in understanding elements of institutional preparedness, such as the levels of seniority of anaesthetists delivering direct patient care, and how this varies during the working week and across weekends. Estimates of incidence, and risk of anaphylaxis with particular agents, can be made only if the number of exposures are known, and, to that end, the third part of NAP6 was a quantitative survey of patients' exposure to potentially allergenic drugs and other substances during anaesthesia (Chapter 9). The final, and perhaps most important element, was a one-year registry of cases.

What did we find and how can NAP6 help patients?

The findings of all elements of NAP6 are summarised in Chapter 6, Summary of Main Findings relating to particular trigger agents and patient groups are described in further detail in Chapters 10 to 21. A flavour of our findings is provided in the paragraphs below.

Where several alternative anaesthetic drugs are available, some anaesthetists may avoid particular drugs because of perceptions of a high likelihood of triggering perioperative anaphylaxis. These perceptions may or may not be founded in fact. We discovered that avoidance of drugs as a result of perceived anaphylaxis risk is not always based on evidence.

The multidisciplinary NAP6 panel reviewed more than 300 cases of suspected perioperative anaphylaxis and included 266 in the final analysis. Emphasis was placed on assessing quality of management, both by the team providing initial clinical care and by the allergy clinic. We used national guidelines to inform our assessment process wherever possible. As you will read, clinical management was not faultless (Chapter 11). We highlight ways in which improvements can be made, and provide information on setting up anaesthetic anaphylaxis treatment and investigation packs, as well as providing templates for written communication with the patient and their general practitioner. We also suggest ways in which departments of anaesthesia can help by appointing departmental lead anaesthetists with defined responsibilities.

NAP6 received extensive details of the investigations performed by the specialist allergy clinics, and the tests performed and their interpretation were scrutinised by the panel's Allergists and Clinical Immunologists. The quality of investigation and of communication with the patient and the referring team were analysed. The NAP6 review panel did not always agree with the diagnosis made by the allergy clinic or the information given to patients, and this is discussed in Chapter 14, Investigation.

Most previous studies have found that neuromuscular blocking agents (NMBA) are the most common cause of perioperative anaphylaxis. An important finding of NAP6 was that antibiotics are now the most common trigger of anaphylaxis during anaesthesia (Chapter 15, Antibiotics). Antibiotics are administered for prophylaxis against surgical infection in almost 60% of all surgical procedures. Antibiotic stewardship is becoming increasingly important: accelerating antibiotic resistance may even restrict the feasibility of some surgical procedures in the future.

Another notable finding of NAP6 was that the highest risk among the antibiotics was not with penicillins, which are widely prescribed in primary care, but with teicoplanin, a long-acting antibiotic that is only given as an injection, mainly in hospital. Teicoplanin is often a replacement for penicillin in patients who give a history of penicillin allergy, and there are several recent reports of perioperative anaphylaxis caused by this antibiotic (Savic 2017). Most patients who give a history of penicillin allergy are not in fact allergic, and we discuss how 'mis-labelling' could be reduced by better training and communication in the healthcare setting.

The provision of allergy services in the UK has been the subject of several reports which have highlighted the prevailing 'postcode lottery' in the availability of specialist allergy clinics (Select Committee on Health 2003; Royal College of Physicians, 2010) We wished to obtain a UK-wide view of the provision of NHS allergy clinics for the investigation of perioperative anaphylaxis in adults and children, and NAP6 included a detailed national survey of these services, the findings of which strongly support the need for change (Chapter 13, Allergy clinic baseline survey).

We were interested to discover whether presentation, management and adverse effects differ in the obstetric population and in children, as well as identifying any differences in the way these cases are investigated. Our findings are described in Chapter 20 and Chapter 21.

We followed patients through the acute event and into the postoperative period. Patients have a right to high standards of continuing care and we recorded length of stay in hospital and explored the use of critical care services, especially the need for continuing cardiovascular and respiratory support as well as the frequency with which patients had to be transferred to a different hospital for critical care (Chapter 22, Critical care).

More than 1.5 million surgical procedures are performed in independent sector hospitals each year in the UK (Leys 2014), suggesting that approximately a third of cases of perioperative anaphylaxis could be expected to occur in that setting. We invited independent (non-NHS) UK hospitals to contribute case reports to NAP6. Our, somewhat unexpected, findings are described in Chapter 23.

By recording detailed information about all aspects of perioperative anaphylaxis, our ambition is to reinforce best practice and stimulate the introduction of new practices, with the aims of improving clinical management of the acute event, enhancing communication with patients, and strengthening the quality of the specialist allergy services to which patients are referred for investigation after the event.

Improvements in patient care can be achieved only by making detailed recommendations for change. The NAP6 panel makes more than 100 recommendations at national, institutional and individual levels, ranging from how UK specialist allergy clinic services should be structured, to the volume of IV fluids that should be administered during resuscitation. While some of these reiterate existing guidance, it is important to note that all recommendations are based directly on the findings of the data reviewed within NAP6.

Patients expect that all doctors and nurses should have at least basic training in allergy. Allergy-training of medical and nursing staff is patchy, and formal training in allergy history-taking seems to be uncommon at the undergraduate level. We wished to establish to what extent the preoperative allergy history was relevant to perioperative anaphylaxis; could more focused history-taking or better health records have prevented life-threatening reactions?

Introduction

Immediate management of very uncommon life-threatening incidents is challenging. Anaesthetists can expect to see, on average, fewer than one case of perioperative anaphylaxis every seven years (Kemp 2017). It is particularly important, therefore, that anaesthetists' training is up-to-date, and that guidelines for immediate management are immediately available at all anaesthetising sites. NAP6 recorded real-life availability and use of guidelines and algorithms during the management of perioperative anaphylaxis, as well as assessing clinical management in a structured and detailed fashion.

We were particularly interested in how hypotension and cardiac arrest are being managed in practice (Chapter 12). National guidelines on cardiopulmonary resuscitation (CPR) in cardiac arrest are well known (Soar 2015), but some of the parameters within the guidelines such as 'signs of life' are not applicable to anaesthetised patients who are unable to respond. There is little published guidance on the blood pressure below which CPR should be initiated during anaesthesia, and expert opinion was sought by the NAP6 review panel before setting our threshold. We expect to generate debate and we look forward to future discourse on this important subject.

Outcomes of perioperative anaphylaxis have been poorly studied in the past, and NAP6 sought to record adverse sequelae of all types. We wanted to know whether any aspects of immediate management, such as drugs given in resuscitation or subsequent admission to a critical care unit, affected the likelihood of adverse health consequences. We were also interested to know how often surgery is abandoned as a result of anaphylaxis, and what arrangements are then made to reschedule urgent surgery. When urgent surgery is abandoned it should be rescheduled without delay. This is possible even before the identity of the trigger is known, and we set out a clear and safe plan for providing anaesthesia in these circumstances – to our knowledge the first of its kind to be published.

Patients have a right to expect that their suspected perioperative anaphylactic reaction will be investigated promptly and expertly, so that they are aware of the drugs and other substances they can receive safely in the future, and those they should avoid. We hope our findings and recommendations will lead to quality enhancements and an improved patient experience.

Individual and organisational learning from critical events can only happen if they are reported and investigated at hospital level. NAP6 recorded whether events had been reported to Trust incident-reporting systems, and by whom. Reporting to the Medicines & Healthcare products Regulatory Agency through the Yellow Card Scheme is central to pharmacovigilance: our findings were disappointing and are discussed in Chapter 24.

Finally, we would like to thank those who have made this report possible. The National Audit Projects of the Royal College of Anaesthetists rely entirely on case reports and survey returns submitted voluntarily by UK anaesthetists. NAP6 includes data from all UK NHS hospitals, collected survey data from more than 11,000 anaesthetists and patient surveys from 15,000 anaesthetic episodes, and received more than 500 case reports. The level of engagement of anaesthesia community remains very high. This requires significant coordination within hospitals and diligence by individual anaesthetists. We thank all who contributed, particularly the anaesthetists who reported cases, the tireless Local Coordinators, members of the NAP6 panel and the NAP6 Moderator, all of whom gave their limited spare time freely and without complaint.

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2 Key findings and recommendations

Tim Cook

Nigel Harper

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.

When you know you're going to have an operation you are naturally apprehensive but trusting, not implicitly, but faithfully.

The one person I tend to put most of my faith in is the anaesthetist. To that end I was ready to meet my anaesthetist to discuss my medical history, my medication and my known allergies. As he was leaving I quipped, as I always do, with any anaesthetist "Now, you won't lose me will you?" The young man looked at me slightly uncomprehendingly, as my daughter chipped in "Oh mum!"... as in our family we pay due deference to highly trained experts, especially over-worked NHS staff and she thought this was a bit forward.

I was all set except that I had to remind someone to put on my red allergy alert bracelets on.

After the operation, the next thing I remember was vaguely hearing my name and opening my eyes to what can only be described as a waking nightmare! I was uncontrollably shaking, very nauseated and feeling as if I'd been run over by a bus! There was, what seemed to be a large number of people standing around me, chattering and looking down at me. I felt like I was in an advert about 'Injury Lawyers For You.' Shot in monochrome, this features many people including a (very scary) clown, scrabbling to get to you. It felt like I was being spoken to by everybody, and all at once. Not true of course, but that was the sensation.

I had uncontrollable shaking and was feeling very scared and peculiar. I began to recognise a sort of panicky, concern and relief on the faces above me. Something was definitely wrong!

I was spoken to by a senior anaesthetist who introduced himself as the mentor for the poor young anaesthetist whom I had met earlier and whom I did spot lurking in the background. He explained that my blood pressure had dropped, my heart had "blipped" and it became clear that I was in anaphylactic shock. He told me that I'd "reacted to something" during or at the end of the operation, possibly fentanyl... "and given us a scare... You're looking much better now." He reassured me. Then a cardiologist reiterated everything the anaesthetist had said and after both reassured me that follow up appointments for allergy and cardiac clinics would be made, they disappeared! That's when I stopped blaming myself for being a nuisance to these nice people and attempted to gain some composure and take it all in.

Sometime later my consultant gynaecologist came to say the operation had been successful, what she'd found, what she'd removed and she also confirmed that I'd "given them a fright... glad that you're looking much better". Then she too disappeared.

Being left alone, trying to keep calm and take anything in was difficult. A nurse was beside me all this while and she was just the best. She was calm and kept talking to me in a more down to earth way "You are much better... you did give us a scare but you're doing fine... just let me know if I can do anything... Is there someone waiting for you?" I rallied, but then she told me I was supposed to go ICU. We patients are not as daft as you think we are and ICU is not what we want to hear after a routine operation!

With the nurse talking to me about ordinary things, the shakes began to abate and because my vital signs were so much better, I was returned to the ward and avoided the need to go to ICU.

All this time my daughter had not been given any useful information and having waited for four hours asked one more time about me and was told to go home. She then had to relay – well, 'nothing' – back to the family who of course became worried and ended up ringing and bothering busy ward staff by trying to gain more information.

I spent a restless, sleepless night on the ward eventually vomiting for some while. The next morning brought back a parade of juniors from the various teams all reassuring me that appointments for follow-up clinics had been made and that I would be hearing soon about those. I was doing so well by then that I was able to go home. Well it was polling day and I needed to vote!

However, I went home without a completely clear picture of what had happened or what drug might have caused the reaction other than "Fentanyl is the most likely drug" and "you might want to mention this if you have an emergency event before seeing an allergist." I bought myself an 'allergy alert card' and stickers for my purse and handbag.

Then the appointment system failed. I was sent an allergy clinic appointment but for the wrong doctor and clinic. It took me two months to find anyone who could explain who had made the original appointments and sort it out.

My drug allergy clinic appointment came after a couple of months. My GP had to intervene with the cardiology clinic as well in order for me to be seen and this took the same time. At the cardiology appointment I was told that I would have the results within a fortnight and be called back to talk to the consultant about them. This didn't happen and again my GP intervened to find that the results had been sent electronically, that there were no problems and it would not be necessary for another visit. Good news but, to this day, I have never seen or been sent a copy of those results!

After leaving hospital and while I was in no great pain, it was clear that I needed to recover. Being forced to rest is not 'my thing'. Inevitably reflection took over and my mood was affected. I had faced my mortality head on and my brain took a while to process this fact. It was a struggle. It took a while, but after some reflection I'm glad that firstly, I'm still here, secondly, I wouldn't be if I'd been born in the 19th century and finally I'm damn glad you lot were around to help.

Finally I got to the allergy clinic, and I cannot thank my allergy clinic doctor enough for being the amazing person she is. She is now known as 'Dame F' in our house. She asked me about previous operations and procedures and when I said I had a similar experience after an operation in 1979, she chased up and found my records from that operation to reveal similarities which were, I believe useful to her sleuthing! I am so grateful for her extraordinary skills and ability in finally finding the cause of my allergy but also the diligence and lengths she will go to in making her patients' well-being her prime concern in her consultations.

She gave me a letter detailing her investigations and recommended that I keep a copy of her letter in my handbag. The letter gave for a full account of the operation including the drugs used and timings of administration etc. I have now purchased an 'alert bracelet' and registered my allergies and medical history.

My final plea to 'you all' is to have patience with your patients. The majority of us try not to take you or your phenomenal skills and expert work for granted. We don't mean to be rude or difficult: it's just that feeling ill and the resulting fear put us in a difficult place. Putting our faith in you is what we end up doing, and we want to be a testament to the extraordinary skills you have used in making us well again. Please let us work with you. You can explain the mysteries away but you can also listen to what we have to say because sometimes it is worthwhile.

Thank you to the NAP6 team for giving me this opportunity to tell my story and thank for your continued and amazing work for this project.

Jan Auvache

John Hitchman   Amena Warner

What we knew before NAP6

Perioperative anaphylaxis, unlike accidental awareness and wrong site surgery, may not be perceived as one of the most feared risks by the 3.5 million patients anaesthetised each year. Media and anecdotal sources would indicate that public awareness and experience of anaphylactic shock is associated with triggers such as nuts, sea foods, penicillin and venom rather than the anaesthetic process. It is probable that the body of public knowledge of perioperative anaphylaxis lies more with those who have experienced it, their families and the patient allergy organisations.

The variability of services that patients receive after life-threatening perioperative anaphylaxis is a matter of concern. Access to and waiting times for clinic appointments to investigate the incidents are hugely variable but generally significantly long and more commonly at least 18 weeks rather than the ideal of six weeks after the event (see Chapter 13, Allergy clinic baseline survey and 14, Investigation). As a result the original treatment that needed to be rescheduled may be delayed while the patient waits for a clinic appointment.

Poor and ineffective communication between clinicians and between clinicians and the patient has been noted in NAP6. The patient needs to know the cause of the event and to be provided with factual written information that they can understand, rather than the clinic letter being written with medical terminology appropriate primarily for the general practitioner (GP). Both the NAP6 Allergy clinic baseline survey and the findings of the main study, reported in Chapters 13 and 14, raise concerns about timeliness of investigation and quality of communications.

The NAP6 survey of existing allergy services (Egner 2017 and reproduced as Chapter 13) provides an accurate backdrop to the patient experience. It notes, "Guidelines exist for the investigation and management of perioperative drug allergy. The distribution and quality of diagnostic services is unknown." "Variation in workload, waiting times, access, staffing and diagnostic approach was noted."

Variation can lead to a 'postcode lottery' referral system for patients. Rare events such as perioperative anaphylaxis mean that clinical experience may be limited, including the necessary protocols and experience for identifying culprits, safe alternatives and communicating effectively to patients. Services may not therefore have the ideal resources to meet the unpredictable demand. This is more specifically seen in the care of children with suspected allergy to anaesthetic drugs (Egner 2017).

NAP6, the patient journey and patient expectations

Preoperative information

In order that the patient can make the right decisions about their care, they require good information about any proposed activity, and consent must be 'informed'. Accordingly, information should be provided about the potential risks and causes of anaphylaxis during anaesthesia. The risk of severe complications such as drug reactions should be discussed before the patient attends for anaesthesia and further explored as necessary at the anaesthetist's preoperative visit. In addition, the surgeon, when taking consent, should discuss the relevant risks of adverse reactions, eg. Patent Blue dye (see Chapter 18, Patent Blue dye). The extent of the conversation will be widened by the questions and fears expressed by the patient. The challenge of providing truly informed consent in this setting has been robustly discussed recently (Chrimes 2018), but that responsibility undoubtedly lies with the clinician (Montgomery 2015, Yentis 2017).

It is not possible to comment on whether information on the incidence of anaphylaxis is currently given during the preoperative period. It is likely that many, or even most, patients will not have been advised of the risks and that relevant information is only provided after the event. Section 9 of the RCoA's Risks Associated with your Anaesthetic (RCoA 2017) clearly explains the risks of perioperative anaphylactic shock without being unduly alarmist.

Reassurance can be given by a risk assessment of the individual patient's situation and by giving information on how quickly and successfully anaphylaxis can be recognised and treated. The patient can be further assured that there is always an anaesthetist there to respond and manage the complication immediately. In this respect the findings of NAP6 (Chapter 11, Immediate management and departmental organisation) can provide considerable reassurance to patients. Providing the patient with this information in advance may also reduce sequelae and complaints. It is not known how many patients are provided with copies of Section 9 (or equivalent information) and equally how many read the information they are given.

Patients' allergy history

In 2014 NICE Clinical Guidance 183 (NICE 2014) provided a stark judgement on the quality of patients' medical notes: "Major issues identified by this guideline include poor clinical documentation of drug allergy and a lack of patient information." The NAP6 survey of existing allergy services (Egner 2017) provides patients with little confidence that the situation has improved since then.

Of the 266 reported cases included in NAP6, 162 (61%) anaesthetic charts noted a previous drug allergy. In two cases an anaesthetist administered a drug of the same class as one which the patient was known to be allergic to. Communication failures contributed to these cases. Examples of a different situation were also reported, in which patients claimed an allergy to a drug and received an alternative to which they were subsequently proven to be allergic, later to discover in the allergy clinic that they were not allergic to the drug that had been avoided. Patients may provide unreliable or incomplete accounts of their past medical history for many reasons. These include pain, stress, cognitive state, previous poor communication, confusion between allergy and intolerance, and rushed consultations to mention only a few. Reducing the likelihood of poor communication of allergy history requires robust processes to improve the reliability of information provided about past allergy, rather than relying solely on the recollection of patients.

Until anaesthetists can put a greater reliance on the allergy history as presented to them, it is important that they have the time to try to establish whether the patient is reporting a true allergy.

> A patient presented for elective surgery. They reported an allergy to penicillin and received teicoplanin prophylaxis as an alternative. They had an Grade 3 anaphylactic reaction to teiciplanin confirmed by allergy testing, which also determined that the patient was not actually allergic to penicillin.

Improved and more standardised methods of establishing accurate past allergy information at the preoperative assessment would have further benefits. A timely alert to possible problems, such as penicillin allergy, would provide time for any issues to be investigated further prior to elective surgery (see Chapter 15 Antibiotics).

Rapid diagnosis and immediate care

At a risk rate of around 1 in 10,000, (Chapter 6 Main findings), patients can take some solace that perioperative anaphylaxis is rare. Many anaesthetists will never encounter a case in their career. The speed of reaction of anaesthetists to the first symptoms presenting themselves is reassuring. In 66% of 266 cases the anaesthetist recognised the signs of a critical incident and started treatment within 5 minutes. In a further 17% cases treatment was started between 5 and 10 minutes after first presenting signs. In only 5% cases was a delay in starting anaphylaxis-specific

treatment reported. In addition in 49% of cases the anaesthetist recognised anaphylaxis as a cause of the incident within 5 minutes of the first clinical sign; anaphylaxis is not always an easy diagnosis as other acute events can present in the same ways as anaphylaxis, eg. low blood pressure due to an acute cardiac problem.

Figure 1. Elapsed time (minutes) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis
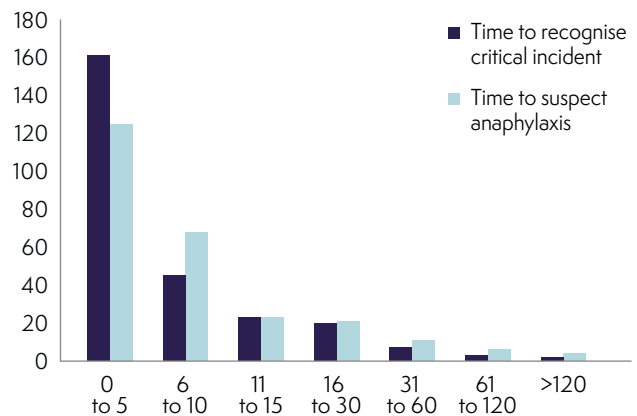
Unplanned hospital stay and unexpected harm can be concerns held by patients. Data on length of stay was available for most (78%) of patients reported to NAP6. In spite of the life-threatening nature of all the perioperative anaphylaxis reviewed in NAP6 one quarter of these patients had a normal outcome and length of stay was not extended. Thirty-seven percent of these patients had their length of stay increased by one day and 38% by more than this. Delayed discharge and levels of harm are reported in full in Chapter 12.

Providing support and information

It is important that patients are provided with details of the adverse event and advice for future care, as soon as is practical after the incident. Oral advice by itself is inadequate since recall is unreliable. The number of patients given written or written and oral advice by the department of anaesthesia was 131, which is 49% of all cases and 58% of cases where this question was answered. Some anaesthetists voiced disappointment that they had not managed to debrief appropriately with the affected patient. In narrative reports, the most common reason for the anaesthetist not visiting after the event was because the patient had been discharged on the same day or early the next. Best care requires that written advice is given in every case; we have included a template letter from the anaesthetist to the patient, as well as the GP, in Appendix B of Chapter 11.

For the other patients discharged without advice from the anaesthetist, communication depended upon the discharge letter sent to the GP. NAP6 did not seek information on whether departments of anaesthesia offered telephone helpline facilities. Most patients would be unlikely to consider a spontaneous call to the anaesthetist to allay their anxieties.

Forty-two cases were confirmed to have been reported to the Medicines and Healthcare products Regulatory Agency (MHRA) before the allergy clinic appointment and sixty three after the allergy clinic, though there was uncertainty as to who did the reporting this appeared to predominantly be done by anaesthetists. These are surprising low results given the regulatory and pharmacovigilance role undertaken by the MHRA. Patients may benefit from reports of adverse drug reactions to the MHRA as this organisation monitors for trends, and can alert clinicians to change practice as necessary.

The MHRA might also provide improved analysis of reports of anaphylaxis that it receives and these should focus on learning. Publications and communications from organisations need to be accessible to patients as well as clinicians and this includes those from the National Patient Safety Reporting Advisory Review Panel (NatRAP), the Safe Anaesthesia Liaison Group and the AAGBI Safety Committee.

Surprisingly, from a lay perspective at least, only 107 (40%) of patients were known to have been issued with a Medic Alert or other hazard warning card either by the anaesthetist or the allergy clinic.

The Allergy clinic baseline survey (Egner 2017) noted "Poor access to services and patient information provision require attention". It would appear that there is no data available indicating how many patients were referred to an allergy charity or given literature regarding the availability of information and help from an allergy charity.

Investigation – immediate care and allergy clinic

National guidance exists for the immediate care and investigation of suspected perioperative anaphylaxis. Panel review of the NAP6 data shows that collection and analysis of blood samples for mast cell tryptase was insufficient in 16% of cases. In allergy clinics, adherence to published guidelines on investigation of suspected perioperative anaphylaxis was poor (Chapter 14, Investigation).

Widespread availability and use of Anaesthetic anaphylaxis investigation packs and patient safety algorithms should improve patient outcomes (Chapter 11, Immediate management and departmental organisation).

Of the 252 patients referred to allergy clinics (98% of survivors), the time taken to be seen was available for 233: the average wait time before they were seen was 101 days. The range was large – 0 days and 450 days. Narratives from the audit indicated that many of the expedited times related to prioritised referrals of cancer surgery – however wait times for urgent cases were not shorter than non-urgent cases. There appears to be a lack of clear pathways for the prioritising and fast tracking of patients who require urgent investigation prior to surgery – accepting that genuinely urgent surgery may need to take place before allergy clinic investigation can be arranged. While there were exceptions (see vignette) these were very infrequent.

An elderly patient presented for elective cancer surgery and had a Grade 4 anaphylactic reaction after induction of anaesthesia. The index anaesthetist communicated with the allergy clinic and the patient was seen in a little over a week. Surgery was rescheduled in a timely manner thereafter.

A young patient presented for elective general surgery. Although the procedure was abandoned at the time of the reaction, it was completed before review in the allergy clinic. The clinic appointment was delayed for over 3 months.

Figure 2. Allergy clinic waiting times (days)
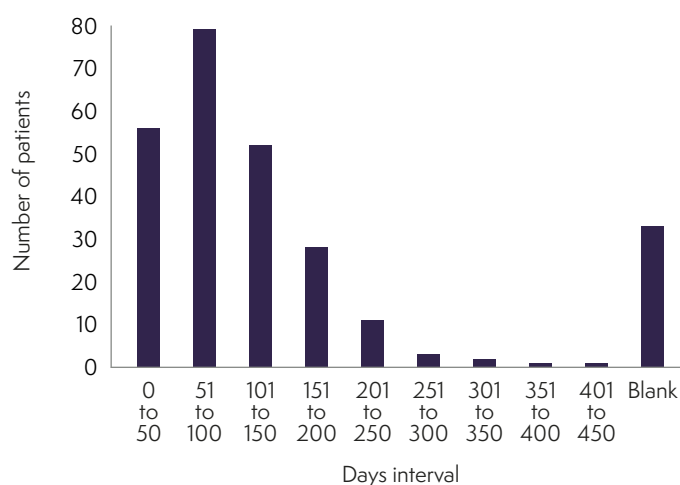
There was a considerable variety in the range of testing carried out by clinics (Chapter 14, Investigation) which may not give rise to the individual patient anxieties but is an important quality issue. Patients should receive care delivered to a set standard wherever they are referred. The standard is set in NICE guidance CG183 (NICE 2015). This issue should be addressed further as part of accreditation and monitoring of clinical standards, currently via IQAS (Improving Quality in Allergy Services).

The clinic investigation and diagnosis of anaphylaxis is, however, extremely complex and although this is guided by nationally and internationally agreed guidelines, the time to patient review is hugely variable and the interpretation of test results includes subjective decision-making. Add to this individual patient circumstances and the variation in practice takes on a different complexion. Some inconsistency of service may therefore reflect the complexities of the investigations and personalisation of consultations rather than major inconsistencies of a service where 'one size fits all' algorithms may not be appropriate.

NAP6 indicates room for improvement in terms of:

- The expediting of and the reduction in variations of wait time for allergy clinic appointments/investigations
- Consistent investigation of perioperative anaphylaxis, adhering to published guidelines including identifying a culprit agent, excluding other possible culprits and identifying safe alternatives to the culprit agent

- Improvements in delivery and clarity of allergy information given to the patient
- Consistency of reporting to MHRA, Trusts and GPs.

Medium to long term patient harm

Information on psychological and physiological sequelae as reported by patients, family members or carers was recorded after the event (Part A) and at allergy clinic review (Part B). Submission of data was limited and so the results may well provide an under estimation of the side effects associated with severe perioperative anaphylaxis. The most commonly reported longer term harm was anxiety about future anaesthetics and sedation: this was reported by 59 patients when Part A was completed and 36 patients when Part B was completed, suggesting some improvement of symptoms over time. Overall there were 104 adverse sequelae reported at the time of filling in form A (67 mild, 29 moderate and 8 severe) reducing to 73 at the time of filling in form B (41 mild, 27 moderate and five severe). Adverse sequelae (other than anxiety) included mood and memory changes, occasional alteration in coordination, mobility or PTSD-like symptoms, and a small number of patients who experienced a myocardial infarction, acute kidney injury or new shortness of breath.

These reports provide us with only limited information about long-term adverse sequelae a patient may experience. In particular there is no data available on the effect of perioperative anaphylaxis on the levels of anxiety patients experience when they actually plan for or present for another operation. In looking at long term adverse sequelae for patients, one area of particular concern meriting further analysis is the impact of perioperative anaphylactic shock on women who have a suffered an incident, while awake, during a caesarean section.

In light of the limited available evidence, there may be benefit in creating methods which enable and promote patients, carers and relatives to report complications following perioperative anaphylaxis through the NHS reporting systems.

Comment

An aspirational recommendation would be that all allergy services, as part of accreditation schemes, should gain expertise in investigation of perioperative anaphylaxis, using clear guideline-based protocols. The question, however, remains if it is pragmatic to invest in such provision at the expense of other health services.

One solution that might improve patient outcomes would be the development of arrangements for remote access to existing drug allergy centres across the UK by those clinicians who rarely receive this type of referral. Advice and expertise might well be obtained via webinar conferences. Additionally such information could be used as part of team learning for doctors, nurses, pharmacists and other health professionals as part of a multidisciplinary approach.

While allergy charities can and do provide support to patients who have suffered a perioperative anaphylactic event, they can only help those who are aware of and seek their advice. In an age of competing medical priorities, it is unlikely that the NHS will be able to provide adequate support to allergy care without significant additional funding. The charitable sector may have something to offer.

Recommendations

Institutional

1. 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.

2. 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 in addition to the discharge summary and a copy should be sent directly to the patient's GP.

3. The practice of NHS drug allergy clinics should be standardised so that patients and commissioners can expect a consistent service. British Society for Allergy & Clinical Immunology guidelines should be followed. Regulators and inspectors should pay heed to this too.

Research

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.

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5 Methods

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Key findings

- The 6th National Audit Project of the Royal College of Anaesthetists examined the incidence, predisposing factors, management, and impact of life-threatening perioperative anaphylaxis.
- NAP6 included: a national survey of anaesthetists' experiences and perceptions, a national survey of allergy clinics, a registry collecting detailed reports of all Grade 3–5 perioperative anaphylaxis cases for one year, and a national survey of anaesthetic workload and perioperative allergen exposure.
- NHS and independent sector hospitals were approached to participate.
- Cases were reviewed by a multidisciplinary expert panel (anaesthetists, intensivists, allergists, clinical immunologists, patient representatives and stakeholders) using a structured process designed to minimise bias.
- Clinical management and investigation were compared with published guidelines.
- This chapter describes detailed study methods and reports on project engagement by NHS and independent sector hospitals.
- The methodology includes a new classification of perioperative anaphylaxis, and a new structured method for classifying suspected anaphylactic events and the degree of certainty with which a causal trigger agent can be attributed.
- NHS engagement was complete (100% of hospitals).
- Independent sector engagement was limited (13% of approached hospitals).
- We received more than 500 reports of Grade 3-5 perioperative anaphylaxis, with 266 suitable for analysis.

Life-threatening allergy during anaesthesia and surgery (perioperative anaphylaxis) is a subject of importance to both patients and clinicians (Garvey 2013). This importance relates to the impact on patient safety and in relation to specific subsets of patients or drugs (Garvey 2013).

A number of factors mean that data from historical studies or from other geographical locations may not be transferable to current practice or UK practice. No major prospective study of perioperative anaphylaxis has previously been performed in the UK.

The National Audit Projects of the Royal College of Anaesthetists have an established role in examining clinically important, rare complications of anaesthesia that are incompletely studied (Cook 2009, 2011a, 2011b, 2014; Pandit 2014a, 2011b). The established methodology of the National Audit Projects (NAPs) is to perform a national survey or surveys of relevant national activity (Sury 2014; Kemp 2017) and establish a national registry for reporting of relevant cases for a time-limited period. This enables an examination of (a) pre-existing practices and beliefs, (b) relevant activity (denominator data), and (c) a large cohort of relevant cases (numerator data); and thence (d) incidence data.

Methods

The 6th National Audit Project (NAP6) was commissioned by the Health Services Research Centre (HSRC) of the National Institute of Academic Anaesthesia for the Royal College of Anaesthetists (RCoA). It is the sixth in a series of 'national audits' (though these are more correctly described as service evaluations) conducted by the specialty.

The topic for NAP6 was selected by open tender for proposals in 2013. There were 91 proposals covering 33 topics (Cook 2013). The topic of perioperative anaphylaxis was selected by a committee composed of members of the HSRC executive board.

The intention of the project was to establish:

- What proportion of cases of suspected perioperative anaphylaxis are referred and or investigated?
- What proportion of investigated cases is proven or unproven?
- How well does management, referral and investigation match published guidelines?
- Is there any correlation between drugs used in resuscitation, (eg. adrenaline, alpha-agonists, vasopressin) and outcome for severe cases?

The methodology of NAP6 is similar to, and builds upon, that used for NAP3, NAP4, and NAP5 (Cook 2009, Cook 2011a, Pandit 2014a).

The NAP6 project was approved by Confidentiality Advisory Committee of the NHS Health Research Authority, the National and Local Caldicott Scrutiny Processes in Scotland, and the Privacy Advisory Committee for Northern Ireland. The Confidential Advisory Committee deals with approvals for the handling of patient-identifiable information across the NHS. If such information

is required, then approvals are required under Section 251 of its governance procedures. Since no patient-identifiable information was used, no Section 251 application was necessary. The National Research Ethics Service confirmed it to be a service evaluation, not requiring formal ethical approval. The project received the endorsement of all four Chief Medical Officers of the UK.

All hospitals in the UK performing surgical procedures with anaesthetist involvement were contacted. This included 356 UK NHS hospital centres and 304 independent sector hospitals believed to perform surgical work. All NHS centres volunteered a Local Coordinator (LC) – a consultant anaesthetist who became responsible for delivering the project at their hospital and for liaising with the central NAP6 team. Several LCs were responsible for more than one hospital within a Trust (England, Northern Ireland) or Board (Scotland, Wales). During efforts to engage with the independent sector hospitals more than 300 hospitals were contacted on several occasions.

There were four elements to the project. First, a baseline survey collected retrospective data on anaesthetists' previous experiences with perioperative anaphylaxis, and their perceptions and patterns of risk avoidance (Kemp 2017 and Chapter 7). Second, UK allergy clinic services were surveyed to identify clinics that investigated suspected perioperative anaphylaxis and to compare their practices against guidelines (Egner 2017 and Chapter 13). Third, the main prospective study collected anonymised case reports over a one-year period. Fourth, a prospective survey, also in 2016, collected comprehensive information on workload, demographics and patients' exposure to potentially allergenic drugs and other substances during anaesthesia and surgery (Chapters 8 and 9).

LCs were sent detailed information (available at http://www.nationalauditprojects.org.uk/NAP6-Resources#pt) and were tasked with disseminating and coordinating all phases of the project locally.

All allergy clinics investigating perioperative anaphylaxis were contacted and informed of the project. Materials were made available to enable them to give LCs detailed information about tests performed and their results when investigating suspected perioperative anaphylaxis.

LCs were asked to ensure the reporting of all cases of suspected life-threatening perioperative anaphylaxis to the NAP6 team. Anaphylaxis was defined as 'a severe, life-threatening, generalised or systemic hypersensitivity reaction'. Perioperative anaphylaxis was defined as:

Anaphylaxis which occurs in patients undergoing a procedure requiring general or regional anaesthesia or sedation or managed anaesthesia care (anaesthetist monitoring only) under the care of an anaesthetist between the period of first administration of a drug (including premedication) and the post-procedure transfer to the ward, or critical care.

As we only wished to collect cases of life-threatening anaphylaxis, it was emphasised that only anaphylaxis Grades 3–5 (Table 1) were to be included. Cases were to be included irrespective of age or hospital location, but patients in critical care or the emergency department were excluded unless undergoing procedural general anaesthesia.

Table 1. Grading of perioperative hypersensitivity/ anaphylaxis used for determining inclusion or exclusion in the NAP6 project

Grade	Features	NAP6
1 *Not life-threatening*	Rash, erythema and/or swelling	Excluded
2 *Not life-threatening*	Unexpected hypotension – not severe, eg, not requiring treatment and/or bronchospasm – not severe, eg, not requiring treatment +/- Grade 1 features	Excluded
3 *Life-threatening*	Unexpected severe hypotension and/or severe bronchospasm and/or swelling with actual or potential airway compromise +/- Grade 1 features	Included if perioperative anaphylaxis suspected
4 *Life-threatening*	Fulfilling indications for CPR	Included if perioperative anaphylaxis suspected
5 Fatal	Fatal	Included if perioperative anaphylaxis suspected

Each month the LC was required to provide the central NAP6 team with a monthly 'return' indicating the number of reports of suspected life-threatening perioperative anaphylaxis identified that month, using a system developed by the UK obstetric surveillance system (Knight 2007) and also used in NAP5 (Pandit 2014a). Where no reports were received the LCs returned a 'nil' report.

Presentations, posters and promotional material were provided to each LC, and the project was widely advertised nationally (Figure 1). Information provided to LCs included advice on interpretation of grades of anaphylaxis and a series of 'frequently asked questions', with answers. For example, LCs were advised to regard hypotension that was mild or required modest doses of a vasopressor or fluid as meeting the definition of Grade 2, whereas hypotension that was profound, sustained, resistant to treatment, or requiring extensive treatment met the criteria for Grade 3.

Figure 1. Supporting information on which cases should be reported to NAP6
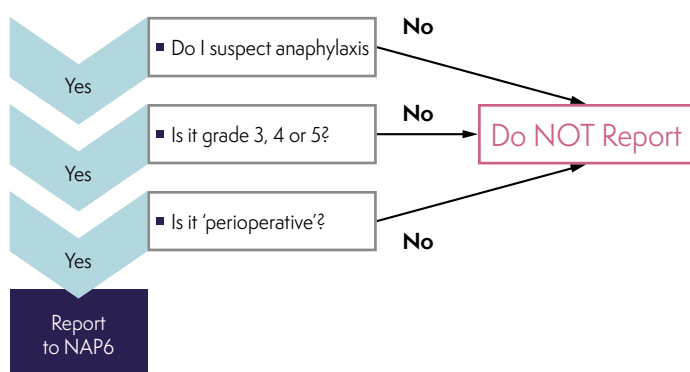
Reporting cases

Reporting was in two parts.

Part A included details of the patient, drugs administered, the clinical features, management and timings relating to the event, outcomes, contributory factors, referral for investigation, and details of reporting of the event and communication to the patient. LCs were asked to submit Part A as soon as possible after the suspected anaphylactic event. Definitions of clinical features associated with anaphylaxis that should be reported were provided in the webpage supporting information (Table 2).

Table 2. Definitions of clinical features

Term	Definition
Cardiac arrest	Absence of effective cardiac output
Hypotension	Fall in blood pressure greater than could be explained by coexisting co-morbidities, neuraxial blockade, or daily medication
Bronchospasm	Wheeze and/or raised ventilatory pressure greater than could be readily explained by coexisting co-morbidities
Cyanosis/ oxygen desaturation	Subjective appearance of cyanosis or unexpected fall in SpO_2
Reduced/absent capnography trace	Unexpected low amplitude of capnography trace, or absent trace
Flushing/ non-urticarial rash	Erythema or non-raised rash
Urticaria	Raised wheals
Laryngeal oedema	Glottic swelling seen at laryngoscopy or stridor suggestive of glottic swelling
Swelling/oedema (non-laryngeal)	Any other swelling
Tachycardia	Rise in heart rate not readily explicable by coexisting co-morbidities or a light plane of anaesthesia
Bradycardia	Fall in heart rate not readily explicable by coexisting co-morbidities, concomitant drug administration, coexisting beta adrenergic blockade, or vagal reflex
Patient feeling unwell	The awake patient complains of acutely feeling unwell
Itching	The awake patient complains of itching

The following text accompanied the table: "Some of the clinical features are subjective. The anaesthetist should use their own judgement when interpreting these definitions. If unsure whether to report a particular clinical feature, the general guidance is to include rather than exclude. NAP6 includes only severity Grades 3, 4 and 5, ie, severe anaphylaxis. Some non-life-threatening clinical features may be additionally present and these should be recorded".

Part B was to be completed by the LC after allergy clinic investigation was complete. It included full details of allergy clinic investigations, sought to confirm patient outcomes, and updated the data for reporting to national registries and the information given to patients. Part B was not required for fatalities.

Between them, the two parts of the case reporting form collected detailed information on all aspects of the event and patient care.

The questions are not reproduced here but are available at http://www.nationalauditprojects.org.uk/NAP6-Data-Entry#pt.

Cases were included if the event occurred between 00:00 hours on 5 November 2015 and 23:59.59 hours on 4 November 2016. Reports were accepted until May 2017 to allow for allergy clinic waiting times.

Case reporting was confidential. When an LC or other anaesthetist wished to report a case, they contacted the NAP6 administrator. The reporter was required to confirm:

- That this was a case of suspected perioperative Grade 3–5 anaphylaxis, as defined above
- That the case occurred in the data-collection period
- Whether the case took place in an NHS or independent sector hospital.

After confirmation that the case met the inclusion criteria, the reporter was issued with a unique identifier and password. These were used to submit case details to a password-protected, secure and encrypted website. Before accessing the webform the LC was required to change their password. Cases arising from NHS and independent sector hospitals were assigned different series of numbers for easy identification. No patient, clinician or hospital data was admissible, and the webpages repeatedly reminded reporters not to include such information.

The NAP6 administrator could track progress of reporting ('not started', 'started but incomplete', 'complete', 'submitted') but could not access forms. Once completed and submitted, the anonymised form was automatically transferred electronically to the project clinical lead, who was able to raise queries and receive replies about case reports via a blind email (ie. he was blinded to where the email went to or from where replies came). No other panel members received reports or had access to the website. In this manner, no panel member was aware of the geographical origin of any case, nor of any individuals involved in managing the case.

A moderator, a consultant anaesthetist with appropriate expertise, was available to discuss cases when there was uncertainty about inclusion. The moderator was not on the review panel and had no contact with the review panel throughout the project.

Review of cases

The NAP6 panel met monthly to review and classify cases. The panel was composed of 25 representatives of patient support groups, patient representatives, and clinicians in relevant fields (anaesthesia, critical care, allergy, immunology) representing stakeholder and subspeciality organisations. Clinicians were selected by stakeholder organisations and, while many had specific expertise in allergy, this was not a requirement for joining the panel.

The panel reviewed each case in detail and in a structured manner, three times. First, the clinical care (Part A) was reviewed by a small group of 3–5 clinical and patient representative panel members. Second, Allergists and Immunologists reviewed drug administration and allergy investigations (relevant parts of Part A and all of Part B). Several groups performed these tasks on different cases concurrently. The outputs of the reviews were used to populate a structured output form (Appendix 1) and spreadsheet for subsequent analysis. When sufficient cases were reviewed, all groups joined into a large panel – typically 12-15 panel members – and the cases were again reviewed to combine the outputs of the clinical and allergy/immunology reviews, and to check and moderate each small group's findings.

This process was used in an attempt to avoid 'outcome bias' (where the known poor outcome leads to an unreasonably harsh judgement) (Caplan 1991), 'hindsight bias' (where retrospective review leads to a tendency to believe that an adverse outcome was predictable or avoidable) (Henriksen 2003) and 'groupthink' (where a desire to agree within groups leads to a lack of independent scrutiny) (Turner 1998).

In judging quality of care, we referred to guidelines from:

- The Association of Anaesthetists of Great Britain and Ireland on management of suspected anaphylaxis associated with anaesthesia (Harper 2009)
- The Resuscitation Council (UK) on management of anaphylaxis (RCUK 2016)
- The European Resuscitation Council on cardiopulmonary resuscitation (Soar 2015)
- The British Society for Allergy and Clinical Immunology (BSACI) guidelines on investigation of anaphylaxis during general anaesthesia (Ewan 2010).

In addition, the review panel referred, where appropriate to NICE Clinical Guidance – *NICE CG183 Drug allergy: diagnosis and management of drug allergy in adults, children and young people* (NICE 2014, Dworzynski 2014), and *NICE CG134 Anaphylaxis: assessment and referral after emergency treatment* (NICE 2011).

As these guidelines were used to measure deviation from standards of care, NAP6 had a greater genuine 'audit' component than previous NAPs. Overall quality of care (initial management, clinic referral by anaesthetist and allergy clinic investigation) were also each judged as 'good', 'poor', 'good and poor' or 'unassessable' based on adherence to guidelines, and ultimately by panel consensus.

It became rapidly apparent that cardiopulmonary resuscitation (CPR) was frequently not started when there was profound hypotension. We therefore defined a systolic blood pressure, below which we judged that CPR should be started, which we set at 50 mmHg (see discussion). These cases were classified as Grade 4. When CPR was not started, we judged this as failure to initiate CPR when indicated, and judged this to be a deviation from resuscitation guidelines.

The case report form included specific questions about potential errors related to allergy history or administration of cross-reacting substances. Preventability of each case was classified as 'yes', 'no', or 'uncertain', and reasons for the judgement that the event could have been prevented were recorded.

Patient outcomes were measured in two ways. Individual patient outcomes were captured on the case report form, including new anxiety about future anaesthetics, symptoms consistent with post-traumatic stress disorder, change in mood, impaired memory, impaired coordination, impaired mobility, myocardial infarction, heart failure, renal impairment, and stroke. Overall severity of patient outcome, was recorded using the National Patient Safety Agency (NPSA) classification of severity of harm from patient incidents shown in Table 3 (NPSA 2008). In most cases Grade 3 anaphylaxis itself meets the definition of moderate harm. When resuscitation had only involved minimal doses of vasopressor or other drugs and no further action had been taken, the case was deemed to meet the criteria for minimal harm. Apparently permanent sequelae (ie. persisting symptoms or deficits at follow-up) were recorded as severe harm, as were cardiac arrest and ICU stay of more than 14 days.

Table 3. Degree of physical harm
Modified from: NPSA Seven steps to patient safety (NPSA 2008).

Severity grade	Description (tick against the most severe feature)
Uncertain	Insufficient information
Mild	Minimal harm necessitating extra observation or minor treatment*
Moderate	Significant, but not permanent harm, or moderate increase in treatment** Includes delayed cancer surgery
Severe	Permanent harm due to the incident***, including cardiac arrest; adverse sequelae recorded as 'Severe' in Part A or Part B; ICU stay of 14 days or longer
Death	Death due to the incident

* first aid, additional therapy, or additional medication. Excludes extra stay in hospital, return to surgery, or re-admission.

** return to surgery, unplanned re-admission, prolonged episode of care as inpatient or outpatient, or transfer to another area such as Intensive Care.

*** permanent lessening of bodily functions, sensory, motor, physiologic or intellectual.

Table 4. Immunological classification of reports to NAP6

Class of event *In addition to history of reaction Grade 3, 4, 5*	High certainty	Intermediate certainty
Allergic anaphylaxis (IgE-mediated)	Timeline – within 60 min Evidence of mast cell mediator release tryptase Evidence of positive sIgE (blood or skin tests)* Differential diagnoses excluded 4/4 criteria; *essential	Timeline – within 60 min Evidence of mast cell mediator release tryptase Evidence of positive sIgE (blood or skin tests)* Differential diagnoses excluded 3/4 criteria; *essential
Non-allergic anaphylaxis (non-IgE-mediated)	Timeline – within 60 min Evidence of mast cell mediator re-release tryptase *(see note 2)* *No evidence of* positive sIgE (blood or skin tests) Differential diagnoses excluded 4/4 criteria	Timeline – within 60 min Evidence of mast cell mediator re-release tryptase *No evidence of* positive sIgE (blood or skin tests) Differential diagnoses excluded 3/4 criteria
Anaphylaxis - mechanism uncertain	Timeline – within 60 min Evidence of mast cell mediator release tryptase Skin tests or blood sIgE not available 3/3 criteria	-
Anaphylaxis uncertain	Meeting 2/3 criteria in 3 above, *and/or* Differential diagnoses more likely: Airway management Drug side effect Drug overdose Cardiac disease/event	-
Not anaphylaxis	Not meeting clinical criteria for diagnosis (as per grading)	-

Each event was classified as 'allergic anaphylaxis', 'non-allergic anaphylaxis', 'anaphylaxis mechanism uncertain', 'anaphylaxis uncertain' or 'not anaphylaxis' using the classification shown in Table 4.

In order to classify the type of each event, a definition of 'mediator release' was required. Providing mast cell tryptase samples were taken at appropriate times after the event (broadly: soon after the event and approximately 1 to 3 hours after the event and a baseline sample either taken before the event or ≥24 hours after the event) the following definition was used:

- Peak mast cell tryptase ≥1.2 x nadir value + 2μg.L^{-1} (Valent 2012) or
- Peak mast cell tryptase ≥14 μg.L^{-1} (ie, >99th centile for normal mast cell tryptase levels) (Egner 2016).

This was a pragmatic definition, and made in the knowledge that the second part of the definition might not fully exclude a very small number of cases of mastocytosis.

Where there was uncertainty, differential diagnoses other than anaphylaxis were carefully considered by the full review panel.

In determining adequacy of allergy clinic investigation, BSACI guidelines (NICE 2014, Mirakian 2009 and 2015) were used by the immunologists and allergists to set the following rules.

- Where testing for allergy to a neuromuscular blocking agent (NMBA) was necessary, given variable access to some NMBAs the NAP6 'minimum panel of NMBAs' (Egner 2017) was applied: suxamethonium, rocuronium and either atracurium or cisatracurium should have been tested, and at least one safe alternative should have been sought
- Chlorhexidine and latex should have been investigated routinely because of the widespread risk of exposure
- For skin prick tests (SPTs) and intradermal tests (IDTs) to be judged appropriate, there should be no tests performed that were not indicated. This was to exclude 'scatter-gun' testing being judged as good practice
- Allergy to antibiotics and particularly beta-lactams could only be excluded if a negative skin test was followed by negative provocation testing.

The allergists and immunologists reviewed each case that was confirmed to be anaphylaxis, to determine all possible causative agents (culprits). Reviewing the clinical data and allergy clinical tests, they identified these drugs as having high, intermediate or low culpability.

We recorded 'identified culprits' as follows:

■ 'Definite': where one sole agent was recorded with a high degree of confidence and any other agents with intermediate or low confidence

■ 'Probable': where:

- Only one agent was recorded with an intermediate degree of confidence and any other agent was identified with low confidence

- Two agents were both recorded with a high degree of confidence

■ 'Possible': where two agents were recorded with an intermediate degree of confidence and none with a high degree of confidence

■ 'Do not count': where:

- More than two agents were recorded with a high degree of confidence

- More than two agents were recorded with an intermediate degree of confidence

- The only agents recorded were identified with a low degree of confidence.

Agents meeting the criteria for Definite or Probable were considered to be 'identified culprits': agents meeting the criteria for Possible or Do not count, were not.

Approximately 10–12 cases were fully reviewed each day in the early part of the review process, increasing to up to 22 per day in the latter stages as the panel became more familiar with the process. Due to the high number of cases submitted we were not able to perform full reviews of all cases. The remaining cases in the main dataset had a briefer review that determined: the diagnosis of anaphylaxis, the grade of anaphylaxis, all potential culprits, and 'identified culprits'.

Results

The results of the Allergy clinic baseline survey (Egner 2017, Chapter 13), Anaesthesia baseline survey (Kemp 2017, Chapter 7) Anaesthetic Activity Survey (Chapter 8) and Allergen Survey (Chapter 9) are each reported separately and are not considered further here.

There were no technical or security breaches of the website, or concerns about identification of patients, clinicians or hospitals.

All 356 (100%) NHS hospitals where surgery was undertaken agreed to take part in the project and volunteered an LC. These 356 hospitals were served by 282 LCs. Eighty-four percent of NHS hospitals returned all scheduled monthly reports: the overall return rate of monthly reports from NHS hospitals was 94%.

Responses were considerably fewer from independent sector hospitals. In total 41 (13%) independent sector hospitals volunteered to participate, and these hospitals were included in data collection. Thirty-nine percent of these independent sector hospitals returned all monthly reports: overall return rate of scheduled monthly reports from these independent sector hospitals was 70%.

In view of the small number of independent sector hospitals that agreed to participate, it was decided that this sample would not be representative of practices or events in this healthcare sector and a decision was made to include their data only for examination of isolated events and not for numerical analysis.

The full results of analysis and the findings of reports of anaphylaxis are presented in the accompanying chapters. We present here the results of the NAP6 process.

There were 628 requests made for login details to the reporting website. A total of 541 cases were submitted: 412 with Part A and Part B completed or fatalities, 125 survivors with only Part A completed, and four with only Part B completed. Amongst these there were seven requests for an identifier for the reporting website from independent sector hospitals but only two cases were fully reported. These cases were not included in the main dataset.

Only those cases with Part A and Part B (n=402), or deaths (n=10) were considered for review. Of these, 93 were not suitable for review due to lack of detail or not meeting entry criteria, 27 were uninterpretable, 15 were not anaphylaxis, nine were excluded as being Grade 2, and two were from independent sector hospitals.

A total of 266 (256 with Part A and B and 10 fatalities) NHS cases met inclusion criteria, were interpretable, and were Grade 3–5 anaphylaxis: these formed the main dataset.

A total of 217 cases were fully reviewed, including 184 of the main dataset. The remaining 82 cases underwent limited review, as described above.

Figure 2. Flowchart of included cases
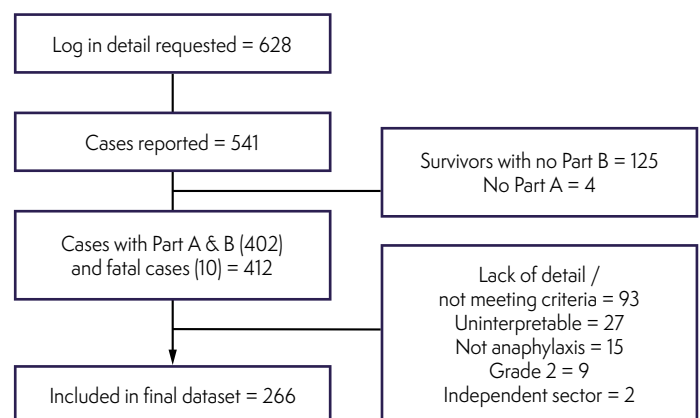
Discussion

NAP6 is likely to be the most comprehensive prospective study of perioperative anaphylaxis ever undertaken. It provides prospective data on a large number of cases which have all been subject to structured multidisciplinary expert review. It presents the opportunity to learn about preparedness of hospitals and clinicians, clinical presentation of perioperative anaphylaxis, severity, immediate management, referral for investigation, and outcomes. It collates significant epidemiological data about distribution of anaphylaxis grade, suspected and actual triggers, and non-standard treatments. Further, it describes the quality of management and investigation in a 'real world' setting, and of communication between clinicians and with patients.

In order to collect and analyse these data in a meaningful manner it was important to perform a structured analysis of cases. That structure was underpinned by clear definitions of which events should be included or excluded, and also by classification during review. We followed the review process previously used in previous NAPs which included multiple, serial, multidisciplinary reviews incorporating patient representation, formal moderation and a structured output. Review of events that have already happened is always prone to the limitations of 'looking backwards' and this may be exacerbated when the outcome of the event is known. Our processes made every effort to produce balanced judgements, accepting these known limitations.

Anaphylaxis is "a severe, life-threatening generalised hypersensitivity reaction" (Johansson 2003). Lesser hypersensitivity reactions should not be included in the term anaphylaxis. Unlike many previous large-scale studies of hypersensitivity we have focused only on genuinely life-threatening reactions (ie. true anaphylaxis). We judged this would enable us to gather the most clinically powerful lessons, to improve engagement in the project and to increase capture rates. These are also the cases where most is to be gained (or lost) in efforts to improve care.

There are numerous gradings scales and definitions of severity of hypersensitivity/anaphylaxis and the cut-offs between grades vary considerably. This has implications for data analysis and comparisons between studies. Ring and Messmer's 1977 classification included four grades, with Grade 3 defined as "shock, life-threatening spasm of smooth muscles (bronchi, uterus etc.)" and Grade 4 as "cardiac and/or respiratory arrest" (Ring 1977). Garvey in 2001 described only three grades with the highest grade (Grade 3), including all "Very severe reactions requiring prolonged treatment, eg, anaphylactic shock, usually, but not always, involving two or more organ systems" (Garvey 2001). Mertes in 2003 included in Grade 3 the life-threatening events – "cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm", and in Grade 4 "circulatory inefficacy, cardiac and/or respiratory" (Mertes 2003). In 2007 Krøigaard introduced Grade 5: fatal anaphylaxis (Krøigaard 2007). A consensus on diagnostic criteria for definition of anaphylaxis was reported in 2006 but this has significant limitations if applied to perioperative anaphylaxis (Sampson 2006). In 2010 yet another classification was published – classifying all hypotension as Grade 4 (Cox 2010).

Despite this apparent surfeit of grading systems, we found none that was entirely clear or satisfactory, and developed the classification shown in Table 1. This classification aimed specifically to accommodate the normal variations in vital signs and physiology that can be seen in the perioperative setting, particularly in elderly, frail or co-morbid patients. The NAP6 classification of perioperative (hypersensitivity and) anaphylaxis uses the pragmatic terms 'unexpected' and 'severe' in the belief that anaesthetists can distinguish the usual from the unusual, and a reaction requiring rescue treatment from one which does not. We used a clear cut-off for Grade 4, ie. if indications for initiating CPR are fulfilled. During the NAP6 project another group published a new classification, and this also usefully reviews many of the existing classifications and their limitations in respect to perioperative anaphylaxis (Rose 2016). This used three Grades A–C: Grade A is not life threatening and therefore does not meet the accepted definition of anaphylaxis, and Grade B includes some Grade 2–3 characteristics of other groups, with Grade C being similar to Krøigaard's Grade 4.

During early case reviews it became apparent that 'indication for CPR' might not be as clear-cut as we had thought. The case report form asked both for the lowest blood pressure recorded and whether CPR was started. In a large number of cases the lowest systolic blood pressure was very low, often being <60 mmHg or <50 mmHg or even unrecordable, but CPR was not performed. This was discussed at length in the panel. We took external advice from experts in resuscitation and anaphylaxis, and their guidelines and concluded that it was logical to set a lowest systolic blood pressure at which it was reasonable that CPR should start in adult patients. In the awake patient it is now routine to start CPR when 'there are no signs of life/signs of responsiveness'. As perioperative anaphylaxis most commonly takes place after induction of anaesthesia, these signs are absent. In invasively monitored patients a blood pressure of <50 mmHg is predictive of central and peripheral pulselessness (Deakin 2000), which should trigger CPR. As non-invasive blood pressure monitors tend to over-estimate the blood pressure in severe hypotension, a non-invasive blood pressure recording of <50 mmHg implies that the true blood pressure is even lower. We therefore judged that when the lowest systolic blood pressure was <50 mmHg, CPR was indicated. This rule was then applied to all adult cases. These cases were recorded as Grade 4, and if CPR was not started recorded as 'CPR not started when indicated'. We also judged this to be a deviation from (resuscitation) guidelines and recorded whether this was the only such deviation. This group of patients (lowest systolic blood pressure and no CPR) were examined as a separate cohort to explore whether their outcomes differed from other patient groups (Chapter 12, Deaths, cardiac arrest, and profound hypotension). The NAP6 classification of grade of anaphylaxis was therefore updated to include this critical blood pressure cut-off (Table 5).

Table 5. Grading of perioperative hypersensitivity/ anaphylaxis used for analysis in the NAP6 project

Grade	Features	NAP6
1 *Not life-threatening*	Rash, erythema and/or swelling	Excluded
2 *Not life-threatening*	Unexpected hypotension – not severe, eg, not requiring treatment and/or bronchospasm – not severe, eg, not requiring treatment +/- Grade 1 features	Excluded
3 *Life-threatening*	Unexpected severe hypotension and/or severe bronchospasm and/or swelling with actual or potential airway compromise +/- Grade 1 features	Included if perioperative anaphylaxis suspected
4 *Life-threatening*	Fulfilling indications for CPR including systolic blood pressure <50 mmHg	Included if perioperative anaphylaxis suspected
5 Fatal	Fatal	Included if perioperative anaphylaxis suspected

In the analysis of investigation of anaphylaxis the allergists and immunologists on the panel required a clear way to classify the type of immunological event, and devised that shown in Table 4. The presence of a dynamic tryptase rise was determined using an accepted consensus method (Valent 2012), which has (since NAP6 started) been confirmed to have high specificity (78%), positive predictive value (98%) and a moderate negative predictive value (44%) in perioperative anaphylaxis (Baretto 2017). Where there was no dynamic rise in tryptase we used a value of >99th centile as indicating elevation: this has been shown to improve sensitivity of the above test (Egner 2016). This goes well beyond previous reports which have often simply classified cases as 'IgE-mediated' (hypersensitivity with skin prick test positive), 'non-IgE-mediated' (hypersensitivity with skin prick test negative), or 'unclassified'. Assessing the utility and quality of the allergy clinic investigation was further aided by including the consensus view that the NAP6 minimum panel of NMBAs (Egner 2017) should be used, and that allergy to both chlorhexidine and latex should be tested routinely because of their widespread (and often hidden) presence in healthcare settings (Egner 2017, Ewan 2010, Scolaro 2017, Mertes 2011). Finally, we used a structured method to define the degree of certainty with which culprit agents were identified, and only included those that were Definite or Probable culprits in reporting our findings.

The published guidelines selected for providing standards against which the quality of practice was assessed (Harper 2009, RCUK 2016, Soar 2015, NICE 2011, NICE 2014) were chosen to encompass immediate resuscitation (including from cardiac arrest), secondary clinical management, referral to an allergy clinic, primary and specialist allergy investigation, record keeping, and communication with patients and healthcare professionals. UK guidelines were selected, being the most relevant to the patient population being studied.

Using this method, we received more than 500 reports of perioperative anaphylaxis. We were able to include 266 cases and identify 199 culprit agents in 192 cases. Our findings are discussed in context and with full numerical analysis in the following chapters.

As with previous NAPs, NAP6 is the product of a concerted national effort by all departments of anaesthesia in the UK, and, through its various phases, the vast majority of UK anaesthetists. This project has also involved considerable multidisciplinary working with both allergists and immunologists. The project could not take place without the generous voluntary efforts of many people and we acknowledge that here and offer them our thanks. The NAPs require anaesthetists to report cases where a significant critical incident has occurred, and harm may have come to the patient.

We rely on anaesthetists' openness and honesty. The NAP6 panel, including the clinical lead, had no access to any identifiable information regarding the geographical source of any report, the identity of the reporter, or any patient, hospital or clinician identifiable details. This anonymity, embedded within the project design, remains central to its success.

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Appendix 1:
Panel review form

Date of review: Case ID:

Does the report meet the inclusion criteria?   ☐ **Yes**   ☐ **No**
If no, why?

Might it be a duplicate?   ☐ **Yes**   ☐ **No**
If yes, action taken:

Is the report interpretable?   ☐ **Yes**   ☐ **No**
If no, action taken:

Timing of event ("induction" refers to first drug/substance administered by the anaesthetist)

☐ Pre-induction   ☐ After induction and before surgery/intervention

☐ During surgery/intervention   ☐ After completion of surgery/intervention

Class of event (as determined by review panel)

☐ Allergic anaphylaxis   ☐ Non-allergic anaphylaxis   ☐ Anaphylaxis, mechanism uncertain

☐ Not anaphylaxis   ☐ Uncertain   ☐ Not stated

Class of event (as determined by allergy clinic)

☐ Allergic anaphylaxis   ☐ Non-allergic anaphylaxis   ☐ Anaphylaxis, mechanism uncertain

☐ Not anaphylaxis   ☐ Uncertain   ☐ Not stated

Grade of event as determined by review panel: ☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5   ☐ Uncertain

Immediate care (tick)

	Yes	No	Unclear	N/A
Resuscitation by anaesthetist of appropriate grade				
Prompt recognition of critical event				
Prompt recognition of anaphylaxis				
Appropriate airway management				
Prompt pharmacological treatment for anaphylaxis				
Comprehensive pharmacological treatment for anaphylaxis				
Prompt initiation of cardiac compressions				
Administration of adrenaline when indicated				
Appropriate iv fluid management				
Suspected culprit agent discontinued promptly				
Actual culprit agent discontinued promptly				
Intervention abandoned appropriately				

Clinical management by the anaesthetist:

☐ Good ☐ Poor ☐ Good and poor ☐ Unassessable

Subsequent care (tick)

	Yes	No	Unclear	N/A
Transfer to different hospital for HDU/ICU				
Written information given to patient prior to clinic appointment				
Appropriate MCT samples requested				
Appropriate MCT results available				
Investigation impacted by unactioned MCT sample request(s)?				
Was the patient referred to an allergy clinic if appropriate?				
Was adequate information provided to the allergy clinic at referral?				
Was the clinic waiting time significantly detrimental to the patient?				
Patient given written information by anaesthetist prior to clinic appointment				
Patient given hazard warning, eg, Medic Alert by anaesthetist				
Case reported to MHRA by anaesthetist				

Referral to allergy clinic:

☐ Good ☐ Poor ☐ Good and poor ☐ Unassessable

Allergy clinic investigation (tick)

	Yes	No	Unclear	N/A Unclear	If no specify
All potential culprits investigated					
Sufficient panel of muscle relaxants*					
Chlorhexidine investigated*					
Latex investigated*					
Appropriate SPTs*					
Appropriate IDTs*					
Appropriate blood tests					
Was it necessary to measure baseline MCT in clinic					
Appropriate challenge tests					
Appropriate advice on future avoidance					
Written information to patient, eg, copy of clinic letter					
Clinic letter to anaesthetist					
Clinic letter to GP					
Patient given Hazard Warning, eg, Medic Alert by clinic					
Case reported to MHRA by clinic					

*see crib sheet

Referral to allergy clinic:

☐ Good ☐ Poor ☐ Good and poor ☐ Unassessable

Culprit agent(s)

Identity of drugs/ substance suspected by:	Drug/substance 1	Certainty H/I/L/Not stated	Drug/substance 2	Certainty H/I/L/ Not stated	Unable to identify (tick)	Not recorded (tick)
Anaesthetist						
Allergy clinic						
Review panel						

CONTRIBUTORY AND CASUAL FACTORS

Specific (tick those that apply)

	Yes	No	Unclear	N/A
Incomplete pre-intervention allergy history				
Pre-intervention allergy history not heeded				
Possibility of cross-sensitivity not heeded				
A previous reaction was not appropriately investigated				

Was the index event preventable? ☐ Yes ☐ No ☐ Uncertain

If yes, how might it have been prevented?

If there was a further reaction, could it have been prevented? ☐ Yes ☐ No ☐ Uncertain ☐ N/A

If yes, how might it have been prevented?

SEVERITY OF PHYSICAL HARM (NPSA)

This is the harm occasioned by the whole episode (see crib sheet)

Severity grade	Description (tick against the most severe feature)	Tick
Uncertain	Insufficient information	
None	No harm (whether lack of harm was due to prevention or not)	
Low	Minimal harm necessitating extra observation or minor treatment	
Moderate	Significant, but not permanent harm, or moderate increase in treatment	
Severe	Permanent harm due to the incident	
Death	Death due to incident	

DEPARTURE FROM GUIDELINES

Significant departure from:	Unclear	N/A	Yes	No	If yes specify
AAGBI Safety Guidelines					
RCUK Guideline					
BSACI Guideline on investigation					

Lessons to be learned:

Any possible recommendations arising:

Amend Summary Narrative ☐ Yes ☐ No

Action taken:

Consider: Any further information needed. If yes, action taken:

Is this case suitable for a vignette? ☐ Yes ☐ No

If yes, why?

Nigel Harper   Tim Cook

This chapter describes summary findings from NAP6 in two parts.

Part A: Epidemiology and clinical features of perioperative anaphylaxis

Key findings

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

- Poor outcomes were associated with increased age, ASA grade, obesity, beta-blocker, and/or ACE inhibitor medication.
- Seventy per cent of cases were reported to the hospital incident reporting system and only 24% to the Medicines and Healthcare products Regulatory Agency via the Yellow Card Scheme.

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

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

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

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

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

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

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

Methods

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

Results

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

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

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

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

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

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

Clinical features

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

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

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

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

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

Figure 1. First clinical feature (%) in allergic anaphylaxis and all patients with Grade 3-5 perioperative anaphylaxis
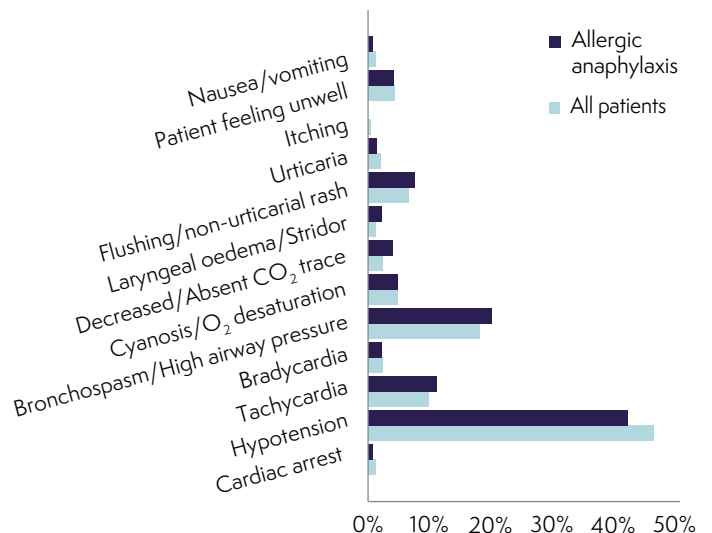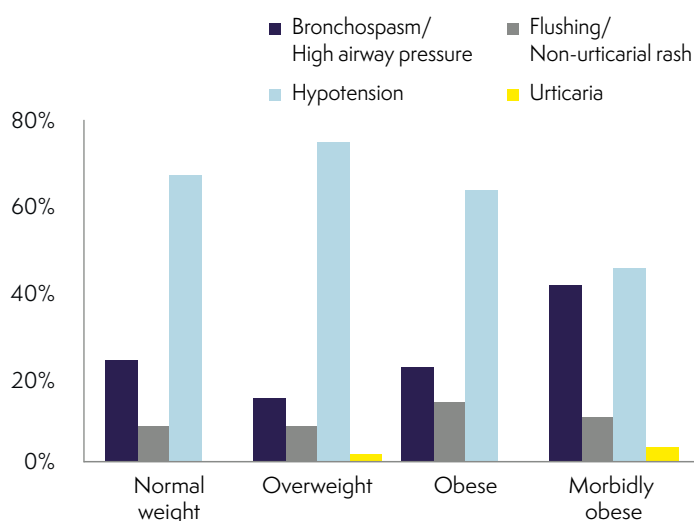
Figure 2. Presenting features and body habitus in Grade 3-5 perioperative anaphylaxis


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

Figure 3. Presenting features of Grade 3-5 perioperative anaphylaxis in female and male patients
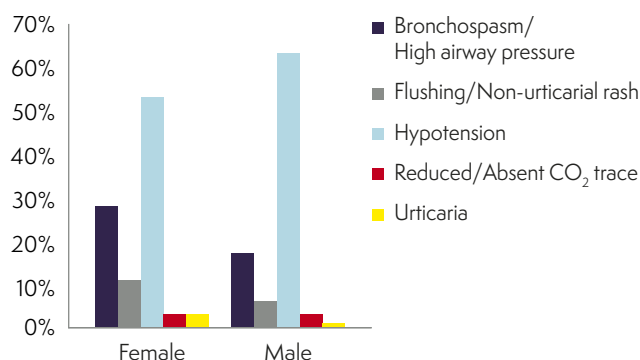
There was a marked difference between NMBAs: bronchospasm was the most common presentation when suxamethonium was the trigger and hypotension with atracurium (Figure 4).

Figure 4. Presenting features of Grade 3-5 neuromuscular blocking agent-induced anaphylaxis
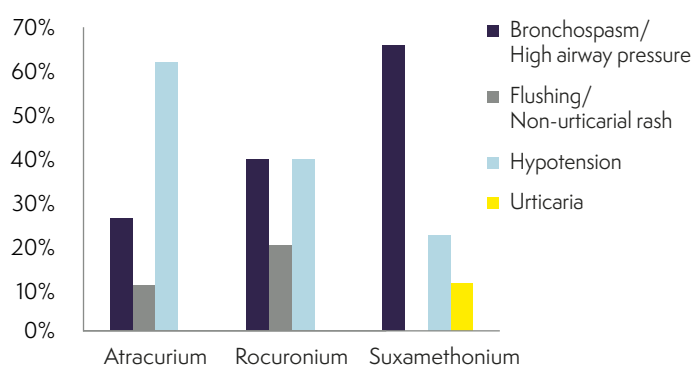
Considering clinical features present at any time during the anaphylactic episode, hypotension was universal. Rash, seldom a presenting feature, developed in 56.4% of cases, bronchospasm/high airway pressure in 48.5%, tachycardia in 46.2%, cyanosis/oxygen desaturation in 41.4% and a reduced/absent capnograph trace in 32.7%. Bronchospasm at any time was also seen in a higher proportion of patients with asthma (59%) than others (46%). Again, this clinical pattern was very similar in the subgroup of allergic anaphylaxis patients (Figure 5).

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

Figure 5. Clinical feature (%) present at any time during Grade 3-5 perioperative anaphylaxis: allergic anaphylaxis and all patients
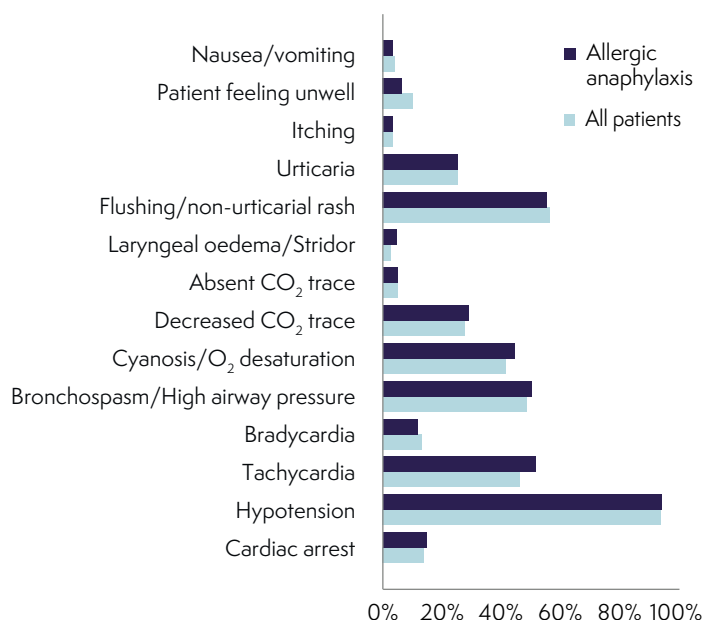
Considering all cases, onset time was <5 min in 66.2%; <10 min in 82.7%; <15 min in 87.6% and <30 min in 94.7%. Onset times for individual agents are discussed below.

Fatalities, cardiac arrests, and profound hypotension

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

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

45

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

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

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

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

Figure 6. Clinical features of ten fatal cases of perioperative anaphylaxis (presenting, and at any time)
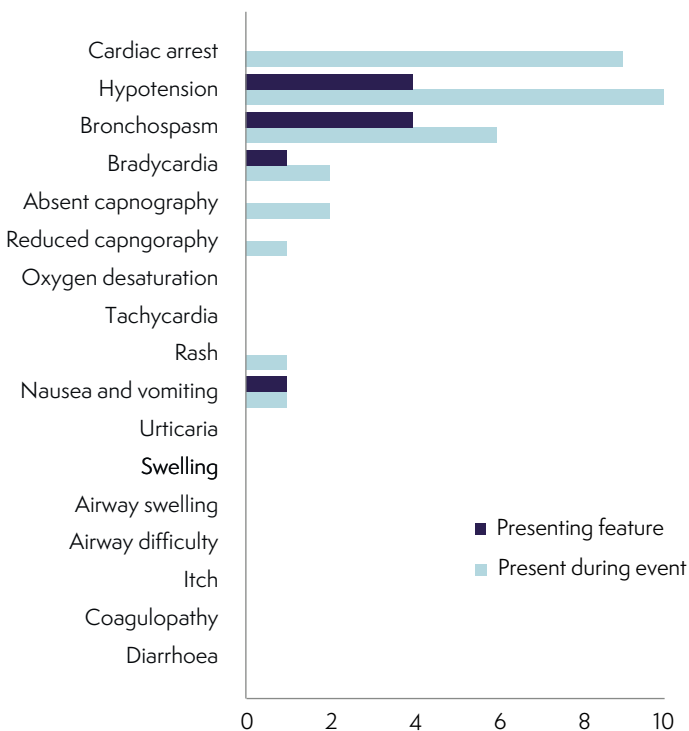
Forty (15%) patients, all of whom were adults, experienced cardiac arrest, including nine of the patients who died. Thirty-one (77.5%) survived. Most (81%) events occurred after induction of anaesthesia

and before surgery. A consultant was involved in all resuscitations. No particular trigger agents were associated with a higher risk of cardiac arrest. However, survivors of cardiac arrest were younger, fitter and had less co-morbidity than patients who died (Table 3).

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

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

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

Figure 7. Clinical features of 37 non-fatal cardiac arrests from perioperative anaphylaxis (presenting, and at any time)
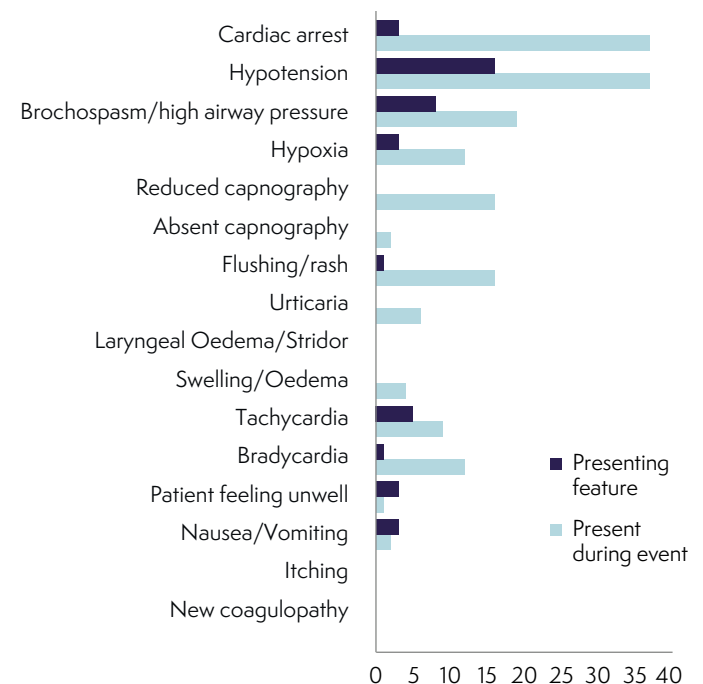
Table 4. Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6
*Annual usage identified from the Allergen Survey (Chapter 9)

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

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

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

Antibiotics

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

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

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

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

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

Neuromuscular blocking agents and reversal agents

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

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

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

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

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

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

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

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

Chlorhexidine

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

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

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

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

Patent Blue dye

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

Figure 8. Presenting clinical features and those occurring at any time during chlohexidine-induced perioperative anaphylaxis
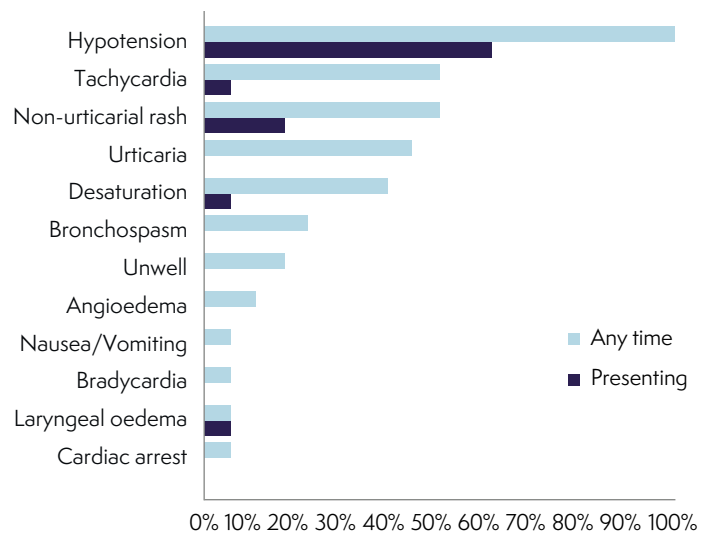
Onset was slower than other trigger agents, with only two cases <5 minutes; four presented after >15 minutes, including two after >60 minutes. Hypotension was the commonest presentation: all patients became significantly hypotensive, and in three cases systolic blood pressure fell below 50 mmHg. Four patients desaturated to <90%. Cutaneous features were present in six patients.

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

Miscellaneous trigger agents

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

Reporting

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

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

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

Discussion

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

Presenting features

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

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

Fatalities

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

Cardiac arrest and survivors

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

Profound hypotension

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

Antibiotics

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

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

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

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

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

NMBA and reversal agents

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

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

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

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

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

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

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

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

Chlorhexidine

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

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

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

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

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

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

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

Patent blue

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

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

As Patent Blue dye interferes with pulse oximetry (causing spuriously-low readings) this has the potential to delay recognition of the onset of anaphylaxis. While two studies examining this effect reported mean reductions in digital oxygen saturation

(SpO_2) of <2% (Mertes 2008, Ishyama 2015), in some individuals considerably greater falls in oximetry values may be observed (Takahashi 2013, Murakami 2003).

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

Miscellaneous agents

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

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

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

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

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

Reporting

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

Conclusions

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

Part B: Management of, and outcomes after perioperative anaphylaxis

Key findings

- All patients were resuscitated by anaesthetists of appropriate seniority.
- A management guideline was immediately available in 86% of cases.
- Immediate management was judged 'good' in 46% and 'poor' in 15% of cases.
- Recognition of and treatment of anaphylaxis were judged prompt in 97.3% and 83.4% of cases, respectively.
- Adrenaline was administered IV in 76% of cases, IM in 14% and both in 6%.
- No adrenaline was administered in 11% of cases.
- The majority received other vasopressors (metaraminol, phenylephrine) before adrenaline.
- An IV infusion of adrenaline or noradrenaline was administered in 30.7% and 18.9% of cases respectively.
- Two patients received vasopressin and one glucagon.
- Steroids and antihistamines were generally administered early.
- Careful examination of the role of antihistamines found no clear evidence of harm or benefit.
- Sugammadex was given to treat anaphylaxis in 7.1% of cases.

- IV fluid administration was inadequate in 19% of cases.
- Cardiac arrests (15% of cases) were promptly treated; mean duration of cardiac compressions was 14 minutes, but cardiac compressions were performed in only 50% of patients with unrecordable blood pressure.
- The surgical procedure was postponed or abandoned in two thirds, and urgent surgery was delayed in 10% of all cases.
- More than half of patients required admission to critical care: 70% for level 3 care and most of these patients required catecholamine infusions after admission.
- Adverse sequelae were reported in a third of cases, including new anxiety, change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of post-traumatic stress disorder, myocardial damage, heart failure and new renal impairment.
- Ten deaths (3.8%) were attributable to anaphylaxis, a per case mortality rate of 1 in 26.6 cases.
- Six per cent of survivors underwent surgery (all uneventfully) between the index event and the patient being seen in the allergy clinic.

Successful management of perioperative anaphylaxis is critically dependent on early recognition and prompt initiation of specific treatment. Recognition that a critical event occurring during anaesthesia is likely to be anaphylaxis may not be straightforward, and the differential diagnosis is wide. The onset may be immediate or delayed and the patient's medical history rarely provides any

clues. Rash, the classical sign of an allergic reaction, is present in approximately half of cases but may be not visible under surgical drapes or delayed, especially in more severe cases. Hypotension is usually the first sign of perioperative anaphylaxis (see earlier section of this chapter). A modest fall in blood pressure is a frequent accompaniment of general anaesthesia (Reich 2005) as well as during neuraxial anaesthesia, and vasopressor drugs are often required during routine anaesthesia. It is only when the blood pressure does not respond that less common causes of hypotension are sought, including ischaemic cardiac event, cardiac arrhythmia, embolus, pneumothorax, covert haemorrhage and anaphylaxis.

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

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

The beneficial actions of adrenaline include venoconstriction, which increases venous return; reduced capillary permeability; increased cardiac contractility and cardiac output; bronchodilatation; and inhibition of mast cell and basophil mediator release. These benefits exceed the disadvantages of vasodilatation in skeletal muscle and the potential risk of cardiac arrhythmias. Early administration of adrenaline is associated with improved outcomes in out-of-hospital anaphylaxis (Pumphrey 2011).

McLean-Tooke concluded that adrenaline is not contraindicated in patients with coronary artery disease as continuing anaphylaxis is likely to further reduce coronary artery perfusion (McLean-Tooke 2003). However, excessive dose or over-rapid IV administration can cause arrhythmias. Intravenous (IV) adrenaline is more likely than intramuscular (IM) to result in cardiac complications in treatment of out-of-hospital anaphylaxis in elderly patients (Kawano 2017), but there is no published information regarding the perioperative setting. The IV and IM routes are both recommended for the treatment of perioperative anaphylaxis, with the IV route restricted to patients with continuous vital-signs monitoring, including continuous ECG (RCUK 2016). The AAGBI guidelines recommend an initial IV dose of 50 mcg, repeated as necessary (Harper 2009). The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) guidance for Grade 3 reactions recommend an initial IV dose of 100 mcg followed, if necessary, by 100-200 mcg every 1-2 minutes and a continuous infusion after three IV boluses (Scolaro 2017).

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

Figure 1. Physiological mechanisms responsible for anaphylactic shock
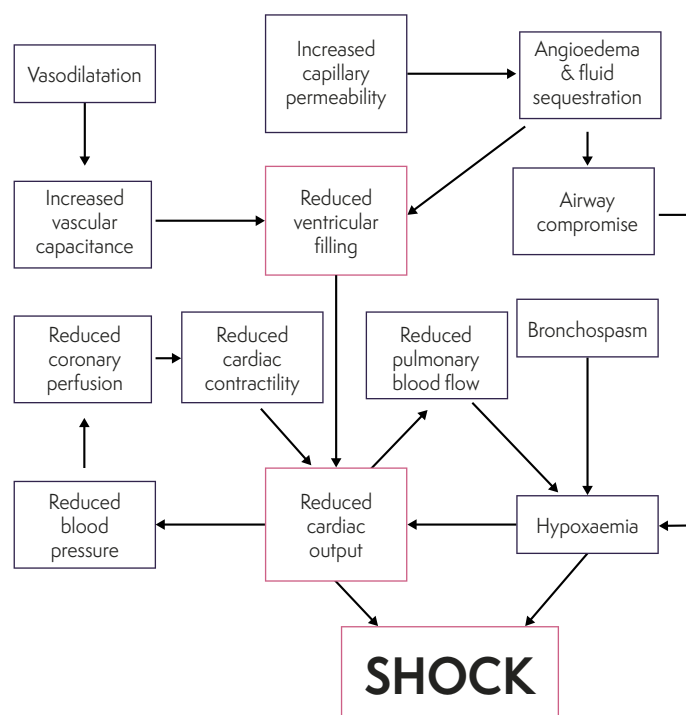
2-15 units (antidiuretic hormone) in the management of intractable perioperative anaphylaxis (Schummer 2008, Bensghir 2013, Meng 2008, Hussain 2008), and this drug is included in the ANZAAG guidelines (Scolaro 2017). The benefit of adrenaline is likely to be reduced in the presence of beta blockade. There are single case reports of glucagon use in beta-blocked patients leading to rapid resolution of hypotension (Zaloga 1986, Javeed 1996). European guidelines (Mertes 2011b) and ANZAAG guidelines (Scolaro 2017) recommend glucagon 1-2 mg every 5 minutes until response, but it is not known how commonly glucagon and vasopressin are used to treat perioperative anaphylaxis in UK practice.

There are no published randomised controlled trials (RCTs) investigating the efficacy of corticosteroids in the acute management of anaphylaxis. The rationale for their administration in anaphylaxis appears to be down-regulation of the late-phase response by altering gene expression, and is an extrapolation of their effectiveness in the long-term management of allergic asthma (Liu 2001). Hydrocortisone is recommended in published guidelines. Dexamethasone 7.5 mg has an equivalent glucocorticoid effect to hydrocortisone 200 mg.

The use of antihistamines in relatively minor out-of-hospital allergic reactions benefits urticaria and pruritus. A Cochrane review of H1 anti-histamines for anaphylaxis was unable to make any recommendations, as a result of lack of evidence (Sheikh 2007). This statement, together with side-effects of promethazine, has resulted in some expert groups recommending that antihistamines should not be administered (Scolaro 2017). We aimed to establish whether administration of chlorphenamine, the most commonly used antihistamine, influenced outcome.

Several case reports may be considered supportive of administration of sugammadex during rocuronium-induced anaphylaxis (McDonnell 2011, Kawano 2012, Barthel 2012). The hypothesis that encapsulating the antigen may halt the clinical features of anaphylaxis is unproven, despite in vitro and clinical studies (Clarke 2012). Platt *et al* reported sugammadex administration during immediate management of suspected rocuronium-induced anaphylaxis, in 13 cases, of which five were not rocuronium-induced (Platt 2015). Clinical features improved in six patients, including three without rocuronium-induced anaphylaxis, raising the possibility that sugammadex may exert a vasopressor effect via a mechanism other than encapsulating the antigen. We sought to determine to what extent sugammadex has been incorporated into current management of perioperative anaphylaxis.

Anaphylaxis is associated with an acute fall in actual and effective circulating blood volume as a result of vasodilatation, increased vascular permeability and fluid sequestration, causing reduced venous return and cardiac output (Figure 1); there is consensus for rapid IV infusion of crystalloid fluids. Recent guidelines emphasise the need to give rapid, repeated IV fluid challenges while monitoring the response: ANZAAG guidelines (Scolaro 2017) recommend giving repeated boluses of 20 ml/kg. There is a paucity of information concerning IV fluid management in 'real-life' management of perioperative anaphylaxis, but we support these recommendations.

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

Methods

Methods are discussed in detail in Chapter 5, Methods. At panel review the quality of immediate management was assessed and classified, including factors such as timeliness, accuracy and completeness. In doing this we also referred to current guidelines of the AAGBI (Harper 2009) and the Resuscitation Council of the United Kingdom (RCUK) on management of perioperative anaphylaxis (RCUK 2016) and cardiac arrest (Soar 2015) where relevant. The overall initial management was graded as 'good', 'good and poor' or 'poor'.

Although administration of adrenaline is the accepted standard for the immediate management of perioperative anaphylaxis, the review panel recognised that anaphylaxis is an uncommon cause of hypotension or bronchospasm during anaesthesia. It is therefore reasonable for anaesthetists to start treatment with vasopressors and bronchodilators such as metaraminol, ephedrine and salbutamol before instituting anaphylaxis-specific treatment, unless anaphylaxis was clinically obvious from the outset. Results here are based on a dataset of the 266 reviewed cases of confirmed anaphylaxis. For some analyses a smaller dataset is used. The quality of delivered care is based on a full panel review of 184 cases (see Chapter 5, Methods).

Results

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

Figure 2. Quality of management of perioperative anaphylaxis by anaesthetists (% of cases)
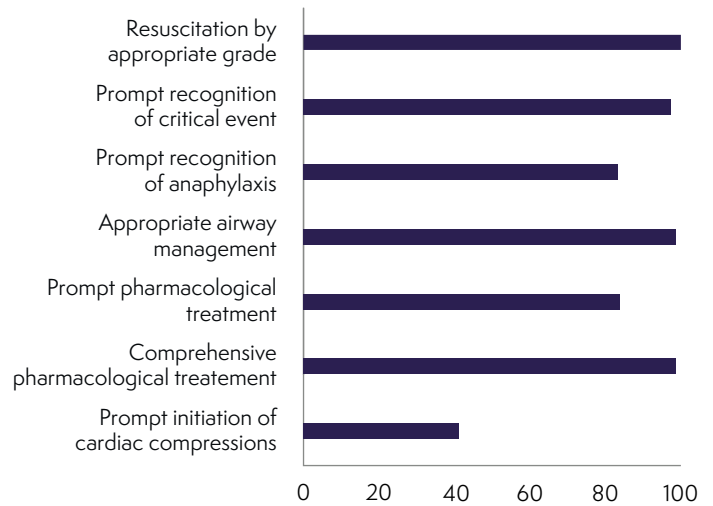
Recognition of a critical incident and suspicion of anaphylaxis was within five minutes in 60% and 49% of cases, respectively. By 10 minutes, the corresponding figures were 78% and 74%. Recognition of anaphylaxis and treatment were judged prompt in 97.3% and 83.4% of cases respectively (Figure 3).

Figure 3. Elapsed time (minutes) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis
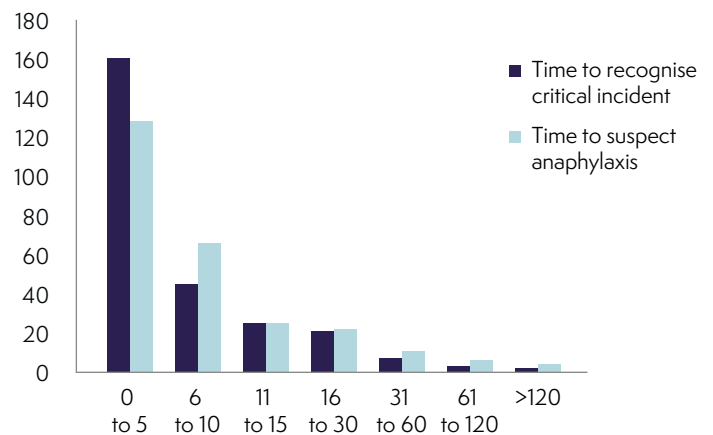
Specific treatment for anaphylaxis following the first clinical feature was started in <5 minutes in 64% of cases and <10 minutes in 83%. (Figure 4). Reported reasons for delay included confounding differential diagnoses such as pulmonary embolism, tension pneumothorax, gas embolism during abdominal endoscopy, primary cardiac events, surgical haemorrhage and neuraxial blockade-associated hypotension.

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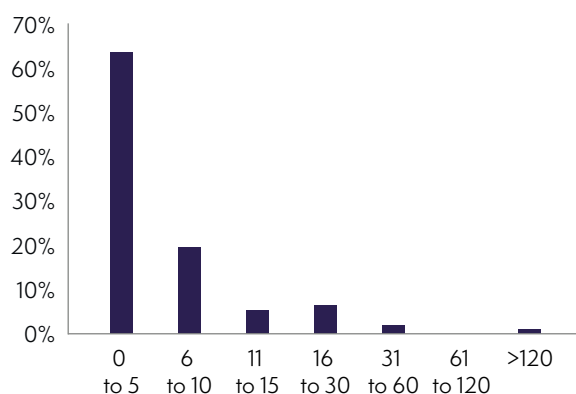
Pharmacological treatment was judged prompt and comprehensive in 83.9% and 98.8% of cases respectively. The vasoactive drugs administered are shown in Figure 5. Adrenaline was administered in 82.3% of cases, as IV boluses in 75.9%, and was more likely to be given as severity increased. The median total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

Figure 5. Vasoactive drugs administered during initial management of perioperative anaphylaxis (% of cases)
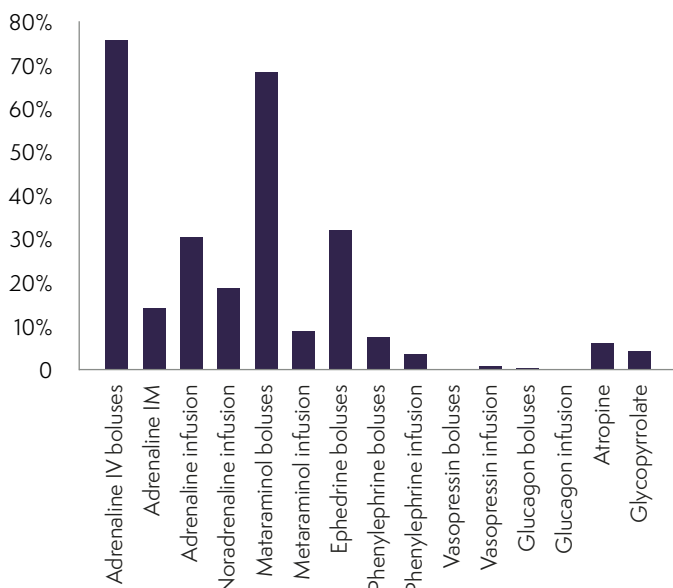
An IV infusion of adrenaline was used in 30.7% of cases, preceded by bolus doses in all except a single case. Adrenaline was judged not to have been given when indicated in 19.4% of cases – either not administered (11%) or given late (8.4%).

Metaraminol boluses were administered in 68.7% of patients, of whom 73.6% also received adrenaline. Phenylephrine was administered by IV bolus in 7.8% of cases, and an infusion in 3.5%. Most cases were obstetric. An IV infusion of noradrenaline was administered in 18.9% of cases. Only two patients received vasopressin (antidiuretic hormone) and one received glucagon. In both cases these drugs were given late in the resuscitation process and each was preceded by ephedrine, metaraminol and adrenaline.

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

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

Intravenous chlorphenamine was administered in 73.6% (median 10 mg, 5-40 mg) (Table 1) and intravenous ranitidine in 5.3% of cases. Nine (3%) patients received both drugs. We performed further analysis using a logistic regression model to elucidate benefit or harm associated with chlorphenamine. Variables included; initial resuscitation drugs, (adrenaline bolus, corticosteroids, metaraminol, ephedrine and chlorphenamine); patient factors (age group intervals excluding children and over 75 years due to small numbers) and ASA status (excluding ASA 5 due to small numbers). Outcome was level of harm (no harm, low, moderate/severe harm/ death) as defined in Chapter 5. In spite of the univariate analysis, in the logitistic regression analysis chlorphenamine administration was associated with an increased probability of no harm and a decreased probability of a moderate/severe harm and death: odds ratios 2.20 (1.05-4.58) and 0.41 (0.18-0.91), respectively. Chlorphenamine had no effect on the probability of low harm. However, in order to exclude chlorphenamine as a surrogate for good (as opposed to 'poor' or 'good and poor') clinical management (noting that chlorphenamine administration was not used as a measure of quality of care during panel discussions) we performed a Fisher exact test. This confirmed a significant association between administration of chlorphenamine and care being judged as good (P<0.005). Thus, we were not able to determine with any clarity whether administration of antihistamine was associated with harm or benefit.

Table 1. ASA grade, level of care and outcomes in patients receiving chlorphenamine or no chlorphenamine for grade 3-5 perioperative anaphylaxis *physical harm was based on 138 cases and 40 cases with this information available who did or did not receive chlorphenamine, respectively

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

Sugammadex

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

IV fluids

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

Ninety-eight per cent of patients received IV crystalloids in the first hour after the reaction, 86% during the subsequent 2 hours and 69% during hours 3-5. The median volume administered during each time period was 1L (range 0.1L to 6.0L); 1L (range 0.1 to 3.0L) and 0.5L (range 0.1L to 4.5L). The only IV colloids administered during the first hour after the anaphylactic event were succinylated gelatin products in 25 (9%) cases.

Airway

Airway management was judged appropriate in 98.8% of cases; in 1.2% of cases it was judged that tracheal intubation should have been performed. Airway swelling, airway difficulty and complications were uncommon. Tracheal intubation was performed as part of resuscitation in 13.2% of patients; in the majority this involved removal of a supraglottic airway and replacement by a tracheal tube. In three (1.1%) cases the tracheal tube was removed and replaced as a result of suspected oesophageal intubation as part of the differential diagnosis. A front of neck airway was instituted in one patient who developed laryngeal oedema and stridor, but other details of this case were scarce. In seven patients it was necessary to re-intubate the trachea after completion of the primary surgical procedure; in no case was re-intubation difficult due to airway swelling.

Guideline access

A management guideline was immediately accessible in 86% of cases, mainly as a laminated sheet; 15% of immediately available guidelines were contained in designated 'anaphylaxis-packs'. A smartphone was used to access guidelines in nine cases.

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

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

Fatal cases

Immediate management was prompt in all but one of the ten cases, and all resuscitations followed a guideline and were managed by a consultant. Nine patients had a cardiac arrest and resuscitation was prompt, prolonged and extensive. CPR took place for a median 39 minutes and in all cases for >25 minutes. Resuscitation included extra-corporeal-membrane oxygenation in one case, and immediate cardiac catheterisation to explore or manage an acute coronary syndrome in two cases. Adrenaline was administered IV in all cases, including an infusion in five cases. A median of 5 doses (5 mg) adrenaline was administered (range 2-13 mg). No patient received IM or intraosseous adrenaline. Ephedrine, metaraminol, glycopyrronium and atropine were used early in resuscitation. Five patients received noradrenaline, one vasopressin and one glucagon, administered at 65 minutes after the reaction. Approximately half of cases received chlorphenamine and hydrocortisone. Sugammadex was not used. Fluid resuscitation volumes were relatively modest 1-4.5L (median 1.5L) in the first hour, and in the first five hours 1-9.5L, (median 1.5L); only one patient received >4L in total. Five patients did not survive initial resuscitation, while five did, of whom one died soon after. Of the four remaining patients, all were admitted to critical care and all survived at least one week, but all deaths occurred in <30 days. Four patients developed multiple organ failure.

A mast cell tryptase sample was sent in all cases and a dynamic change was identifiable in five cases. Mast cell tryptase results are discussed in Chapter 14, Investigation. There were no episodes of recrudescence of anaphylaxis.

Good elements of care were: appropriately senior resuscitators (10/10), prompt recognition of the critical event (9/10), prompt recognition of anaphylaxis (9/10), appropriate airway management (10/10), and prompt initiation of cardiac compressions (9/10, 1 uncertain). Inadequate fluid administration was a recurrent theme.

Cardiac arrests

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

Profound hypotension

CPR was initiated in 28 (50%) of those with an unrecordable blood pressure, in five (9%) with systolic blood pressure <50 mmHg and in two (3.8%) with lowest blood pressure of 50-59 mmHg. The panel, after taking external expert advice, used a threshold of <50 mmHg as the point at which CPR was indicated in adult patients. Deakin *et al.* demonstrated using invasive blood pressure measurement that systolic blood pressure <50 mmHg was associated with pulselessness with a 90% positive predictive value (Deakin 2000). When non-invasive blood pressure monitoring is used this will underestimate hypotension (Lehman 2013). So, when the lowest blood pressure was <50 mmHg CPR was deemed indicated. There were 114 (42.9%) such cases. Overall prompt CPR (when the blood pressure was <50 mmHg or unrecordable) was reported in 23% of cases. Pharmacological treatment was judged inadequate in 21% and adrenaline administration was judged inadequate in 17%. Fluid administration was judged inadequate in 24%. Patient characteristics, outcomes and quality of care are summarised in Table 2.

Discontinuation of the trigger agent

The suspected trigger agent was discontinued in 22 of the 26 cases where this would have been possible. Agents that were not discontinued comprised IV gelatin, a chlorhexidine-coated central venous line, a second dose of co-amoxiclav and a second dose of protamine. The actual trigger agent was not discontinued in four of the 14 cases where this would have been possible, comprising IV gelatin, administration of a second dose of protamine and two instances of retained chlorhexidine-coated central venous line.

Continuation of surgery

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

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

	Deaths (n=10)	Non-fatal cardiac arrest (n=31)	sBP <50 mmHg without cardiac arrest or death (n=79)	All others (n=135)
Quality of resuscitation				
Appropriate resuscitator	100%	100%	100%	98%
Prompt recognition	100%	91%	98%	99%
Prompt diagnosis of anaphylaxis	88%	82%	80%	85%
Prompt treatment of anaphylaxis	70%	83%	65%	78%
Adrenaline administered as needed	90%	100%	76%	77%
Prompt CPR when indicated	90%	91%	2%	67%
Appropriate fluid	67%	81%	78%	83%
Good initial management	60%	65%	8%	58%
Poor initial management	0%	9%	34%	8%
Outcomes				
Outcomes where known (median)	Severe	Moderate	Moderate	Low
% experiencing any harm	100%	74%	59%	60%
Critical care for vasopressors (% of all cases)	n/a	67%	32%	23%
Time on Critical care (median, all cases)	n/a	2	0	1
Unplanned hospital length of stay	n/a	2	1	1

Unplanned hospital stay and critical care admission

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

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

Outcomes (cases of all severity)

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

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

As a result of anaphylaxis, cancer surgery was delayed in 19 (7.1%) cases, urgent non-cancer surgery in eight (3%), non-urgent surgery in 76 (28.6%), and other treatment was delayed in nine (3.4%) cases. Total hospital stay was extended as a result of anaphylaxis in 75% of patients (median 1 day, range 0-150 days).

Obstetric cases

We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey (Chapter 8) estimated that 233,886 obstetric anaesthetics are administered per annum in the UK, giving an incidence of severe obstetric perioperative anaphylaxis of 3.4 per 100,000, which is significantly lower than in adult non-obstetric cases. Six patients received neuraxial anaesthesia and two general anaesthesia. Six cases occurred in association with anaesthesia for caesarean section, most commonly after delivery of the baby. There were no cardiac arrests or maternal or neonatal deaths. All patients developed hypotension, which was in some cases profound. In four of six

patients who developed severe anaphylaxis during neuraxial anaesthesia, a common feature was the patient complaining of feeling unwell before the onset of hypotension or other clinical signs. Hypotension commonly developed at a time when spinal-induced hypotension would have been anticipated to have settled.

A consultant anaesthetist was involved in the management of all the cases. In five cases there was prompt treatment, but in three cases there was a delay in diagnosis and treatment was delayed. Resuscitation drugs differed from those used in non-obstetric cases: six patients received phenylephrine, four adrenaline, and three both. Fluid management was appropriate in all cases. An anaphylaxis pack was used to assist management in only two cases. In four cases overall care was judged 'good' and in one 'good and poor'. Identified culprits were chlorhexidine, atracurium, suxamethonium and ondansetron, and in four cases no trigger was identified. Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during neuraxial anaesthesia required tracheal intubation. For three women hospital discharge was delayed, and one patient reported anxiety about future anaesthesia.

Paediatric cases

Eleven cases of perioperative anaphylaxis in patients aged under 16 years were reported, three of which were emergency procedures. With an estimated 403,000 paediatric cases performed per annum, the incidence of Grade 3–4 anaphylaxis is 2.73 per 100,000 paediatric anaesthetics which is significantly lower than in adult cases. Two patients had well-controlled asthma. Six cases presented in the operating theatre, three in the anaesthetic room, one during transfer from the recovery room to the ward, and one in the radiology department. Seven cases presented after induction and before surgery. The first clinical feature was bronchospasm and/or high airway pressures in seven (64%) cases with hypotension being the presenting feature in two, tachycardia in one and non-urticarial rash in the remaining case. Bronchospasm presented within five minutes, whereas hypotension was generally slower in onset. A decrease in end-tidal carbon dioxide levels was noted in three cases, with an absent capnography trace in two of these at some point. Two cases exhibited non-laryngeal oedema, which was delayed in one case. There were no fatalities among the paediatric cases. The clinical features present at any time during the reaction are shown in Figure 6. All cases were judged Grade 3 by the index anaesthetist: on panel review, six were judged as Grade 4.

Figure 6. Number of children exhibiting clinical features at any time during the anaphylactic episode
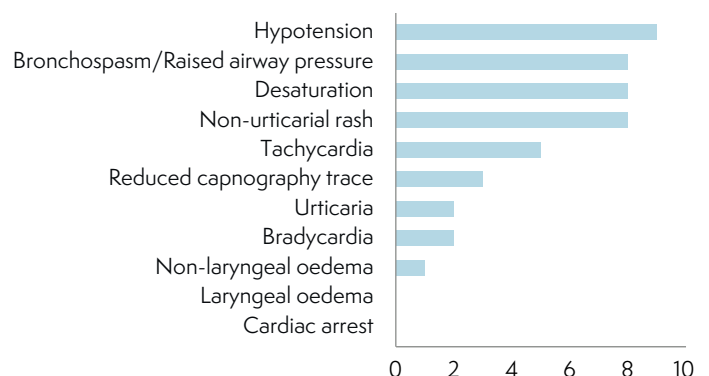
The review panel judged that clinical management was 'good' in four cases, 'good and poor' in two cases and was 'poor' in a single case (where adrenaline was not administered). A consultant was present during resuscitation in all cases. AAGBI guidelines were used in five, and RCUK guidelines in one. In seven cases, there was immediate access to a guideline as a laminated document.

Specific treatment for anaphylaxis was started within five minutes in six of the seven cases where bronchospasm and/or high airway pressures were the presenting features. When hypotension or tachycardia were the presenting features, specific treatment tended to be started later. Adrenaline was administered in ten cases, either IV or IM, and an infusion was required in four cases. Other vasopressors were used in small numbers of cases. Eight patients received chlorphenamine and eight hydrocortisone. Two patients did not receive a corticosteroid. One patient received atropine. No patients received phenylephrine, vasopressin, glucagon, glycopyrrolate, sugammadex or magnesium sulphate. Ten patients received IV crystalloid, one IV gelatin, and one no IV fluid. The volume of IV crystalloid administered during the first five hours is shown in Figure 7.

Figure 7. Volume of IV crystalloid (ml/kg) administered to children during the first five hours after an anaphylactic event (median, range)
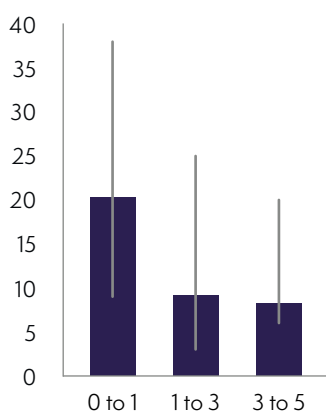
In six cases the procedure was abandoned and four of these were rescheduled; in all cases except one judged to be appropriate. Three patients were transferred to HDU/ICU as a result of the event, including one to a different hospital.

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

Eight cases had at least one mast cell tryptase sample taken with four showing elevation or dynamic changes. The reaction was allergic anaphylaxis in three cases, non-allergic anaphylaxis in one case, anaphylaxis not-specified in two cases and uncertain in five. Culprit agents were: atracurium in three cases and one each of; suxamethonium, aprotinin, cefuroxime, ibuprofen and cryoprecipitate. The trigger was not confidently-identified in the three remaining cases. The mechanism of the reaction to ibuprofen

was judged to be non-allergic anaphylaxis. Overall allergy clinic investigation, in eight cases fully reviewed, was judged as good in one, good and poor in three and poor in four.

Concordance

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

Among cases with an identified trigger, overall concordance was 75% between the anaesthetist and the panel. However, anaesthetists were likely to over-identify NMBAs as triggers and to fail to recognise chlorhexidine-induced anaphylaxis.

Communication

The panel judged that there were considerable shortcomings in communication between the anaesthetist and the patient following the event. Information given to the patient by the anaesthetist about which drugs or other substances they should avoid before attending an allergy clinic for investigation was oral in 26.6%, written in 19.8%, both in 39.2% and none in 14%. In 222 cases where this information was available, 29% were issued with a hazard warning card, 39% of these by the index anaesthetist.

Discussion

Immediate management: all cases

It is reassuring that resuscitation involved a consultant or other career grade anaesthetist in all cases. The majority (88.7%) of UK patients are anaesthetised by consultant or career grade anaesthetists (Chapter 8), nevertheless, anaesthetists in training were willing to call for help and the theatre team contributed effectively to management in almost 90% of cases. Recognition of perioperative anaphylaxis may be difficult but nevertheless was prompt in 83% of cases.

Overall quality of management was judged 'good' in slightly less than half of the cases. The deficits were multi-factorial and included insufficient IV fluids, non-administration or late administration of adrenaline, delays in recognising anaphylaxis and starting specific treatment, and lack of cardiac compressions where the BP was <50 mmHg or unrecordable.

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

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

Vasopressin is recommended for intractable hypotension in several guidelines (Krøigaard 2007, Scolaro 2017), but was administered in only two cases despite the presence of persistent hypotension, evidenced by the administration of noradrenaline infusion in almost 1 in 5 cases. Several cardiac arrests were preceded by prolonged hypotension. It is to be noted that earlier guidelines omitted this drug (Harper 2009), and it likely that awareness is limited. It is also likely that vasopressin is unavailable in many anaesthetising sites, a situation addressed by our recommendations. Similar comments apply to glucagon.

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

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

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

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

The majority of patients in our cohort required transfer to critical care, mostly for Level 3 care; half of the patients required catecholamine infusions and a substantial number of patients were harmed by their anaphylactic event. While the decision to abandon or continue surgery needs to be a balanced one based on individual circumstances, the review panel were of the view that it is inadvisable for surgery to proceed after life-threatening anaphylaxis (Grades 3 and 4) unless there are over-riding reasons

to do so. Sadleir (Sadleir 2018) demonstrated that patients with Grade 3 anaphylaxis whose surgery continued (42.2%) did not require more intraoperative adrenaline or longer postoperative ventilation than those in whom the procedure was abandoned. However, surgery was more likely to be abandoned in the more severe Grade 3 cases. The authors attempted to control for this effect by using the degree of mast cell tryptase rise as a surrogate for severity, but NAP6 data demonstrated no relationship between acute mast cell tryptase levels and indices of clinical severity (Chapter 14, Investigation). In Sadleir's study, surgery was continued in a small proportion of cases of Grade 4 anaphylaxis.

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

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

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

Obstetric cases

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

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

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

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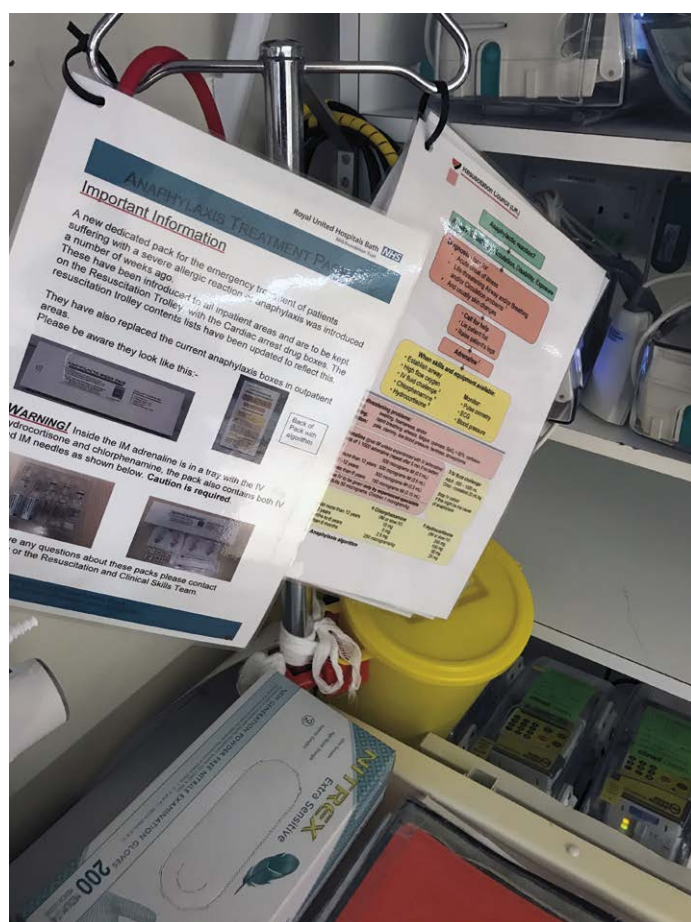
Laminates may guide actions during resuscitation

Paediatric cases

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

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

Unlike in adult patients, bronchospasm and/or high airway pressures were the most common presenting features in children. Bradycardia was also more common in children compared with adults (18% vs 12.6%). Cardiopulmonary resuscitation was not performed in any paediatric case: four children's systolic blood pressure was <50 mmHg, but expert opinion did not favour setting a blood pressure below which CPR should be initiated in children.

Given the small number of cases reported in children, it is not possible to make confident conclusions concerning risk rates with different drugs. However, the number of cases of atracurium and suxamethonium appear to be proportionate to the number of exposures. Atracurium was the most-used NMBA in children (57%) by a large margin, followed by rocuronium (5.2%) and suxamethonium (2.6%). Paediatric cases are increasingly intubated without an NMBA (Sneyd 2010).

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

Conclusions

We are not aware of other studies which investigated a wide range of physical and psychological adverse sequelae. Severe anxiety and mood changes, mild/moderate memory impairment, and impaired mobility were observed. Physical harm was uncommon but did include one front of neck airway and a small number of patients who experienced myocardial infarction, acute kidney injury or new shortness of breath, either as a consequence of perioperative anaphylaxis or during their recovery. It is likely that these sequelae are underdiagnosed. We recommend that all patients should be followed up after perioperative anaphylaxis.

In order to facilitate this and the many other tasks that are needed for a department of anaesthesia to be 'institutionally prepared' to manage perioperative anaphylaxis we recommend that all departments of anaesthesia should have a 'Departmental Lead for Anaphylaxis'. The suggested roles and responsibilities are set out in Appendix D.

Summary of main findings

In Chapter 2 and in each detailed chapter we list a series of recommendations intended to improve care. They are numerous and some simply reinforce known good practice. However, each recommendation is founded on the direct and indirect findings of NAP6. We hope that (as with previous NAPs (Cook 2011, Cook 2016)) the many recommendations we have made will be largely implemented. Others may stimulate discussion or provide hypotheses for future research. We hope this will both increase awareness of the topic and improve institutional and individual preparedness for these infrequent but potentially life-threatening events. This will have the potential to make inroads into preventing avoidable anaphylaxis and improving the quality of care patients receive when it occurs and afterwards, both by anaesthetists and in allergy clinics.

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Key findings

- 11,104 anaesthetists (77% crude response rate) from 341 (96%) hospitals responded to the survey.

- 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, notably rocuronium.

- Suxamethonium and penicillins were avoided by a higher proportion of respondents than would be predicted by the proportion of anaphylactic events attributed to these drugs, while the converse was true for atracurium and teicoplanin.

Introduction

Anaphylaxis is a severe, life-threatening generalised hypersensitivity reaction (Johansson 2003) and is one of the most hazardous emergencies encountered in the perioperative setting. Despite its importance, there is limited published information on UK anaesthetists' perspectives and experiences of perioperative anaphylaxis.

In 2009, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) published guidance on suspected perioperative anaphylaxis (Harper 2009). This document recommended that anaesthetists should refer affected patients to a specialist allergy centre for investigation via a locally agreed referral pathway. A recent multicentre audit suggested that these patients were not being appropriately referred for investigation (Savic 2015a). In addition, the guideline advised anaesthetists to report cases of perioperative anaphylaxis to a national database, such as that of the Medicines and Healthcare products Regulatory Agency (MHRA). It would also be expected that cases would be reported via the local hospital incident-reporting system.

The perception of anaphylaxis risk is likely to influence anaesthetic practice, but little is known about which agents anaesthetists associate with being at high risk of inducing anaphylactic reactions. The limited prevalence studies available have indicated that the most frequently implicated causative drugs are antibiotics and neuromuscular blocking agents (NMBAs) (Mertes 2009), but little is known about what precautions anaesthetists take to avoid anaphylactic reactions and the degree, if any, to which perceived anaphylaxis risk drives clinical practice. Current perioperative practice increasingly exposes patients to chlorhexidine and newer drugs, such as sugammadex, and it is unclear how much risk these agents pose in view of emerging evidence of their association with anaphylaxis (Moka 2015, Takazawa 2014). The use of an antibiotic 'test dose' is actively discouraged in published guidelines, but the degree to which this practice persists has not previously been examined.

The National Audit Projects are a series of service evaluations examining major complications related to anaesthesia, and run by the Royal College of Anaesthetists (Thomas 2016). The 6th National Audit Project (NAP6) is designed to prospectively examine quantitative and qualitative aspects of severe perioperative anaphylaxis. NAP6 comprises four components: a baseline survey of anaesthetists; a survey of specialist allergy clinics; a year-long, anonymised case reporting phase; and lastly a survey of anaesthetic activity and exposure to potential perioperative allergens. This chapter describes the baseline anaesthetic survey.

The survey was undertaken in order to understand current practice and compliance with published guidance. It explores current systems for reporting, referral and management of cases of suspected perioperative anaphylaxis. The survey also examines anaesthetists' practices, perceptions of causative agents, and experiences of severe perioperative anaphylaxis. The baseline survey was not intended to characterise the incidence of perioperative anaphylaxis, which is investigated by the separate case reporting phase of NAP6.

Methods

The NAP6 project was confirmed to be a service evaluation by the National Research and Ethics Service and therefore formal ethical approval was not required. The project was endorsed by all UK Chief Medical Officers and approved by UK statutory patient data security bodies.

All 356 participating hospitals in England, Wales and Northern Ireland appointed a volunteer Local Coordinator (LC) anaesthetist, who was responsible for reporting the number of anaesthetists within their centre, and who took responsibility for advertising and disseminating the survey and recording completion rates. The survey was in the form of a hospital-based 'organisational survey' sent to the LC at each centre and an electronic questionnaire for individual anaesthetists that was accessible from 5 November 2015 until 11 January 2016 (see Appendix 1).

Respondents were asked to provide details of departmental systems for reporting and referral of perioperative anaphylaxis, and to describe their attitudes and perceptions of high-risk causative agents and of any avoidance practices. Anaesthetists were also asked to record details of suspected agents, referrals and outcomes of any cases of suspected perioperative anaphylaxis that they had treated in the previous year. For this purpose, anaphylaxis was defined as a hypersensitivity reaction with severe hypotension and/or bronchospasm and/or swelling with actual or potential airway compromise, and excluding minor reactions or harmless transient cutaneous flushing as an isolated feature.

To avoid double reporting, respondents were requested to specify those cases for which they had been the most senior anaesthetist involved in the case, and separately, those cases where they had been called to assist with management.

Continuous data were described using median (IQR [range]) and categorical data using 95% confidence intervals for Poisson distribution. Due to the observational nature of the survey, no statistical comparison was required.

Since the response rate was high, no adjustment was made for missing data due to non-responders. Unanswered questions in the dataset were highlighted as missing values rather than discarding the entire response or using imputation, which was not appropriate for this survey.

For estimating the number of new cases of perioperative anaphylaxis included in this survey, we used the responses to question 1, which referred to cases directly under the respondents' care. For all other questions we used the reports of all cases of anaphylaxis that the respondents had attended (ie. attendances at anaphylaxis events), either as the primary anaesthetist or assisting a colleague. We used data from NAP5 in 2013 (3,598,500 anaesthetic interventions, including 2,766,600 general anaesthetics) as the denominator for the number of anaesthetic interventions delivered in the UK (Sury 2014). This was adjusted for the survey response rate, to estimate the reported incidence of perioperative anaphylaxis in the twelve months preceding the survey. It is recognised that retrospective recall is not as reliable as prospective data collection, and therefore the main focus of this survey was not to calculate incidence but rather to assess attitudes and practice ahead of the prospective data collection period of the NAP6 project.

Results

Responses were received from 341 hospitals (96%). The organisational survey identified 14,795 anaesthetists working in the UK – 8,522 Consultants, 1,761 SAS/trust grade doctors and 4,512 anaesthetists in training. The median number of years of anaesthetic experience was 13.0 (7.0-21.0 [0-40]), including 634 (6%) anaesthetists with less than one year's experience (Figure 1). The crude sum for the total number of years of anaesthetic experience was 154,689. A total of 11,104 anaesthetists completed the survey (77% crude response rate).

Figure 1. Number of years of anaesthetic experience of respondents, showing a positive skew to shorter career experience
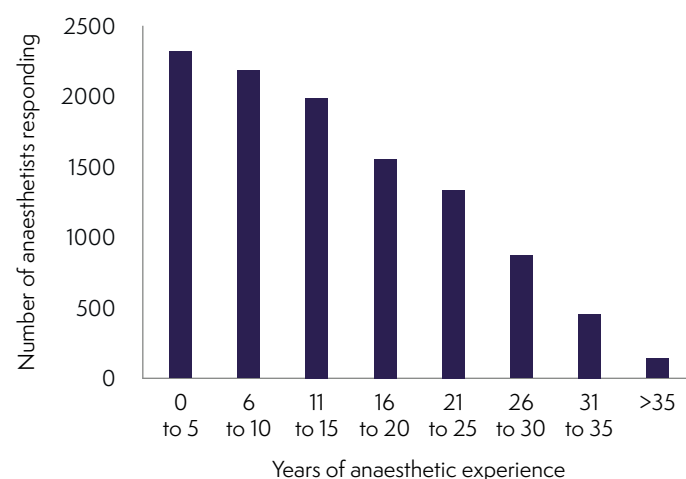
Departmental organisation

A total of 9,617 (87%) of anaesthetists reported having immediate access to guidelines for the treatment of anaphylaxis, and 4,161 (37%) reported a designated 'anaphylaxis treatment pack' being available in their department. The majority of respondents (9,137, 82%) knew where to refer cases of anaphylaxis for further investigation, 7,511 (68%) were aware of a specific departmental pathway, and 3,893 (35%) reported having a departmental lead for anaphylaxis.

Personal experiences

Respondents reported 1,734 cases of suspected perioperative anaphylaxis under their direct supervision in the preceding twelve months and that they assisted in the care of a further 2,237 cases, indicating that on average 2.3 anaesthetists attend each case of perioperative anaphylaxis.

Of the combined attendances at anaphylaxis cases, 49% were known by the anaesthetist to be confirmed as anaphylaxis, 57% were managed in an intensive care or high-dependency unit, and 2% led to death. There was inconsistency of reporting suspected cases to relevant databases: 47% to local hospital critical incident systems and 14% to the Medicines and Healthcare products

Regulatory Agency (MHRA). Eighty-one per cent of cases were referred for specialist allergy investigation by an anaesthetist, 10% by other clinicians and 9% were not referred for further investigation (Table 1). Reasons for not referring the patient for allergy investigation were specified for 1.9% of cases: event judged not to be anaphylaxis (0.8%), the allergy was already known (0.4%), the patient refused or was not fit enough for investigation (0.2%), or that the reaction had happened too recently for the referral to have been made (0.3%).

Table 1. Type of healthcare professionals referring cases of suspected perioperative anaphylaxis in 2014-15 for specialist allergy investigation

Healthcare professional referring case	Number of attendances at a case of anaphylaxis in 2014-15, n (%)
Responding anaesthetist	1,253 (32)
Another anaesthetist	1,960 (49)
General practitioner	88 (2)
Other	309 (8)
Not referred	361 (9)

Drugs and other agents suspected of triggering anaphylaxis

The agents suspected of triggering reactions reported over the preceding twelve months are shown in Table 2. Neuromuscular blocking agents (NMBAs) and antibiotics were each suspected of causing ≈40% of events and together accounted for 77% of suspected causative agents.

Table 2. Distribution of suspected causative agents in suspected episodes of perioperative anaphylaxis attended by anaesthetists in 2014-15

Suspected Agent	Proportion of responses (%)
Neuromuscular blocking agent	38.5
Antibiotic	38.3
Dyes or contrast medium	6.7
Chlorhexidine	3.9
Analgesic	3.3
IV fluid (including colloids)	2.8
Latex	1.5
Induction agent	0.9
Anti-emetics	0.9
Blood products	0.6
Reversal agents	0.5
Local anaesthetics	0.5
Other drugs	1.6

Risk perceptions

The agent most commonly cited by the respondents as having the highest risk of being associated with anaphylaxis was rocuronium, followed by suxamethonium and penicillin. Four per cent of respondents named a single drug, 11% named two drugs and 77%, three drugs.

Avoidance of drugs and other agents

Twenty-six per cent of anaesthetists reported trying to avoid at least one agent perioperatively due to a perception that these drugs carried a high risk of causing anaphylaxis (Table 3). Of those reporting avoidance behaviour, 62% reported avoiding one drug, 30% two drugs and 8% three drugs. The most frequently avoided agents were NMBAs (67.3%), intravenous fluids (12.4%), and antibiotics (10.15%). Intravenous fluids showed the highest 'risk perception ratio' (ratio of the proportion of anaesthetists reporting avoidance of agent to the proportion of anaesthetists reporting a recent reaction to that agent) at 4.4, while chlorhexidine, suspected of causing 1 in 25 reactions, was infrequently reported as being avoided – risk perception ratio of 0.03.

Table 3. Proportion of responses reporting avoidance of an agent due to perceived risk of perioperative anaphylaxis, by class of agent (%) compared to proportion of responses referring to agents suspected of causing perioperative anaphylaxis in the preceding twelve months and as a risk/perception index

Agent	Proportion of responses reporting avoiding agent due to perceived high risk of anaphylaxis (%)	Proportion of responses attributing a suspected anaphylaxis reaction to the causative agent (%)	Risk perception ratio
Neuromuscular blocking agents	67.3	38.5	1.7
Intravenous fluids (including colloids)	12.3	2.8	4.4
Antibiotics	10.2	38.3	0.3
Induction agents	2.5	0.9	2.8
Analgesics	2.3	3.3	0.7
Latex	1.9	1.4	1.4
Dyes or contrast medium	1.5	6.7	0.2
Other drugs	1.0	1.6	0.6
Reversal agents	0.4	0.4	1.0
Anti-emetics	0.3	0.9	0.3
Local anaesthetics	0.2	0.5	0.4
Chlorhexidine	0.1	3.9	0.03

Ninety-five per cent of those reporting avoiding an agent gave at least one reason for doing so (3,725 reasons in total reported). The most common reason was avoidance due to a personal experience of anaphylaxis with the agent specified, accounting for 22% of responses (Figure 2). This and local/colleague experience of anaphylaxis accounted for almost half of all causes of avoidance.

Figure 2. Reasons for avoidance of agents given by responding anaesthetists. Total number of reasons n=3,725. Other includes 'too little evidence in the literature about anaphylaxis risk', 'adherence to departmental or national guidelines', and 'anaesthetist's own allergy'
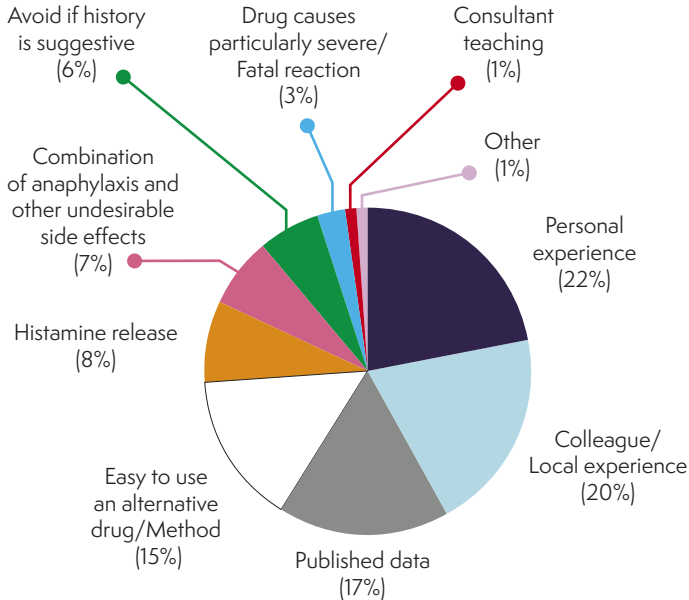
Reasons for avoidance varied between agents (Figures 3 and 4), but personal and colleague experiences were prominent for all agents.

Figure 3. Reasons for avoidance of neuromuscular blocking agents (n = number of times a reason was mentioned by an anaesthetist)

- Personal experience
- Published data
- Easy to use an alternative drug/Method
- Avoid if history suggests
- Departmental guidance/Advice
- Other
- Colleague/Local experience
- Histamine release
- Combination with other side effects
- Consultant teaching
- Fatal/Severe reaction
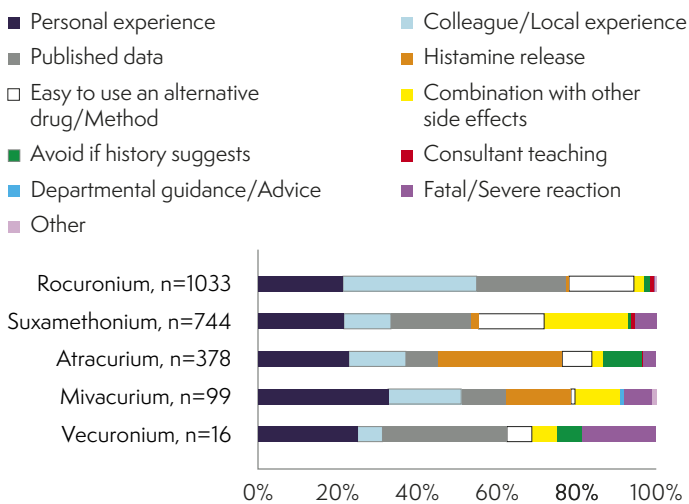
Figure 4. Reasons for avoidance of antibiotics (n = number of times a reason was mentioned by an anaesthetist)

- Personal experience
- Published data
- Anaphylactoid reaction
- Easy to use an alternative drug/Method
- Consultant teaching
- Fatal/Severe reaction
- Colleague/Local experience
- Histamine release
- Combination with other side effects
- Avoid if patient history is concerning
- Departmental guidance/Advice
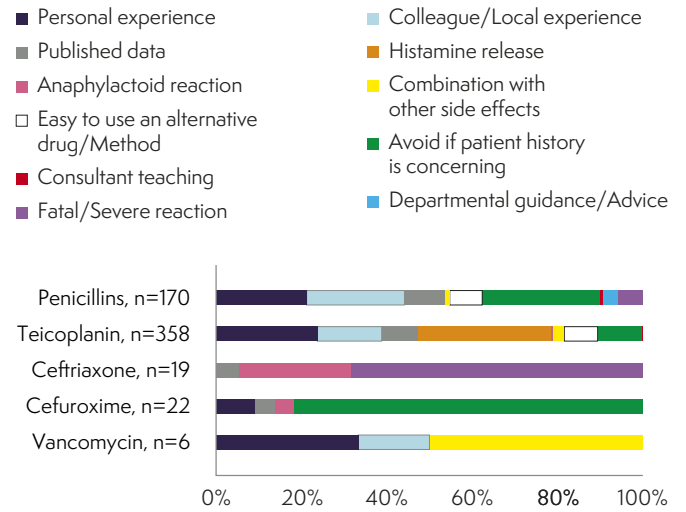
The influence of risk perceptions on avoidance behaviour: neuromuscular blocking agents and antibiotics

The NMBAs and reversal agents were perceived by anaesthetists to be most likely to cause anaphylaxis and the individual drugs avoided by anaesthetists for such reasons are shown in Figure 5. The proportion of anaphylactic events in which each agent was suspected or proven (implicated) is also shown for comparison.

Figure 5. Perceptions surrounding the role of individual neuromuscular blocking (and reversal) agents in causing perioperative anaphylaxis

- Perception of high risk
- Avoided due to high risk
- Suspected in case of perioperative anaphylaxis in last 12 months
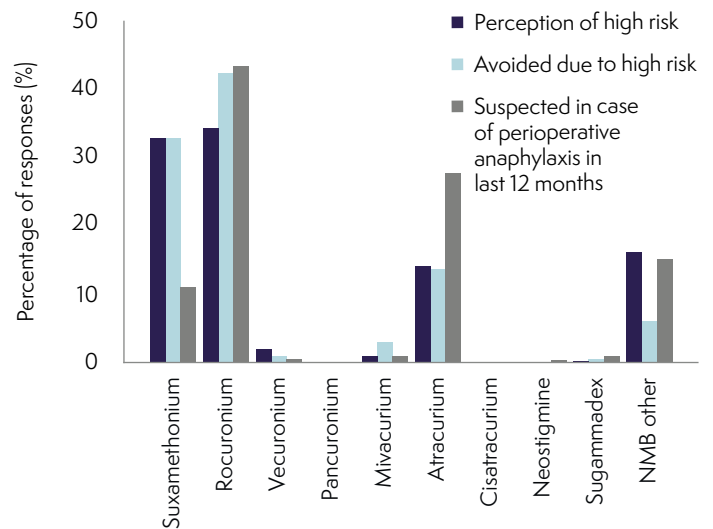
Rocuronium and suxamethonium were perceived to have the highest risk of causing anaphylaxis and were the NMBAs most commonly avoided by respondents, while in actual events, rocuronium and atracurium were most frequently implicated. Suxamethonium, although perceived as high risk, was not frequently the suspected causative agent in cases reported. The absence of data on the frequency of use of suxamethonium prevents further conclusions.

A similar analysis of antibiotic anaphylaxis is shown in Figure 6. Penicillins were both perceived to be the most likely causative agents and were the ones avoided most often. It is notable that teicoplanin, although prominent amongst suspected responsible agents, was not frequently avoided.

Figure 6. Perceptions surrounding the role of individual antibiotics in causing perioperative anaphylaxis
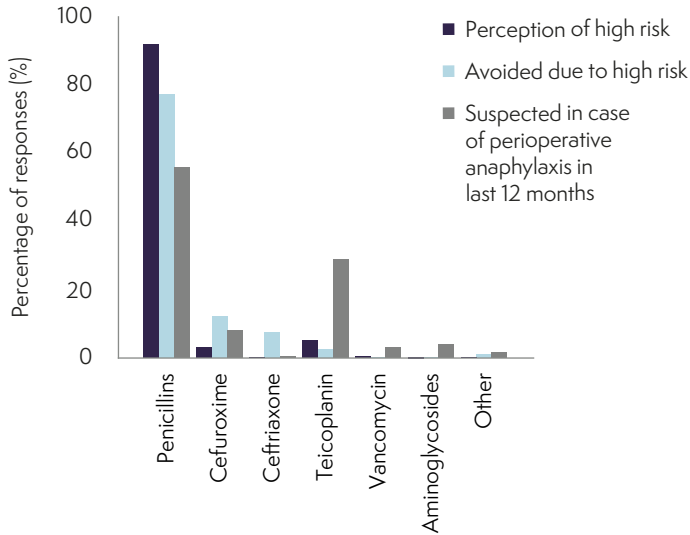
Antibiotic test doses

Nearly one third of anaesthetists (32%) reported routinely using a test dose when administering intravenous antibiotics. Five hundred and twenty-two respondents (4.7%) reported having observed an anaphylactic reaction to a test dose.

Career experience of anaphylaxis

Seventy-six per cent of respondents reported a case of perioperative anaphylaxis during their career. The median number of cases per respondent was 2 (1-3 [0-51]) (Figure 7), which equates to 1 case per 7.25 years of practice (95% confidence interval 1:3-1:14 years). Four per cent of respondents reported a death related to perioperative anaphylaxis in their career, and anaesthetists reported a career prevalence of mortality from anaphylaxis of 498 deaths or 1 death per 311 years of anaesthetic practice (1:277-1:347). This equates to 2.3% of cases of suspected severe anaphylaxis being fatal.

Figure 7. Distribution of cases of suspected perioperative anaphylaxis during the career of the reporting anaesthetists
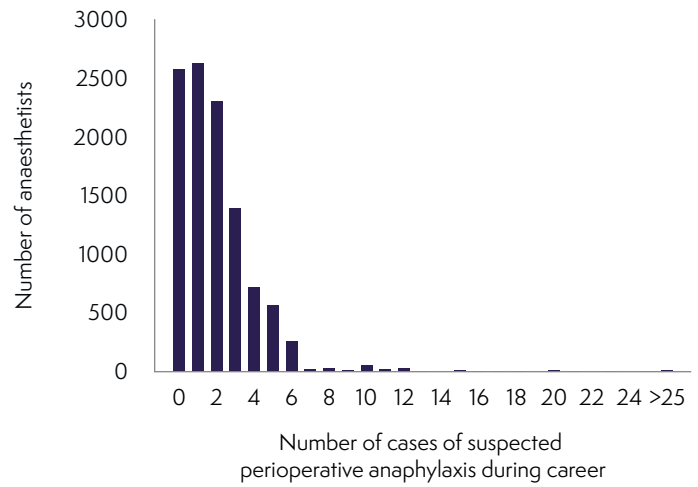
Discussion

This study is the first UK-wide investigation of anaesthetists' perceptions of perioperative anaphylaxis and adherence to current guidelines for reporting and referral. The response rate of greater than 77% indicates that we surveyed a representative sample of UK anaesthetists. With more than 11,000 respondents it is undoubtedly the largest-ever survey on the topic, and this illustrates the continuing commitment of UK anaesthetists to the National Audit Projects. The survey provided useful information about current practice ahead of two further phases of NAP6: a prospective collection of actual cases of perioperative anaphylaxis in 2015-16, and an Activity Survey recording exposure to potential perioperative allergens.

The survey indicates that an anaesthetist can expect to see a case of anaphylaxis every 7.25 years of practice. While three quarters of respondents had personal experience of anaphylaxis, more than 2,500 (24%) respondents had not seen perioperative anaphylaxis during their career. The survey highlights the fact that the vast majority of cases of perioperative anaphylaxis are not reported to national databases and that not all patients are routinely referred for specialist allergy investigations. Uniquely this survey shows that anaesthetists use avoidance behaviours and perceive certain drugs as high risk. These perceptions may not correlate with actual risk. Unsurprisingly, the agents most frequently perceived to cause anaphylaxis remain neuromuscular blocking agents, with rocuronium being considered the highest risk, together with antibiotics, particularly penicillins.

Several organisations have published guidelines for the immediate management and referral of perioperative anaphylaxis, including the British Society for Allergy and Clinical Immunology (BSACI), the Resuscitation Council UK (Ewan 2009, Soar 2012) and the AAGBI (Harper 2009). It appears that anaphylaxis guidelines are readily available in the clinical setting, with the majority of anaesthetists reporting that they had immediate access to guidelines and a similar number being confident of where to refer a patient if required. The AAGBI guidelines indicate that "the anaesthetist who gave the anaesthetic or the supervising

anaesthetist is responsible for ensuring that the reaction is investigated", and 81% of cases in the previous twelve months appear to have been referred for investigation by an anaesthetist. Regarding clinical incident reporting, only 14% were reported to the MHRA. It is possible that some cases may subsequently be reported to the MHRA by the allergy clinic, as per BSACI guidelines (Ewan 2009). Nevertheless, our data suggest that estimates of rates of anaphylaxis and anaphylaxis-related mortality inferred from MHRA data are likely to be inaccurate and to significantly under-estimate true prevalence.

This survey highlights interesting differences in anaesthetists' perception, avoidance practices, and suspected causative agents of perioperative anaphylaxis. It might be expected that the number of anaesthetists choosing to avoid a particular drug due to a perception of high risk of allergy would reflect the actual risk rate, ie. the number of anaphylactic events expressed as a proportion of the total number of administrations of that particular drug in a large published series. However, this was not consistently observed, with several drugs over- or under-represented. Our results indicate that many factors influence an individual's perception of anaphylaxis risk, and that these vary between agents. Personal and local experience appears to be an important factor in generating risk perception, being responsible for 40% of drug avoidance behaviours.

Teicoplanin and atracurium stand out as being implicated in a greater proportion of anaphylactic reactions than would be expected from the number of anaesthetists who try to avoid these agents due to perceived anaphylaxis risk. Teicoplanin was the suspected trigger in 28% of cases of antibiotic-related anaphylaxis, second only to penicillins (Figure 6). A recent case series of reactions to teicoplanin highlighted teicoplanin anaphylaxis as an emerging problem, with anaesthetic allergy clinics reporting seven definite cases from two UK centres (Savic 2015b). Teicoplanin is used both as first-line prophylactic therapy for some major, particularly orthopaedic procedures, and is often the chosen therapy for those reporting penicillin allergy. The prevalence of teicoplanin-induced perioperative anaphylaxis is therefore of clinical consequence, and it is important that anaesthetists do not consider it a risk-free agent.

Atracurium was suspected in 28% of cases in which an NMBA was implicated as the cause of anaphylaxis, yet only half as many respondents reported trying to avoid this drug, and the commonest reason for avoidance was concerns over non-specific histamine release. Conversely suxamethonium was proportionately more avoided than it was implicated in anaphylactic events, with avoidance based on published literature and the impact of other side effects. Risk perception may be influenced by both risk rate (events per use) and event rate (absolute numbers of events), and the latter will be influenced by the frequency with which a drug is used. The pattern of usage of NMBAs in the UK was not known at the time of his survey: the NAP6 Allergen Survey (Chapter 9) provides this information and enables estimation of the relative incidence of perioperative anaphylaxis with specific agents.

The AAGBI guidelines counsel against the use of 'test doses' when administering intravenous antibiotics. In order to be informative, diagnostic drug challenges require the controlled administration of increasing doses at intervals of 15–30 minutes, typically starting with 1/1000th of the therapeutic dose (Ewan 2009). One third of anaesthetists reported using a test dose, possibly believing that this practice would limit the severity of anaphylaxis.

In 2002, Lieberman (Lieberman 2002) suggested that the second most common causative agent for perioperative anaphylaxis was latex, but this was reported by very few anaesthetists as a cause of concern or a causative agent for reactions in the current survey. Important progress has probably been made in the UK in the use of latex-free gloves and indwelling devices, and in developing preoperative screening for identification of at-risk patients. Many hospitals now provide 'latex-free' theatre environments. Conversely, chlorhexidine-anaphylaxis has become more common and may be a common 'missed diagnosis' (Garvey 2012, Guleri 2012, Toomey 2013, Abdullah 2015). Our survey indicates an increasing awareness of chlorhexidine-induced reactions, and it is notable that chlorhexidine was the suspected or actual cause in 1 in 25 cases in 2014-15 – twice as many as latex.

This survey, while not designed to provide accurate incidence data, indicates an approximate incidence of 1:1,556 (1:481–1:1,635) during 2014–15, which is higher than in other studies (Mertes 2009, Gibbs 2013) which estimated between 1:10,000 and 1:20,000.

The proportion of perioperative anaphylaxis events leading to death is 1 in 41 from the 12-month data and 1 in 43 from the career-experience data, suggesting that an anaesthetist might experience one death relating to perioperative anaphylaxis for every 311 years of anaesthetic practice. Older studies, including cases from the 1970s and 1980s, estimate a mortality of 3.9% (Mitsuhata 1992, Light 2006). However, a 2013 publication reported no deaths from perioperative anaphylaxis over a nine-year period in Western Australia, with a mortality rate based on confidence intervals of <1.4% (Gibbs 2013). The number of UK patients dying as a result of perioperative anaphylaxis is unknown, and may have reduced in recent years as guidelines have been implemented (Harper 2009) and critical care outcomes have improved (Nolan 2016).

Limitations and strengths

First, this is a retrospective study relying on recall, potentially over a number of years, and there are limitations with any such study. It is notable that incidence of awareness in the methodologically similar baseline survey of NAP5 (Jonker 2014) were almost identical to those reported in the prospective phase of that project (Pandit 2014). It is possible that in our survey anaesthetists recalled incidents beyond the previous twelve months, particularly if the anaphylactic event was very severe. It is also possible that more than one anaesthetist reported the same case due to lack of clarity over who was the primary anaesthetist. This study also asked for suspected cases of anaphylaxis, and of those only 49% were reported to have been confirmed. Since many anaesthetists work in both a perioperative and critical care setting, recall may have related to cases treated in critical care rather than being truly perioperative. Despite only asking for reports of severe cases,

milder cases may have been reported due to variations in the interpretation of the diagnostic criteria. For all these reasons, it is quite possible that the incidences we derive from these reports may be inaccurate (overestimated) and that the actual incidence of true anaphylaxis is closer to the historical estimates. As stated above the incidence of events is not the main focus of this paper. Second, the data on suspected and proven causative agents is uncertain because it is not known how many suspected events were actually anaphylaxis and how many suspected causative agents were subsequently shown to have been correctly identified: the next phase of NAP6 will shed light on these matters.

Strengths of the survey include its size and the likely generalisability of the results. The survey includes responses from almost all hospitals in the UK and more than three quarters of all potential respondents. Our denominator for respondents is within <4% of the recent census figure of the RCoA (RCoA 2016). As some 'anaesthetists' will primarily practise in pain clinics and critical care, it is likely that our relevant response rate is higher than we report.

Conclusions

This is the largest-ever survey of anaesthetists' experiences of and practices relating to perioperative anaphylaxis. It provides important data about the drugs that are suspected or proven to be, implicated in such events. It also highlights current practice and preparedness for perioperative anaphylaxis.

The survey has identified gaps in referral for further investigation. and also in reporting to the MHRA, which supports the likely value of the NAP6 project in providing a more accurate registry of such events. The survey highlights a mismatch between drugs implicated in events and anaesthetists' perception of risk and avoidance practices. It is particularly notable that atracurium and teicoplanin are not perceived by anaesthetists to be of major concern, and that they are rarely avoided despite both being important agents in suspected anaphylactic events. Chlorhexidine is implicated in a significant number of recent perioperative anaphylaxis events and appears to be a greater problem than latex.

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Appendix 1:

Copy of online questionnaire distributed to anaesthetists

Personal experience of perioperative anaphylaxis

1. In the last 12 months how many cases of suspected perioperative anaphylaxis have you seen in patients directly under your care, ie, where you anaesthetised or sedated the patient?

2. In the last 12 months how many times have you been called to assist in the urgent management of suspected perioperative anaphylaxis in other patients?

3. Of these cases (those you saw directly PLUS those you assisted with, ie, combining answers to Q1 and Q2): what were the causes of each anaphylactic reaction?

4. How many patients were referred for investigation by:
   a. Yourself?
   b. Another anaesthetist?
   c. Patient's GP?
   d. Other? (please specify who).

5. If patients were not referred, it was because:
   a. Patient died
   b. Reaction not severe enough
   c. Unsure about pathway
   d. Forgot
   e. Other (please specify reason).

6. In how many cases was the diagnosis of anaphylaxis confirmed by subsequent investigation?

7. In how many cases did you contact a specialist allergy/immunology clinic for advice by phone or e-mail?

8. How many patients were transferred to HDU or ICU as a direct result of suspected perioperative anaphylaxis?

9. How many patients died as a consequence of perioperative anaphylaxis?

10. How many cases did you report via the MHRA Yellow Card system?

11. How many cases did you report through your hospital incident-reporting system?

12. In how many of your personal referrals did you complete an AAGBI referral form (link to AAGBI form included)?

Career experience of perioperative anaphylaxis

13. How long have you been an anaesthetist? Please specify the number of years from the time you started your specialist training.

14. How many cases of severe anaphylaxis have you seen in your career?

15. How many patients in your direct care have died as a consequence of perioperative anaphylaxis?

Local arrangements - if your next patient has a suspected anaphylactic reaction during anaesthesia or sedation:

16. Do you have immediate access to anaphylaxis guidelines in your theatre?

17. Do you have a departmental pathway for referring suspected anaphylaxis patients for further investigation?

18. Do you know where to refer the patient for further investigation?

19. Do you have a specific, labelled anaphylaxis pack (distinct from the usual emergency drug box) in your theatre or nearby?

20. Do you have a departmental lead anaesthetist for perioperative anaphylaxis?

Personal attitudes to the risk of perioperative anaphylaxis

21. Do you generally try to avoid any particular drug/substance as a result of perceived high risk of anaphylaxis?

22. If you answered yes to the question above, please explain the reasons why? For example, personal experience, heard of several cases, information published in journals, etc.
   a. Drug/substance
   b. Reason for refusal.

23. In your perception, which current perioperative drug (or other substance) has the highest rate of anaphylaxis associated with it? ie, reactions per 1,000 doses. Please record your top 3 in order, most likely first.

24. Do you routinely administer a test dose of antibiotics?

25. Have any of your patients had a reaction to a test dose of an antibiotic?

Harriet Kemp   Susana Marinho   Tim Cook   Nigel Harper

Key findings

- We surveyed 356 National Health Service hospitals to determine anaesthetic activity in October 2016.
- Responses were received from 342 (96%) hospitals, each reporting 96% of their cases.
- 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 <2 years anaesthetic experience lead <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 to data from 2013.
- Depth of anaesthesia monitoring has increased but neuromuscular monitoring has not, suggesting that current guidelines are not implemented.

The 6th National Audit Project of the Royal College of Anaesthetists (NAP6), is a prospective service evaluation across the National Health Service in the United Kingdom, aiming to provide quantitative and qualitative information about life-threatening perioperative anaphylaxis in the UK. A one-year registry collected a report of every suspected case in 2015-16 (Chapter 5, Methods; Chapter 6, Main findings).

In order to interpret the results of the registry created in this period, contemporary information about anaesthetic care provided in participating hospitals was required. The first component of the Activity/Allergen Survey, described here, provides information on patient demographics, anaesthetic workload and anaesthetic technique. The second part of the Survey, (Chapter 9, Allergen Survey), enables estimation of the incidence of perioperative anaphylaxis by providing a denominator for the annual number of cases involving anaesthetic care and individual drug use.

In 2013, the NAP5 project undertook a similar Activity Survey (Sury 2014) providing information on the number of cases involving anaesthetic care in operating theatres, critical care units and emergency departments. Published Hospital Episode Statistics (NHS Digital 2017a) show an increase in patient and day case procedures since 2013, but do not give detailed information on anaesthetists' involvement. NHS Maternity Statistics show a slight decrease in deliveries in NHS hospitals since 2013, of which 60% involved anaesthetic intervention (HSCIC 2013). Such changes over time mean that figures used for NAP5 may not necessarily be applicable for the 2016 data collection period.

The current survey, performed with similar methods to NAP5, enables identification of subsequent changes in anaesthetic practice, including any that might have occurred as a consequence of the recommendations made in the NAP5 report, such as increased used of depth of anaesthesia (DOA) monitoring and peripheral nerve stimulators (Pandit 2014, Cook 2014).

There has been much recent debate about the 'weekend effect', the seniority of physicians administering care outside of routine hours and any consequent impact on patient care (McKee 2016, Freemantle 2012 & 2015, Hunt 2015). Information related to day of the week was not reported in the NAP5 Activity Survey. Reports recording NHS work patterns, such as the 2003 'Who Operates When II' (Cullinane 2003), are now out of date and there is the need for information on anaesthetic-specific workload.

This chapter describes anaesthetic caseload and working practice, examines activity by day of the week, and highlights any changes in the state of UK anaesthesia since the NAP5 survey in 2013 (Sury 2014).

Methods

The NAP6 project was defined as a service evaluation by the Health Regulatory Authority and therefore did not require National Research Ethics Service approval.

Local Coordinators were approached at 356 NHS hospitals, and they organised data collection from every perioperative case involving the care of an anaesthetist. This included all adult and paediatric cases requiring general, regional and local anaesthesia, as well as sedation if involving an anaesthetist. Obstetric cases included epidural pain relief in labour.

Any cases where sedation or local anaesthesia was delivered by a non-anaesthetist were not included. Routine sedation in critical care was excluded.

The majority of data collection took place between 13 and 31 October 2016, during which time there were no public holidays. Seven sites collected data between January and June 2017 for logistical reasons. Data were recorded using a paper pro-forma (Appendix 1), and each form was transferred, using optical character recognition, to electronic storage. Each hospital was randomly designated to record activity on two consecutive days of the week, with specialist hospitals (cardiac, neurology or paediatric centres) block-randomised separately to prevent skewed allocation. Patient characteristics, method of anaesthesia, anaesthetic staffing, induction location, type of monitoring and drugs used, and the presence of any allergy history were reported for each case. Local Coordinators were also asked to record a capture rate at their site to estimate the proportion of cases for which a completed case report form was submitted. Data regarding drug usage and allergy status are reported separately (Chapter 9, Allergen Survey).

Data were analysed using IBM SPSS software (version 23). An annual caseload was estimated by multiplying the number of cases by a scaling factor. This factor was calculated by converting the number of cases from two days to one week (scaling factor of 3.5), and from one week to one year (scaling factor of 50.6, the effective number of working weeks in 2016) (Appendix 2). This was then divided by the hospital response rate, the mean reported capture rate at individual sites and the proportion of interpretable forms, to account for cases that were not reported. Responses marked as 'unknown' and incomplete fields were combined and reported as 'unknown'. Ethnicity data was re-categorised to follow categories stipulated by the Office of National Statistics for comparison purposes.

Results

Data were returned from 342 hospitals, a return rate of 96%. Eleven sites had no cases to report during the data collection period. In total 15,942 case report forms were interpretable (263 forms from 18 sites were not interpretable), and consequently the return rate of interpretable forms was 98%. A median of 39 forms were submitted per hospital. The mean capture rate per site reported by Local Coordinators was 96%. Therefore, the number of reported cases equates to an annual caseload of 15,942 x (3.5 x 50.60)/(0.96 x 0.96 x 0.98) = 3,126,067. The field most

frequently left incomplete was 'NCEPOD priority', which was blank in 6% of cases. All other fields were completed in at least 97% of cases. Figure 1 shows the hospitals contacted and data received.

Figure 1. Summary of cases included in final analysis
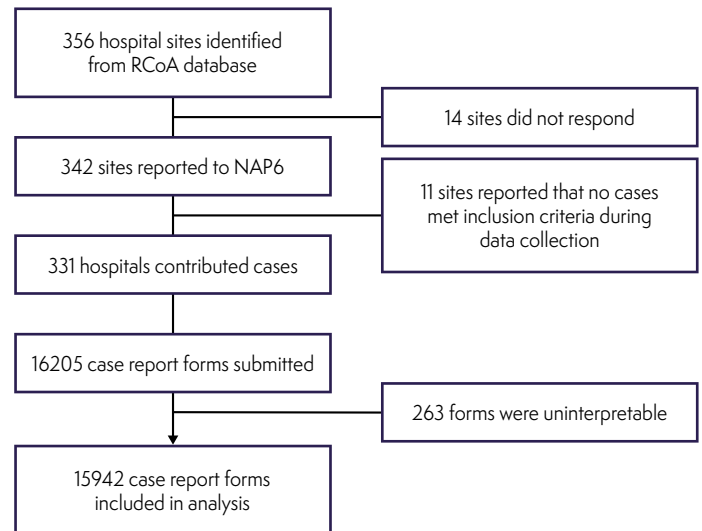
Patient characteristics

Overall more patients were female (n=9,052; 58.7%).
The male: female ratio varied with age (Figure 2).

Figure 2. Age distribution of cases - top chart shows all cases; bottom chart shows male to female ratio for each age group
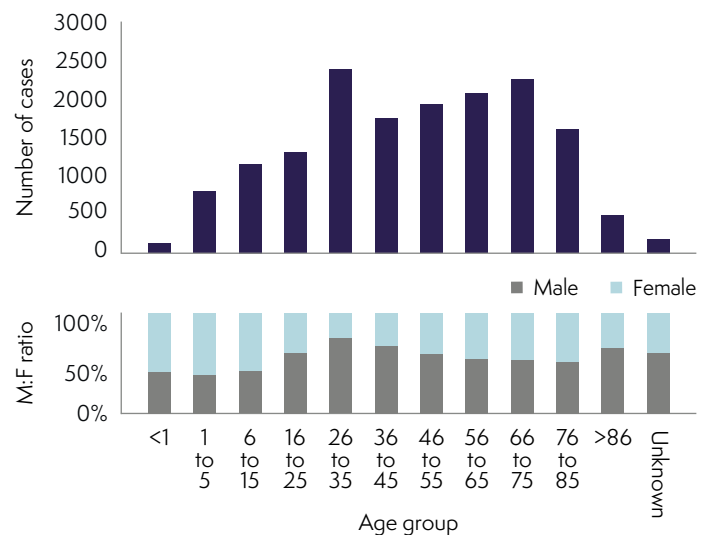
The majority of patients were White Caucasian (n=13 926; 87.4%). Asian and Black/African/Caribbean patients accounted for 5.5% and 3.0% of cases respectively with the remainder classified as multiple/mixed or 'Other'. There was a higher proportion of non-white Caucasian patients in the younger age groups (Figure 3).

Figure 3. Distribution of ethnicity by age group
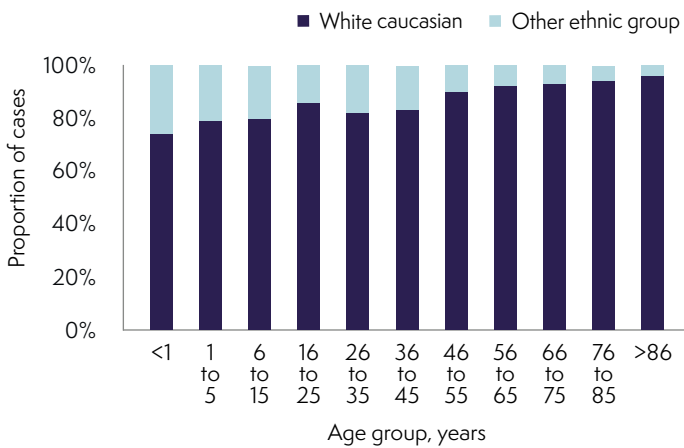
Approximately half of patients (n=7,876; 49.4%) had a 'normal' body mass index (BMI) (18.5-24.9 $kg.m^{-2}$), 22.9% (n=3,648) were overweight (BMI 25-29.9 $kg.m^{-2}$), and 20.2% (n=3,224) were obese (BMI 30-34.9 $kg.m^{-2}$) or morbidly obese (BMI >35 $kg.m^{-2}$). In the remaining cases the patient was underweight (2.9%) or the weight was unknown (4.6%). Significantly more patients (Chi^2 15.14, p=0.004) were morbidly obese compared to NAP5 data (Table 1).

Table 1. Distribution of body mass index (BMI) in NAP6 and NAP5 datasets

BMI category	NAP6 n (%)	NAP5 n (%)
Underweight (<18.4 $kg.m^{-2}$)	468 (2.94)	575 (2.82)
Normal weight (18.5-24.9 $kg.m^{-2}$)	7,876 (49.40)	10,237 (50.18)
Overweight (25-29.9 $kg.m^{-2}$)	3,648 (22.88)	4,701 (23.04)
Obese (30-34.9 $kg.m^{-2}$)	2,099 (13.17)	2,546 (12.48)
Morbidly obese (>35 $kg.m^{-2}$)	1,125 (7.06)	1,262 (6.19)
Unknown	726 (4.55)	1,089 (5.34)

In the paediatric population (age <16 years), 75.3% (n=1,546) of patients had a 'normal' BMI, 5.9% (n=122) were overweight, and 1.9% were obese or morbidly obese (n=40) (Figure 4). Of obstetric cases 12.5% (n=165) were obese and 7.6% (100) morbidly obese.

Figure 4. BMI of patients by age category. Underweight=BMI <18.5 $kg.m^{-2}$; Normal BMI=18.5-24.9 $kg.m^{-2}$; Overweight=25-29.9 $kg.m^{-2}$; Obese=30-34.9 $kg.m^{-2}$; Morbidly obese=>35 $kg.m^{-2}$
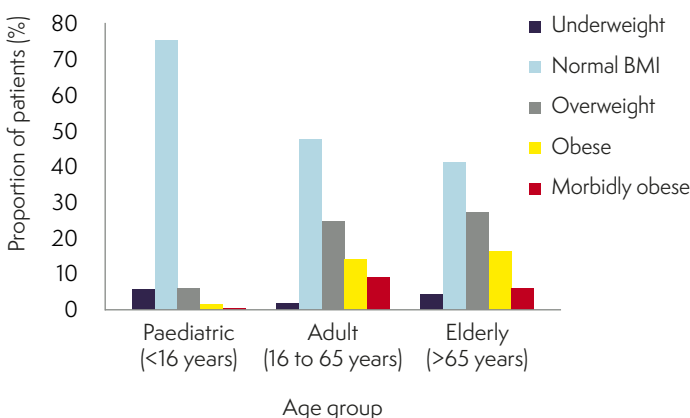
Orthopaedics/trauma (21.1%) and general surgery (16.2%) were the surgical specialties accounting for the largest proportion of activity, and obstetric anaesthesia accounted for 8.3% of the workload (Figure 5). The most common procedures in men were orthopaedics (23.7%), general surgery (18.0%) and urology (16.4%), while in women 31.8% of cases were obstetrics and gynaecology, 19.4% orthopaedics, and 14.9% general surgery.

Figure 5. Number of cases by specialty of main procedure
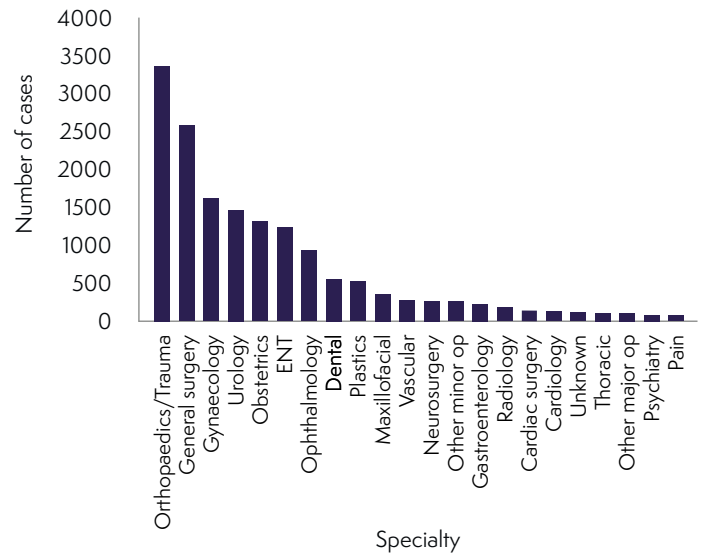
Of the 1,317 obstetric cases, 875 were caesarean sections (classification of urgency: Category 1, n=114 (13.0%); Category 2, n=302 (34.5%); Category 3, n=106 (12.1%); Category 4, n=325 (37.2%); unknown Category, n=28 (3.3%).

The majority of patients were ASA Grades 1 or 2 (77.0%), with only 2.76% being ASA 4 or 5 (Table 2). Two thirds of the workload was elective (65.6%), of which 47.9% was classified as 'day case' (Table 2). Just over one quarter (27.5%) of cases were classified as emergency procedures, and these patients had higher ASA statuses than elective cases (Table 2).

Table 2. Distribution of cases by ASA grade and NCEPOD (National Confidential Enquiry into Patient Outcome and Death) classification for urgency of surgery

ASA	NCEPOD Classification					Total (%)
	Elective	Expedited	Immediate	Urgent	Unknown	
1	3,723	394	132	1,063	496	5,808 (36.43)
2	4,690	420	78	859	425	6,472 (40.60)
3	1,741	347	52	646	114	2,900 (18.19)
4	84	61	61	196	16	418 (2.62)
5	1	-	18	3	1	23 (0.14)
6	0	1	0	2	0	3 (0.02)
Unknown	214	25	3	31	45	318 (1.99)
Total (%)	10,453 (65.6)	1,248 (7.7)	344 (2.2)	2,800 (17.6)	1,097 (6.9)	15,942

Table 3. Urgency of workload by day of the week

NCEPOD classification	Mon	Tues	Wed	Thur	Fri	Sat	Sun	Unknown	Total
Elective	2,202	1,877	1,963	2,056	1,790	453	111	1	10,453
Expedited	203	204	204	221	194	119	103	0	1,248
Immediate	47	31	39	41	46	65	75	0	344
Urgent	381	390	404	403	376	446	400	0	2,800
Unknown	212	174	161	196	152	94	102	1	1,029
Total (%)	3,045 (19.1)	2,681 (16.8)	2,771 (17.4)	2,917 (18.3)	2,558 (16.1)	1,177 (7.4)	791 (4.96)	2 (0.01)	15,942

Timing of anaesthesia and staffing

Weekend working (case reported as commencing on a Saturday or Sunday) accounted for 12.4% of anaesthetic caseload. Monday and Thursday were the busiest weekdays and Friday was the least busy. Sixty per cent of procedures on Sunday, and 43% on Saturday, were urgent or immediate (Figure 6 and Table 3). Of the elective workload, 5.4% occurred at weekends, compared to 1.7% in NAP5.

Figure 6. NCEPOD classification of urgency of procedures performed, by day of the week
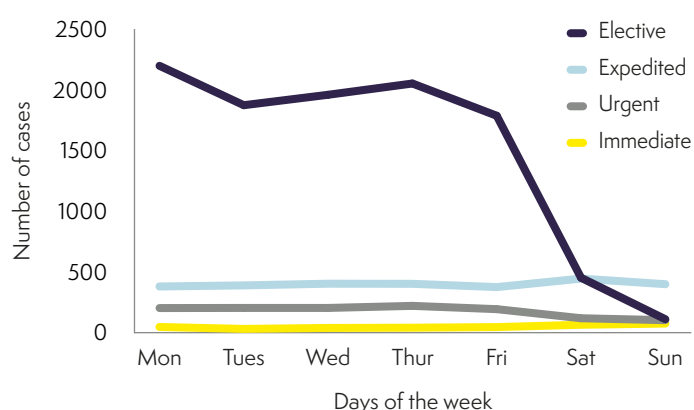
The proportion of ASA 4, 5 and 6 cases remained constant across the week whereas ASA 1–3 reduced at the weekends (Figure 7).

Figure 7. ASA grade of patient, by day of the week
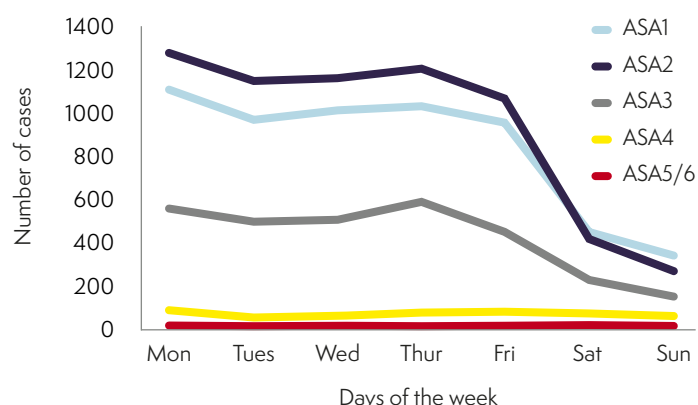
Weekend workload was dominated by orthopaedic, general and obstetric surgery (Table 4), and in obstetrics 30.5%, (ie. approximately 2/7ths of the weekly workload) took place at the weekend.

Table 4. Proportions of each specialty's workload performed at weekends, and proportion of overall weekend workload attributable to each specialty *Includes pain, psychiatry and 'other' major or minor operations

Specialty	% of specialty workload that occurs at weekend	% of weekend workload attributable to specialty
Orthopaedics/Trauma	13.65	23.37
Obstetrics	30.52	20.43
General surgery	13.09	17.17
Urology	10.71	7.98
Gynaecology	5.48	4.52
Ophthalmology	8.97	4.27
ENT	5.08	3.2
Plastics	11.71	3.1
Neurosurgery	15.3	2.08
Maxillofacial	10.89	1.98
Dental	5.59	1.58
Radiology	15.3	1.42
Vascular	9.96	1.42
Gastroenterology	8.0	0.91
Cardiac surgery	11.27	0.81
Cardiology	8.59	0.56
Other*	13.67	5.18

The majority of all cases (88.7%) were under the direct care of a consultant or career grade anaesthetist. On Saturday and Sunday, this proportion decreased to 80.5% and 65.9% respectively. Senior anaesthetist involvement was seen in obstetric care less frequently: consultant or career grade anaesthetists delivered 68.5% of direct care on weekdays and 45.3% at weekends (Figure 8). Conversely a senior anaesthetist was involved in the direct care of 93.4% of emergency orthopaedic procedures on weekdays and 88.8% at weekends.

Figure 8. Seniority of anaesthetist, by day of the week for a) all specialties and b) obstetrics

All specialties

Obstetric cases
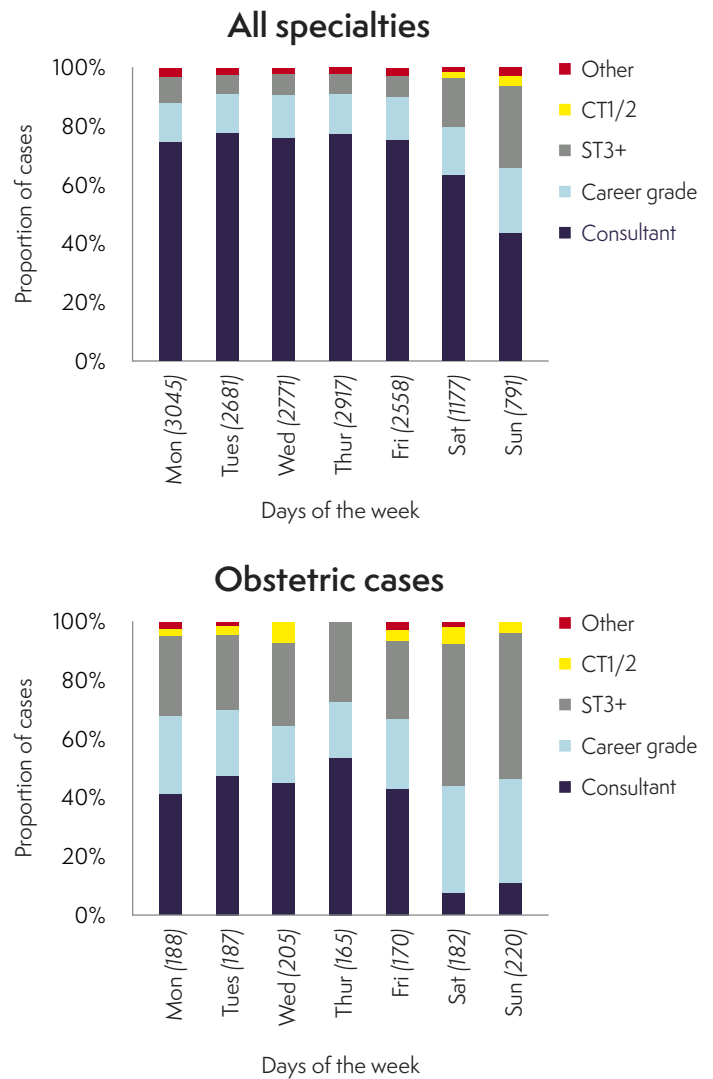
For caesarean sections, 84.3% of Category 4 procedures were under the direct care of a senior anaesthetist, compared to 62.3% of Category 1 deliveries (Figure 9).

Figure 9. Seniority of anaesthetists involved in caesarean sections
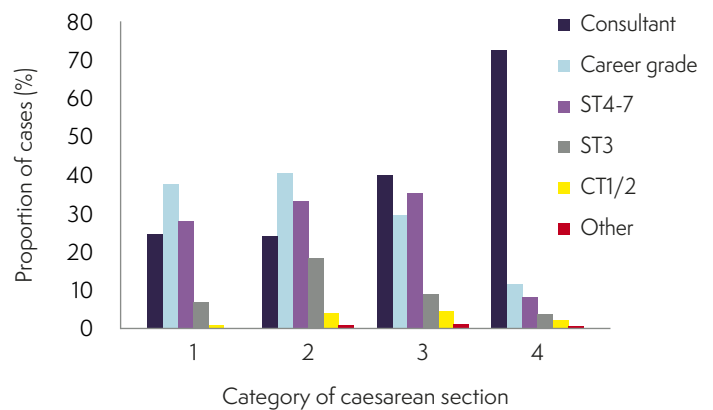
Table 5. Seniority of anaesthetists, by specialty of main procedure

Specialty	Consultant/SAS	ST3-7	CT1-2	Other	Unknown	Total
Orthopaedics/Trauma	3,139	156	13	39	24	3,371
General surgery	2,249	234	54	26	20	2,583
Gynaecology	1,465	96	29	29	4	1,623
Urology	1,324	91	20	16	15	1,466
Obstetrics	799	443	48	9	8	1,307
ENT	1,154	78	3	0	4	1,239
Ophthalmology	900	34	0	1	1	936
Dental	523	32	0	0	0	555
Plastics	414	53	5	8	5	485
Maxillofacial	332	20	0	3	3	358
Vascular	253	20	0	2	6	281
Neurosurgery	228	33	0	2	5	268
Gastroenterology	208	12	2	0	3	225
Radiology	170	9	1	2	1	183
Cardiac surgery	142	0	0	0	0	142
Cardiology	120	6	1	0	1	128
Unknown	86	21	1	0	3	111
Other*	593	31	2	0	6	895

All cases involving a patient less than 1 year old, and 94% of patients over 75 years old, were led by a senior anaesthetist. Specialties with the largest proportion of cases led by anaesthetists in training were obstetrics, neurosurgery, plastics and general surgery, although overall numbers were small for neurosurgery (Table 5). No cardiac anaesthetic was delivered by an anaesthetist in training alone.

Overall, the proportion of cases under the direct care of a senior anaesthetist increased as ASA grade increased (Figure 10). Although the proportion of ASA 5 cases on a Sunday under the direct care of a senior anaesthetist was low, only three ASA 5 cases were reported in total.

Figure 10. Proportion of cases by ASA grade under the direct care of a senior anaesthetist (consultant or career grade) for each day of the week *Total number of ASA 5 cases = 23
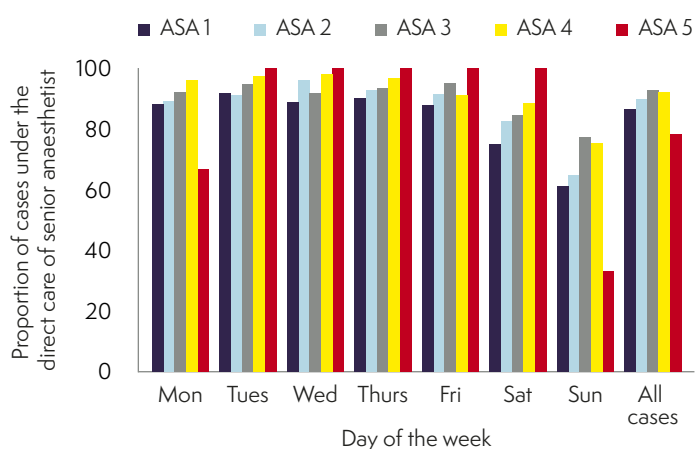
The proportion of emergency cases under direct consultant care was smaller at weekends than during the week.

Figure 11. Proportion of cases by NCEPOD category under the direct care of a senior anaesthetist (consultant or career grade) for each day of the week
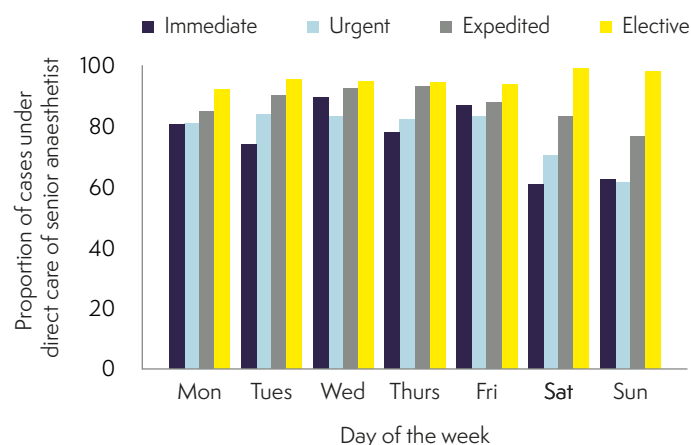
The most senior anaesthetist was a core trainee (CT1-2, ie. an anaesthetist with <2 years' experience) in 180 (1.1%) cases. These cases were mostly in general surgery, obstetrics and gynaecology, and included mainly patients of ASA Grades 1 or 2 (Figure 12 and Table 6).

Figure 12. Number of cases primarily delivered by core trainees, by specialty *Includes pain, psychiatry, 'other' major and minor operations
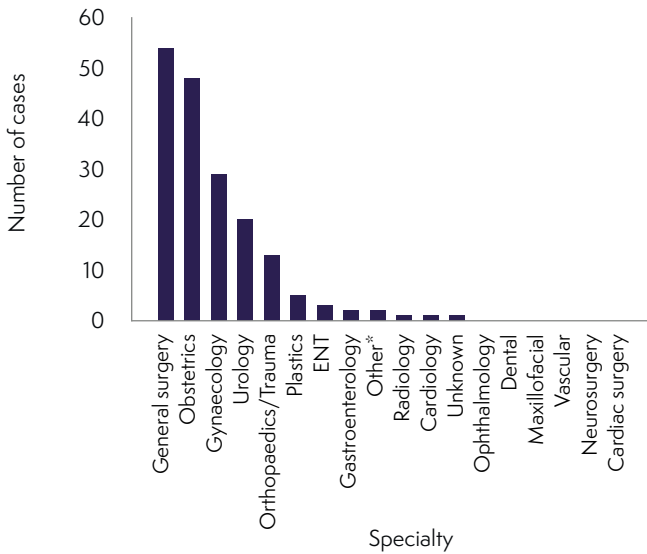
Table 6. ASA grade of cases anaesthetised by core trainees

ASA grade	Number of cases (%)
1	82 (45.6)
2	77 (42.8)
3	15 (8.3)
4	2 (1.1)
5	0 (0.0)
Unknown	4 (2.2)

Anaesthetic conduct

Over three-quarters (n=12,213; 76.6%) of cases were conducted with general anaesthesia (Table 7), an annual estimated caseload of 2,394,847. Cases involving sedation accounted for 8.3% of cases (n=1,317) and in 14.2% (n=2,256) of cases the patient was awake.

Table 7. Proportion of cases by intended level of consciousness for NAP6 and NAP5

Intended level of consciousness	NAP5	NAP6
General anaesthesia	75.8%	76.6%
Deep sedation	1.8%	1.8%
Moderate sedation	3.1%	3.4%
Minimal sedation	3.6%	3.1%
Awake (no sedation)	14.3%	14.2%
Other	0.3%	0.0%
Unknown	1.1%	0.9%

The proportion of cases involving sedation increased with age (Figure 13), and the peak of awake cases in the age group 26–35 years was mainly attributable to caesarean section under neuraxial anaesthesia (95.5% of awake cases). The use of local anaesthetics, delivered by any route, was reported in 74.2% (n=11,831) of cases.

Figure 13. Intended level of consciousness by patient age
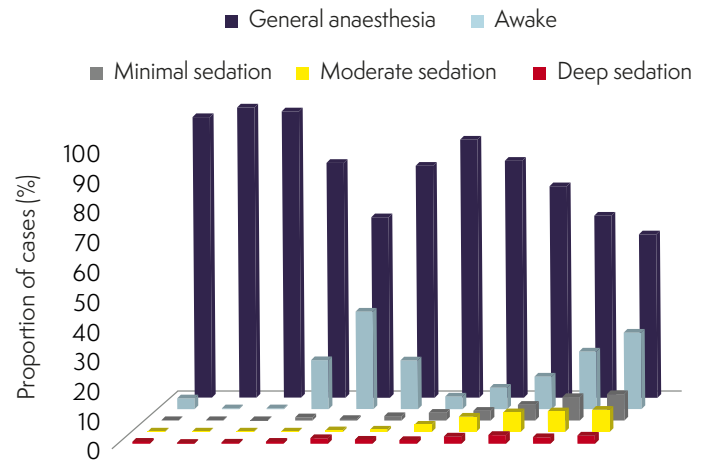
Location

In cases of all ages involving general anaesthesia, induction occurred in the anaesthetic room in 77.3%, in theatre in 18.8%, and less than one per cent of cases were managed in ICU or the emergency department (Table 8). These figures show no significant changes since 2013.

Table 8. Location of induction of cases involving general anaesthesia

Location of induction of anaesthesia	Adult cases, n (%)	Paediatric cases, n (%)	All cases NAP6, n (%)	All cases NAP5 %
Emergency Department	23 (0.23)	3 (0.15)	26 (0.21)	0.5
ICU	59 (0.59)	4 (0.20)	63 (0.52)	0.6
Radiology or Cathlab	87 (0.87)	83 (4.14)	171 (1.40)	1.6
Theatre	1,950 (19.43)	331 (16.51)	2,296 (18.80)	17.0
Theatre anaesthetic room	7,821 (77.92)	1,548 (77.25)	9,440 (77.29)	78.7
Unknown	-	1 (0.05)	88 (0.72)	-
Other	-	34 (1.70)	129 (1.06)	-

For cases involving paediatric patients, induction occurred in an anaesthetic room in 77.2% compared to 77.9% in adults. The proportion of cases induced in the operating theatre was highest for obstetric (92.3%), thoracic (35.8%), dental (34.7%) and vascular cases (26.2%) (Table 9). The proportions of elective and emergency cases for which induction occurred in theatre varied according to the specialty of the procedure being performed (Figure 14).

Table 9. Proportion of general anaesthetic (GA) cases where induction occurred in theatre, by specialty

Specialty of main procedure	% of GA cases where induction occurred in theatre
Cardiac surgery	25 (17.9)
Cardiology	14 (16.5)
Dental	185 (34.8)
ENT	193 (16.1)
Gastroenterology	48 (25.7)
General surgery	510 (20.7)
Gynaecology	295 (20.1)
Maxillofacial	58 (18.3)
Neurosurgery	48 (18.6)
Obstetrics	81 (92.3)
Ophthalmology	26 (9.7)
Orthopaedics/Trauma	283 (12.1)
Other major op	25 (26.3)
Other minor op	19 (10.4)
Pain	2 (100)
Plastics	91 (19.8)
Psychiatry	16 (20.0)
Radiology	2 (1.3)
Thoracic	34 (35.9)
Urology	226 (17.8)
Vascular	15 (26.2)

Figure 14. Proportion of elective and emergency general anaesthetic cases for which induction occurred in theatre, by specialty

Figure 15. Proportion of cases where depth of anaesthesia monitoring was used with different anaesthetic techniques
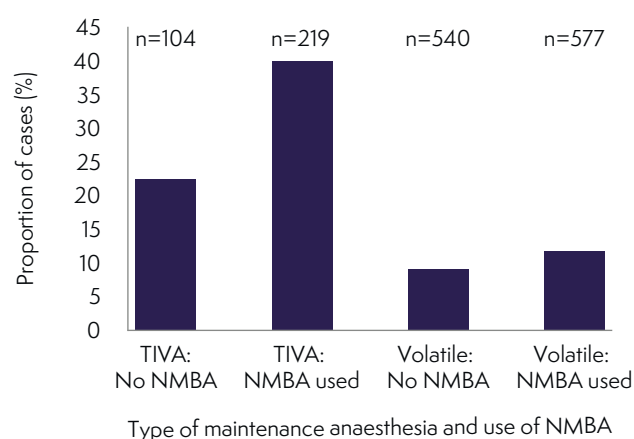
DOA monitoring use was evenly distributed over all BMI categories (Figure 16).

Figure 16. Proportion of cases when depth of anaesthesia monitoring was used, by body mass index category

Among different specialties DOA monitoring was used most frequently in cardiac (42.9% of general anaesthetic cases) and thoracic cases (35.9% of cases). In obstetrics, DOA monitoring was used in 7.7% of general anaesthetic cases (Figure 17).

Depth of anaesthesia (DOA) monitoring

Depth of anaesthesia monitoring was used in 12.0% of general anaesthetic cases, and more commonly in cases involving the use of non-depolarising NMBAs than in those that did not (14.2% versus 10.1%). In cases where propofol was the main agent for maintenance of anaesthesia, DOA monitoring was used more frequently (31.5%) than when an inhalational agent was used (10.0%). DOA monitoring was used when total intravenous anaesthesia (TIVA) was combined with a neuromuscular blocking agent in 39.7% (Figure 15).

Figure 17. Proportion of general anaesthesia cases in which depth of anaesthesia monitoring was used by specialty.
*includes pain, psychiatry or 'other' major or minor procedure

DOA monitoring was used most commonly in cases under the care of a consultant (12%) or a very junior anaesthetist (21%) (Figure 19).

Figure 19. Proportion of general anaesthesia cases in which depth of anaesthesia monitoring was used, by seniority of anaesthetist
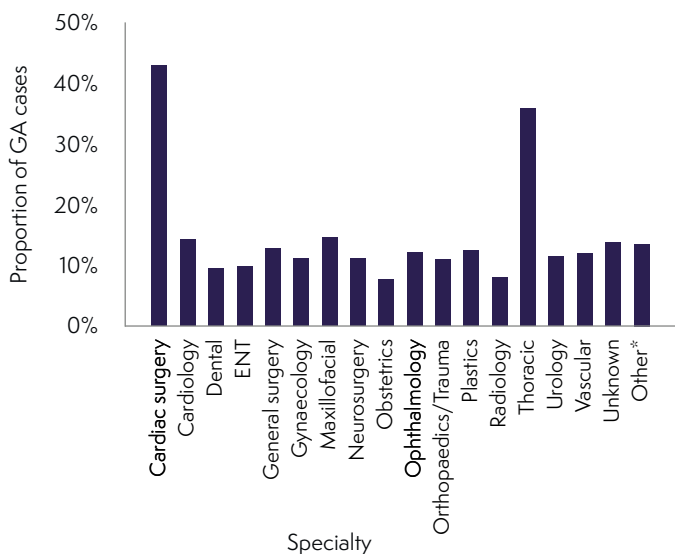
DOA monitoring was used less frequently in paediatric cases than in adults (Figure 18).

Figure 18. Proportion of general anaesthesia cases in which depth of anaesthesia monitoring was used, by patient age
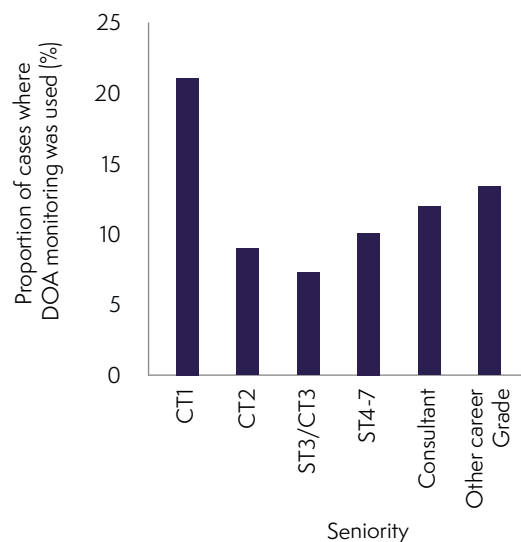
Neuromuscular monitoring

Among general anaesthesia cases 45.3% (n=5,532) received a non-depolarising neuromuscular blocking agent (NMBA). Peripheral Nerve Stimulator (PNS) monitoring was used in 36.7% of these cases (n=2,032) and quantitative neuromuscular monitoring (QM) was used in 2.8% (n=159). Reversal agents were used in 64.6% of these cases (compared to 68% in the NAP5 survey) and, when sugammadex was used, 50.2% of cases included PNS monitoring. When no reversal agent was used, a high proportion of cases did not undergo any type of neuromuscular monitoring. This was most marked if the patient received pancuronium and vecuronium and the majority of these cases were cardiac (all cases involving pancuronium and 54.8% of cases involving vecuronium) or neurosurgical (16.7% of cases involving vecuronium) (Table 10); in many of these cases the patient may receive post-operative care in a critical care unit.

Table 10. Use of peripheral nerve stimulator or quantitative monitoring in cases in which a non-depolarising neuromuscular blocking agent was administered. NMBA = neuromuscular blocking agent; PNS = peripheral nerve stimulator; QM = quantitative monitoring

Agent	Total number of cases	PNS used, n (%)	QM used, n (%)	No reversal agent used, n (%)	Proportion of cases with NMBA, but no reversal agent and no neuromuscular monitoring (%)
Atracurium	2,828	963 (34.1)	67 (2.4)	722 (25.5)	79.2
Cisatracurium	95	38 (40.0)	0 (0.0)	32 (33.7)	59.4
Mivacurium	157	25 (15.9)	0 (0.0)	128 (81.5)	88.3
Rocuronium	2,341	991 (42.3)	86 (3.6)	445 (19.0)	75.1
Vecuronium	124	32 (25.8)	7 (5.7)	46 (37.1)	91.3
Pancuronium	36	0 (0.0)	0 (0.0)	32 (88.9)	100.0
Sugammadex	327	164 (50.2)	17 (5.2)	-	-

PNS monitoring was used most commonly in the theatre environment, but it was also used in 11.5% of emergency department, 20.6% of radiology or cardiac catheter suite, and 10.0% of ICU cases involving NMBA use. Anaesthetists in training were more likely to use PNS monitoring than consultants or career grade anaesthetists (Figure 20).

Figure 20. Proportion of cases involving neuromuscular blockade where peripheral nerve stimulator monitoring was used, by seniority of anaesthetist
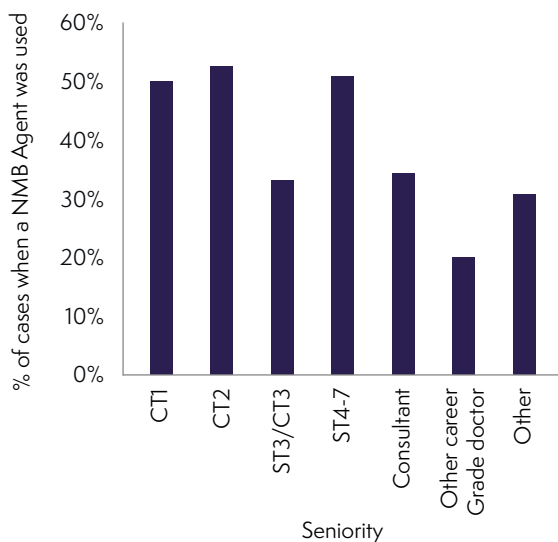
Discussion

This survey represents the most recent, comprehensive snapshot of anaesthetic activity and drug use in the United Kingdom. By using similar methods to those used in the NAP5 project (Sury 2014) it is possible to estimate changes in anaesthetic practice since 2013. NAP5 collected data in two-day epochs, rather on a single-day basis, and the current survey provides a more precise reflection of how the anaesthetic workforce is working throughout the week. We believe that this is the first detailed examination of the variability in anaesthetic workload over the days of the week and highlights the high proportion of cases under the direct supervision of senior anaesthetists.

The 'weekend effect' describes putative variability in hospital mortality associated with the day of the week of hospital admission (Freemantle 2012). The topic is highly controversial, with data being presented to support both sides of the argument. While mostly focused on admissions via the emergency department, the weekend effect has also been identified in some surgical populations (Metcalfe 2017, Smith 2018). The effect has in part been attributed to a lack of availability of senior staff at weekends leading to higher mortality, particularly in complex patients (Bell 2001). These observations have driven plans for changing how hospitals are staffed over the whole week (NHS England 2017).

Our results show that elective workload is increasing at weekends, with 5.8% of elective work being performed at weekends compared to 1.7% in 2013 during NAP5. In 2003 the NCEPOD WOW2 project reported that 4.3% of elective operations took place at the weekend (Cullinane 2003). Explanations for

fluctuations in elective weekend workload could include 'waiting list' initiatives, where extra elective operating lists are carried out at the weekend to meet increasing elective demands (Baker 2018).

Our data enable comment on the impact of delivering a seven day working pattern for staffing in anaesthesia. If, the current total elective work were to be distributed evenly throughout the week so that roughly 14% occurred every day, elective workload on a Saturday would have to increase by 230% and on Sunday by 1,245%. Alternatively, if the current weekday workload were to be continued at the same daily level at weekends, just under 300,000 extra operations on Saturdays and 366,000 on Sundays would need to be funded and staffed each year.

This survey shows that weekend elective work was almost exclusively carried out by consultant or career grade anaesthetists (98.8%). Significant changes in the working practice of consultants would be needed to maintain such a high proportion of senior care for elective operations at the weekend should the number of cases increase. The seniority of anaesthetists involved in weekend elective care appears to have increased in the last 13 years: the 2003 WOW2 report indicated that only 68% of weekend daytime elective care was delivered by senior anaesthetists.

In contrast, our results show that fewer emergency cases are under the direct care of a senior anaesthetist (68.1%) at weekends compared to weekdays (84.5%). Despite this, both during weekends and on weekdays, as ASA grade increased, the proportion of cases under the direct care of a senior anaesthetist increased, suggesting that the most unwell patients are cared for by the most senior anaesthetists. This apparent paradox is explained in part by the high number of obstetric cases at the weekend, which are often emergency procedures in healthy patients (low ASA grade), and are frequently led by anaesthetists in training. Obstetrics stands out as a specialty with both a high weekend workload and a high proportion of cases in which anaesthetic care is led by anaesthetists in training. This was also noted in the NAP5 Activity Survey. Since such a high proportion of obstetric emergency workload occurs out of hours, increasing senior anaesthetic cover for this cohort of emergency cases presents a significant challenge. Indeed, the 2013 joint Obstetric Anaesthetists Association/AAGBI guideline (AAGBI 2013) for obstetric anaesthetic services recognised the provision of a weekend, consultant-led obstetric anaesthetic service as an aspiration for future workforce development.

The WOW2 project reported that the specialties accounting for the majority of non-elective cases were general surgery, obstetrics and orthopaedics, and this appears to have remained consistent over the intervening 13 years.

Changes in anaesthetic practice between NAP5 and NAP6

Our results suggest that a higher proportion of patients undergoing surgical procedures are morbidly obese than in the NAP5 Activity Survey, reflecting the increasing prevalence of morbid obesity in the general population. An unexpected finding is that the adult surgical population overall appears to be slightly less obese than the general population (23% versus 27% (DH 2016)).

The use of DOA monitoring in cases where neuromuscular blockade is used has increased since NAP5 (12% versus 2.8%). One of the NAP5 recommendations was that DOA monitoring should be used in cases involving NMBAs, particularly when TIVA is used. The AAGBI also updated their standards for monitoring of anaesthesia in 2015 to recommend the use of DOA monitoring for cases where TIVA or NMBA are used (Checketts 2016). NICE guidance published in 2012 more broadly recommended DOA monitoring in high risk cases (NICE 2012). DOA monitoring was most common in cardiac and thoracic cases, a group historically recognised and identified in NAP5 as at higher than normal risk of accidental awareness during general anaesthesia (AAGA) (Ghoneim 2009) and where the consequences of excessive depth of anaesthesia are a particular concern (Smith 2015). In obstetrics, despite its being reported as a very high-risk specialty for AAGA in NAP5, use remained low (7.7% of GA cases).

Anaesthesia involving NMBAs has been associated with an increased risk of AAGA (Myles 2004, Avidan 2008), and incomplete neuromuscular recovery can impair respiration and upper airway protection (Fuchs-Buder 2016, Murphy 2008). Residual blockade can be detected more than two hours after administration in a high proportion of patients (Murphy 2008 & 2011), and therefore routine use of PNS monitoring is necessary. In contrast to a reported increase in use of DOA monitoring, the use of peripheral nerve stimulators has not increased since 2013 (36.7% NAP6 versus 38% NAP5). The NAP5 report recommended their use, and the AAGBI minimum-monitoring guideline stated that neuromuscular monitoring is mandatory in all patients receiving a NMBA (Checketts 2016). The AAGBI guidance recommends quantitative monitoring due to the relative imprecision of qualitative monitoring. In this survey the rate of PNS monitoring was low, quantitative monitoring was used in fewer than 1 in 30 relevant cases, significant numbers of patients received NMBAs without reversal agents and monitoring of neuromuscular function was especially low when reversal was not given. While some patients (particularly those undergoing cardiac or neurosurgical procedures) may have been transferred to ICU while still intubated, it appears that overall stewardship of NMBA monitoring falls well below current recommendations.

It is not clear why the use of PNS is so low, although this phenomenon has also been identified outside of the UK, with a Singaporean survey reporting that only 13% of anaesthetists routinely used PNS monitoring (Teoh 2016). Possible reasons for low take-up of neuromuscular monitoring include ignorance of recommendations, disagreement with the guidance, or lack of equipment. There seems to have been little change in use of neuromuscular junction monitoring or use of reversal agents since NAP5.

Data validity

This survey suggests an annual caseload of 3,126,067, which is a 15% reduction compared to that reported in NAP5 (3,685,800). We are not aware of any comparable data against which to benchmark. We note that the NAP6 annual estimate of caesarean section caseload (171,579) is within <2% of that reported in NHS maternity data (174,720) (NHS Digital 2017b). We attempted to control for limitations in data collection by incorporating an estimated capture rate per hospital, by accounting for uninterpretable forms, and by calculating a scaling factor to include bank holidays. The mean capture rate per hospital in NAP5 was slightly higher (98% in NAP5 versus 96% in NAP6), and therefore a slightly larger scaling factor was used in this report.

Although the difference in caseload between NAP5 and NAP6 could be due to a reduced capture rate, it might also be due in part to differences in monthly operating (October in NAP6 versus September in NAP5), or to random variation in the numbers of cases reported in certain hospitals due to sampling on different days of the week. A recent NHS Key Statistics paper (Baker 2018) showed that a higher proportion of operations were cancelled in 2016 (1.06%) compared to 2013 (0.90%) which may have contributed to a decrease in the total number of cases.

The many proportional similarities between the NAP5 and NAP6 datasets, such as the distribution of patient age, gender ratio and operating specialty, suggests that a similarly representative set of cases has been collected.

Conclusion

This national survey of anaesthetic practice in the United Kingdom enables confirmation of important nationwide findings, and gives detailed evidence for modelling the impact of any 'seven day working' policies on anaesthetic workload, staffing and funding. It shows that the proportion of cases under direct senior care is high and appears to be increasing over time. In addition, changes in patient characteristics, such as increasing morbid obesity, are likely to influence demands on heath service resources. Since NAP5 there have been significant increases of DOA monitoring, but monitoring of neuromuscular function remains non-compliant with current guidelines.

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NAP6 Anaesthetic Activity/Allergen Exposure Survey

NAP6 Hospital Code: ☐☐☐   **Date:** ☐☐/☐☐/☐☐ (dd/mm/yy)

PLEASE INDICATE ALL SPECIFIED DRUGS/SUBSTANCES THE PATIENT WAS EXPOSED TO DURING THE PERIOPERATIVE PERIOD (until patient discharged to the ward or HDU/ICU) *PLEASE SELECT ALL BOXES THAT APPLY IN EACH CATEGORY*

Theatre Number/Location: ☐☐☐☐☐☐☐☐☐☐☐☐☐   **Actual List Order** (first patient is 01): ☐☐

Please complete this form for all patients where anaesthesia care is provided by an Anaesthetist during the two day survey period

Day of the Week
- ☐ Mon ☐ Tues ☐ Wed
- ☐ Thurs ☐ Fri ☐ Sat
- ☐ Sun

Admission Type
- ☐ Elective Day Case
- ☐ Elective Inpatient
- ☐ Emergency
- ☐ Other
- ☐ Unknown

Main Procedure
- ☐ Cardiac surgery
- ☐ Cardiology
- ☐ Dental
- ☐ Maxillo-facial
- ☐ ENT
- ☐ Gastroenterology
- ☐ General surgery
- ☐ Gynaecology
- ☐ Neurosurgery
- ☐ Obstetrics
- ☐ Ophthalmology
- ☐ Orthopaedics/Trauma
- ☐ Pain
- ☐ Plastics
- ☐ Psychiatry
- ☐ Radiology
- ☐ Thoracic
- ☐ Urology
- ☐ Vascular
- ☐ Other minor op
- ☐ Other major op

Either
NCEPOD Priority
- ☐ Immediate ☐ Urgent
- ☐ Expedited ☐ Elective
- ☐ Unknown

Or
Caesarean Category
- ☐ 1 ☐ 2
- ☐ 3 ☐ 4
- ☐ Unknown

Age of Patient (yrs)
- ☐ <1 ☐ 1-5
- ☐ 6-15 ☐ 16-25
- ☐ 26-35 ☐ 36-45
- ☐ 46-55 ☐ 56-65
- ☐ 66-75 ☐ 76-85
- ☐ >86 ☐ Unknown

Sex of Patient
- ☐ Male ☐ Female
- ☐ Unknown

ASA Grade
- ☐ 1 ☐ 2 ☐ 3
- ☐ 4 ☐ 5 ☐ 6
- ☐ Unknown

Body Habitus (BMI)
- ☐ Underweight (<18.5)
- ☐ Normal weight (18.5-24.9)
- ☐ Overweight (25-29.9)
- ☐ Obese (30-34.9)
- ☐ Morbidly obese (>35)
- ☐ Unknown

Ethnicity
- ☐ British (White)
- ☐ Irish (White)
- ☐ Any other White Background
- ☐ White and Black Caribbean (Mixed)
- ☐ White and Black African (Mixed)
- ☐ White and Asian (Mixed)
- ☐ Any other Mixed Background
- ☐ Indian (Asian or Asian British)
- ☐ Pakistani (Asian or Asian British)
- ☐ Bangladeshi (Asian or Asian British)
- ☐ Any Other Asian Background
- ☐ Caribbean (Black or Black British)
- ☐ African (Black or Black British)
- ☐ Any other Black Background
- ☐ Chinese
- ☐ Any Other Ethnic Group
- ☐ Unknown

Premed Given on the Ward
- ☐ Yes ☐ No ☐ Unknown

Induction Location
- ☐ Theatre anaesthetic room
- ☐ Theatre
- ☐ Radiology or Cath-lab
- ☐ ICU
- ☐ Emergency Department
- ☐ Other
- ☐ Unknown

Intended Conscious Level
- ☐ General anaesthesia
- ☐ Deep sedation
- ☐ Moderate sedation
- ☐ Minimal sedation
- ☐ Awake

Was Your Choice of Drugs Influenced By Previous Allergy History?
- ☐ No ☐ Yes - antibiotic
- ☐ Yes - other ☐ Unknown

Latex Exposure During This Case
- ☐ Yes (gloves)
- ☐ Yes (other latex)
- ☐ Latex-free environment
- ☐ Unknown

Povidone Iodine Exposure During This Case
- ☐ None
- ☐ Skin prep (anaesthetist)
- ☐ Skin prep (surgeon)
- ☐ Surgical irrigation
- ☐ Other
- ☐ Unknown

Chlorhexidine Exposure During This Case
- ☐ None
- ☐ Coated/impregnated CVC
- ☐ Urethral
- ☐ Skin prep (anaesthetist)
- ☐ Skin prep (surgeon)
- ☐ Surgical irrigation
- ☐ Other
- ☐ Unknown

Induction Agents
- ☐ None
- ☐ Propofol
- ☐ Thiopental
- ☐ Etomidate
- ☐ Midazolam
- ☐ Ketamine
- ☐ Sevoflurane
- ☐ Other volatile agent
- ☐ Other

Maintenance Agents
- ☐ None
- ☐ Sevoflurane
- ☐ Other volatile agent
- ☐ Nitrous oxide
- ☐ Propofol
- ☐ Other

Analgesics (any route)
- ☐ None
- ☐ Paracetamol
- ☐ Morphine
- ☐ Diamorphine
- ☐ Fentanyl
- ☐ Alfentanil
- ☐ Remifentanil
- ☐ Codeine
- ☐ Dihydrocodeine
- ☐ Oxycodone
- ☐ Methadone
- ☐ Tramadol
- ☐ Clonidine
- ☐ Parecoxib
- ☐ Ketorolac
- ☐ Diclofenac
- ☐ Ibuprofen
- ☐ Naproxen
- ☐ Other

Neuromuscular Blockers
- ☐ None
- ☐ Suxamethonium
- ☐ Atracurium
- ☐ Cisatracurium
- ☐ Mivacurium
- ☐ Rocuronium
- ☐ Vecuronium
- ☐ Pancuronium

Reversal Drugs
- ☐ None
- ☐ Neostigmine
- ☐ Sugammadex
- ☐ Other

Local Anaesthetics (any route)
- ☐ None
- ☐ Lidocaine
- ☐ Bupivacaine
- ☐ Levobupivacaine
- ☐ Ropivacaine
- ☐ Prilocaine
- ☐ Other

Was anaphylaxis (requiring urgent treatment) suspected during this case?
- ☐ Yes ☐ No

Antibiotics
- ☐ None
- ☐ Co-amoxiclav
- ☐ Flucloxacillin
- ☐ Tazocin
- ☐ Other penicillin
- ☐ Metronidazole
- ☐ Teicoplanin
- ☐ Gentamicin
- ☐ Vancomycin
- ☐ Cefuroxime
- ☐ Other Cephalosporin
- ☐ Other

IV Colloids/Blood Products
- ☐ None
- ☐ Gelatin or gelatin-containing
- ☐ Starch or starch-containing
- ☐ Albumin (any concentration)
- ☐ Red cells
- ☐ Platelets
- ☐ Fresh Frozen Plasma
- ☐ Specific coagulation factors
- ☐ Other

Anti-Emetics (any route)
- ☐ None
- ☐ Ondansetron
- ☐ Dexamethasone
- ☐ Cyclizine
- ☐ Prochlorperazine
- ☐ Metoclopramide
- ☐ Droperidol
- ☐ Other

Coagulation Drugs
- ☐ None
- ☐ Heparin (any)
- ☐ Tranexamic acid
- ☐ Aprotinin
- ☐ Protamine
- ☐ Vitamin K
- ☐ Other

Miscellaneous Exposure
- ☐ Patent blue dye
- ☐ Methylene blue dye
- ☐ Bone cement
- ☐ X-Ray contrast

Monitoring
- ☐ Depth of Anaesthesia
- ☐ Peripheral nerve stimulator
- ☐ Quantitative neuromuscular monitoring
- ☐ Cardiac output

Most Senior Anaesthetist Present
- ☐ Consultant
- ☐ Other career grade doctor
- ☐ ST4-7
- ☐ ST3/CT3
- ☐ CT2
- ☐ CT1
- ☐ Other (e.g. research fellow)
- ☐ Unknown

Appendix 2:

Scaling factor workings

It is not possible to simply multiply the weekly caseload by 52 to estimate a yearly caseload because a number of weeks have bank holidays. Assuming that the activity on a bank holiday is similar to that on a weekend day, the 'effective' number of weeks can be calculated. For 2016, the number of weeks used as a scaling factor to estimate annual activity was 50.60, as per the workings below.

There were 366 days in 2016, and 52.29 weeks (366/7 = 52.29).

Using the number of weekdays, a scaling a factor x, and y as the number of 'effective' weeks in 2016:

$5/7 * x = 52.29$ and $253/366 * x = y$

Therefore $x = 7 * 52.29/5 = y * 366/253$

And $y = (7 * 52.29 * 253) / (5 * 366) = 50.60$

Calculations to account for cases not reported

Return rate

LCs were asked to estimate their site's return rate. The median return rate was 0.96.

Forms scanned rate

Out of 16,205 forms returned, 326 could not be scanned, giving a form-scanned rate of 0.98.

Site return rate

Forms were received from 342 out of 356 sites, giving a site return rate of 0.96.

Scaling factor to annualise number of cases

Scaling factor = $(3.5 * 50.60) / (0.96 * 0.98 * 0.96) = 196.09$

Estimated annual caseload = number of scanned forms* Scaling factor = 3,126,067

9 The Allergen Survey: perioperative drug exposure

Susana Marinho   Harriet Kemp   Nigel Harper   Tim Cook

Key findings

- 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 United Kingdom NHS hospitals for this purpose. Where relevant we compared results to 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 (GA).

- Propofol was the dominant induction agent (90.4%) and was used more often in caesarean section than in NAP5.

- Nitrous oxide use (17% of cases) has fallen by 30% since NAP5.

- Neuromuscular blocking agents were used in 47.2% of general anaesthetics. Suxamethonium use has fallen.

- Use of reversal agents is overall unchanged, but sugammadex use increased four-fold.

- Analgesics were used in 88% of cases – opioids in 82.1%, paracetamol in 56.1%, and non-steroidal anti-inflammatory drugs in 28.3%. Local anaesthetics were used in 74.2% of all 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. Among more than 3 million annual perioperative administrations gentamicin (19.7% of cases), 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 in 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 a denominator in the main NAP6 analysis, and the data provide significant insights into many aspects of perioperative practice.

The Royal College of Anaesthetists National Audit Projects (NAPs) study major complications of anaesthesia, and concurrently review current practice and use the findings to improve patient care. The 6th National Audit Project of the Royal College of Anaesthetists (NAP6), is a large-scale prospective service evaluation of perioperative anaphylaxis across the hospitals of the United Kingdom. It has gathered comprehensive quantitative and qualitative information on these clinical events, enabling the anaesthetic and allergy/immunology communities to collaborate in order to make recommendations for the improvement of the quality of patient care (Chapter 5, Methods; Chapter 6 Main findings; Chapter 14, Investigation).

During the NAP6 project, a one-year registry was established to collect reports on all suspected cases of perioperative anaphylaxis in 2015-16. This provided a numerator, but in order to interpret the results from the registry and to estimate the incidence of perioperative anaphylaxis overall and of its causes (drugs/other substances), contemporary information about anaesthetic activity, drug use, and exposure to other relevant substances (such as antiseptics and dyes), was required. This data would provide a denominator.

In 2013, the NAP5 project undertook a similar activity and drug survey (Sury 2014), providing information on aspects of anaesthetic activity and some drug uses, but these were insufficient for the needs of NAP6. Published Hospital Episode Statistics (NHS digital 2017a) show an increase in inpatient and day-case procedures since 2013, but do not give detailed information on anaesthetists' involvement. NHS Maternity Statistics show a slight decrease in deliveries in NHS hospitals since 2013, of which 60% involved anaesthetic intervention (HSCIC 2013). Such changes over time mean that figures collected for NAP5 may not necessarily be applicable for NAP6. In addition, the NAP5 survey did not collect sufficient detailed information on perioperative administration of drugs and other potential allergens. National data for hospital

drug usage is collected by IQVIA™ and recorded in the Hospital Pharmacy Audit Index database (Prescribing costs 2014). This records all medication that is issued by pharmacies for use on wards, in operating theatres and on patient discharge. It does not, however, record what is administered to the patient nor in what context a certain drug is delivered, and so does not provide information on actual perioperative drug use.

An Activity Survey and Allergen Survey were therefore designed to collect such data, and these are detailed in this report. During the surveys, anaesthetic activity data and drug/allergen exposure data were collected. The Activity Survey is reported separately (Chapter 8), and in this chapter we report results of the Allergen Survey.

Methods

The NAP6 project was defined as a service evaluation by the Health Regulatory Authority, and therefore did not require National Research Ethics Service approval. All NHS hospitals, trusts and boards in the UK believed to undertake surgery were invited to, and did, volunteer a Local Coordinator who supervised all aspects of the study at that location.

Local Coordinators were approached at 356 NHS hospitals, and they organised data collection from every perioperative case during a period of 48 hours in which care was delivered by an anaesthetist. This included all adult and paediatric cases requiring general, regional and local anaesthesia, as well as sedation if involving an anaesthetist. Obstetric cases included epidural pain relief in labour. Any cases where sedation or local anaesthesia was delivered by a non-anaesthetist were not included. Routine sedation in critical care was excluded.

The majority of data collection took place between 13 and 31 October 2016, during which time there were no public holidays. Seven sites collected data between January and June 2017 for logistical reasons. Data were recorded using a paper pro-forma (Appendix 1), and each form was transferred, using optical character recognition, to electronic storage. Each hospital was randomised to record activity on two consecutive days of the week, with specialist hospitals (cardiac, neurology or paediatric centres) block-randomised separately to prevent skewed allocation. Patient characteristics, method of anaesthesia, anaesthetic staffing, induction location, type of monitoring and drugs/substances used, and the presence of any allergy history were reported for each case. Local Coordinators were also asked to record a capture rate at their site to estimate the proportion of cases for which a completed case report form was submitted. Data regarding staffing, workload and anaesthetic activity are reported separately (Chapter 8).

Data were analysed using IBM SPSS Statistics for Windows, Version 23. An annual caseload was estimated by multiplying the number of cases by a scaling factor. This factor was calculated by converting the number of cases from two days to one week (scaling factor of 3.5), and from one week to one year (scaling factor of 50.6, the effective number of working weeks in 2016) (Appendix 2). This was then divided by the hospital response rate, the mean reported capture rate at individual sites

and the proportion of interpretable forms, to account for cases that were not reported. Responses marked as 'unknown' and those with incomplete fields were combined and reported as 'unknown'.

Here we report data relevant to allergen exposure in the perioperative period and relating to anaesthetists' practices in using certain drugs. Where relevant this data is compared to that from the 2013 NAP5 study (Sury 2014).

Results

Out of 356 sites approached, 342 took part in the survey, submitting a total of 15,942 forms. Applying the calculated scaling factor, the estimated annual caseload was 3,126,067. The distribution of numbers of forms returned from each hospital are shown in Figure 1. Where relevant, illogical forms (eg. patients eported to be awake when neuromuscular blocking agents (NMBAs) were used), were excluded but these represented less than 1.0% of any analysis.

The scaling factor was 196.09. Patient Characteristics are described in Chapter 8, Activity Survey.

Figure 1. Distribution of number of forms returned by Local Coordinators
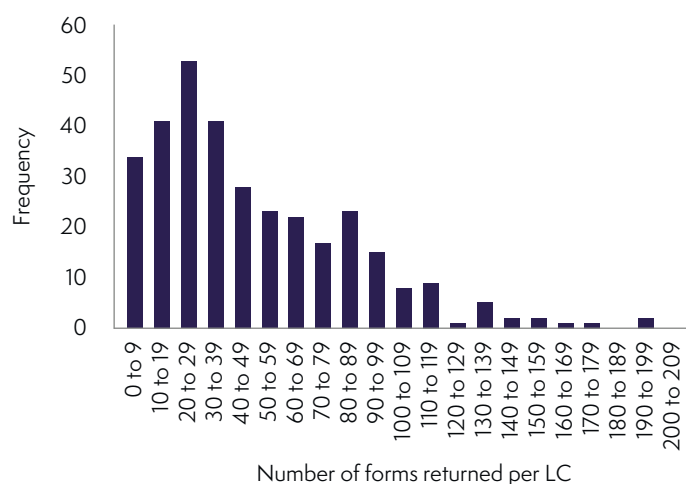
Intended consciousness level was reported as general anaesthesia (GA) 76.6% (annual estimate 2,394,847), sedation 8.2% (258,250 cases) and awake 14.2% (442,379 cases) (Table 1).

Table 1. Intended consciousness level

Intended consciousness level	Number	%
General anaesthesia	12,213	76.6%
Deep sedation	290	1.8%
Moderate sedation	542	3.4%
Minimal sedation	485	3.0%
Awake	2,256	14.2%
Unknown	156	1.0%
Total	15,942	100.0%

Anaesthetic drug use

Previous allergy history and choice of drugs

Choice of drugs was reported as having been influenced by previous allergy history in 1,351 cases (8.6% of 15,723 responses). In 64% of these cases this was because of allergy to an antibiotic, in 35% allergy to another drug, and in 3% to both.

Number of drugs used per procedure

The median number of drugs given in each procedure was 8 – minimum 1 and maximum 20 (Figure 2).

Figure 2. Number of drugs used per procedure
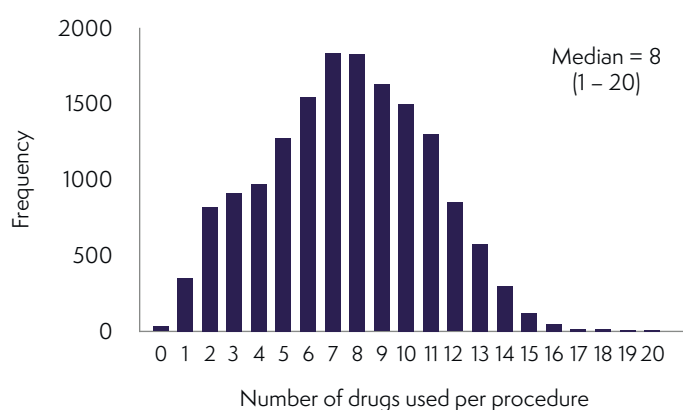
Induction agents

Induction agents were used in 13,019 cases including all intended consciousness levels; the estimated annual exposures was 2,552,896 (Table 2).

Table 2a. Use of induction agents and estimated annual exposures for all levels of consciousness

All cases of general anaesthesia and sedation				
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one induction agent	% of total drug group usage (sum of all; total > total no. of cases)
At least one induction agent used	13,019	2,552,896	100.0%	–
Propofol	11,682	2,290,723	89.7%	74.7%
Thiopental	215	42,159	1.7%	1.4%
Etomidate	36	7,059	0.3%	0.2%
Midazolam	1,515	297,076	11.6%	9.7%
Ketamine	198	38,826	1.5%	1.3%
Sevoflurane	1,662	325,902	12.8%	10.6%
Other volatile agent	166	32,551	1.3%	1.1%
Other induction agents	156	30,590	1.2%	1.0%

Table 2b. Use of induction agents for general anesthesia

General anaesthesia cases only			
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one induction agent
At least one induction agent used	12,143	2,381,121	100.0%
Propofol	11,145	2,185,423	91.8%
Thiopental	211	41,375	1.7%
Etomidate	36	7,059	0.3%
Midazolam	1,057	207,267	8.7%
Ketamine	154	30,198	1.3%
Sevoflurane	1,656	324,725	13.6%
Other volatile agent	166	32,551	1.4%
Other induction agents	147	28,825	1.2%

For cases performed with general anaesthesia (Table 2b), 15% of returns indicated two induction agents, with a volatile reported as an induction agent in 14.8% of cases and a combined volatile/ IV induction in 9%. Of those with volatile co-induction, 51% were adults. As some respondents had probably included both an intravenous (IV) and a volatile agent as an 'induction agent', to determine the primary induction agent we only analysed a subset of these cases where one agent was used.

Considering only patients who received general anaesthesia induced with a single agent or a single agent and midazolam (n=10,969), the distribution of drugs used was propofol 90.4%, thiopental 1.6%, ketamine 0.7%, etomidate (0.3%), sevoflurane (6.2%), and other volatile agents (0.1%) (Table 3). Midazolam was used as a sole agent in 0.1% of cases (predominantly urgent/emergency cases in ASA Grades 4–5 patients) and as a co-induction agent in 7.5%. These proportions did not vary significantly whether midazolam was included or not (Table 3). These results suggest that since 2013 there has been a small reduction in use of thiopental (1.6% from 2.9%) and an equivalent increase in the use of propofol (90.4% from 88%) (Sury 2014). Cases involving a volatile agent alone for induction were predominantly children (86%).

Table 3. Use of induction agents when given as single agents (or with midazolam). Case return forms and proportions

| Drug | GA cases with a single induction agent (or with midazolam) | | | |
	Numbers (only one induction agent)	%	Numbers (only one induction agent and midazolam)	%
Propofol	9,180	90.39%	9,973	90.92%
Thiopental	173	1.70%	179	1.63%
Etomidate	26	0.26%	31	0.28%
Ketamine	79	0.78%	86	0.78%
Midazolam	11	0.11%	11	0.10%
Sevoflurane	677	6.67%	678	6.18%
Other volatile	10	0.10%	11	0.10%
Total	10,156	100.00%	10,969	100.00%

Propofol was the most widely used induction agent in all groups: 57.7% in children (under 16 years), 96.2% in adults and 89.7% in patients aged over 65 years. Distribution of induction agents used by patient's age is shown in Figure 3. Sixty-four patients undergoing caesarean section, received general anaesthesia, and in these cases thiopental was used in 62.7% (97% in NAP5), propofol in 29.7%, and midazolam and ketamine in 1.6% each. Etomidate and sevoflurane were not used (Figure 3).

Figure 3. Use of induction agents by age group and in caesarean sections
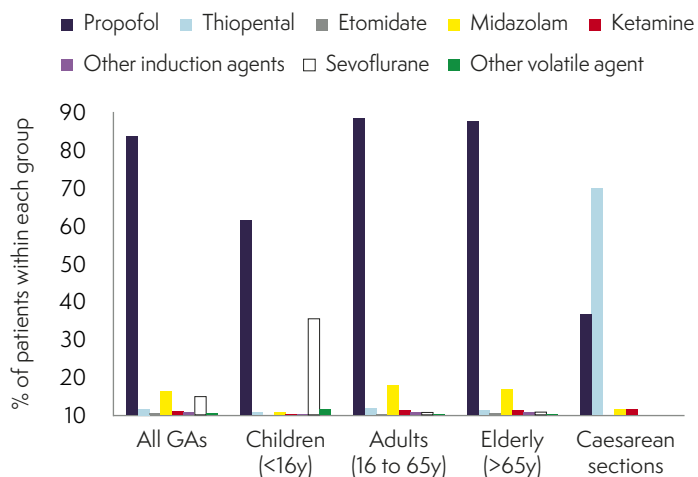
Maintenance agents

Among GAs where a maintenance agent was used, an inhalational agent was used in 94.6% – sevoflurane in 69.9% (58.5% in NAP5), nitrous oxide in 17.1% (25% in NAP5) and propofol in 8.7%. In 2.2% of cases, both a volatile agent and propofol were used as maintenance agents (Table 4).

Table 4. Use of maintenance agents during general anaesthesia and estimated annual caseload

Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one maintenance agent
At least one maintenance agent used	**11,921**	**2,337,589**	**100.0%**
Sevoflurane	8,499	1,666,569	71.3%
Other volatile agent	2,773	543,758	23.3%
Nitrous oxide	2,041	400,220	17.1%
Propofol	1,032	202,365	8.7%
Other	249	48,826	2.1%

Thus, for a large cohort of children an extremely low-risk technique was used as far as antigen exposure is concerned.

The use of maintenance agents by age and in caesarean sections is illustrated in Figure 4. Sevoflurane was the preferred maintenance agent across all age groups and specialties. Induction and maintenance exclusively with sevoflurane was reported in 2.8% of GAs: 14.5% of paediatric and 0.4% of adult GAs. Sevoflurane was used during general anaesthesia for 90.6% of caesarean sections. Nitrous oxide was reported as being used in 17.1% of cases, in 30.1% of children and 60.9% of caesarean sections: a fall from 2013 (25% overall, 45% in children and 71.4% in caesarean sections). Nitrous oxide was used most frequently during general anaesthesia in orthopaedics/trauma, general surgery and ENT cases, perhaps associated with the increased numbers of paediatric cases in these specialties (Sury 2014).

Figure 4. Maintenance agent use by age group and in caesarean section
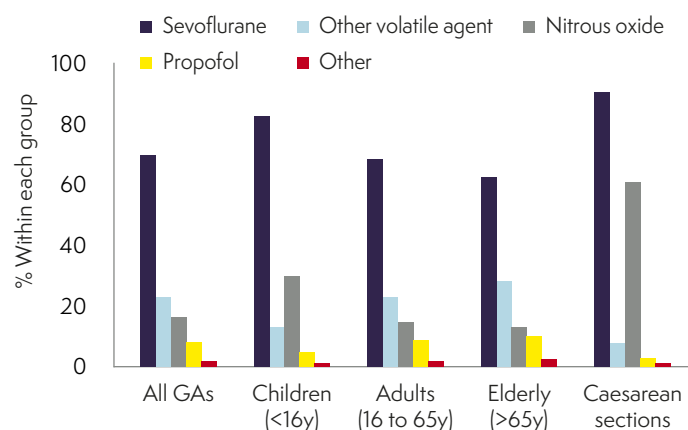
Neuromuscular blocking agents (NMBAs)

NMBAs were reported to have been used in 5,760 (47.2%) cases receiving GA; the estimated annual caseload was 1,129,478 (Table 5).

Table 5. Use of NMBAs and estimated annual exposures

Individual drug/ substance	GA cases				
	Number exposed in Activity Survey	Estimated annual exposure	% of all GAs	% of NMBA use	% of total drug group usage (sum of all; total > total no of cases)
At least 1 NMBA used	**5,760**	**1,129,478**	**47.2%**	**100.0%**	**% of all NMBA use**
Suxamethonium	643	126,086	5.3%	11.2%	10.3%
Atracurium	2,828	554,543	23.2%	49.1%	45.4%
Cisatracurium	95	18,629	0.8%	1.6%	1.5%
Mivacurium	157	30,786	1.3%	2.7%	2.5%
Rocuronium	2,341	459,047	19.2%	40.6%	37.6%
Vecuronium	124	24,315	1.0%	2.2%	2.0%
Pancuronium	36	7,059	0.3%	0.6%	0.6%

Of those receiving NMBAs (12,213), 88.8% received non-depolarising NMBAs only, 4% suxamethonium only and 7.2% both suxamethonium and a non-depolarising NMBA. The distribution of NMBAs was not captured in the NAP5 survey.

Figure 5. Use of all NMBAs during general anaesthesia (whether individually or multiples), as a proportion of all general anaesthetic cases (n=12,213)
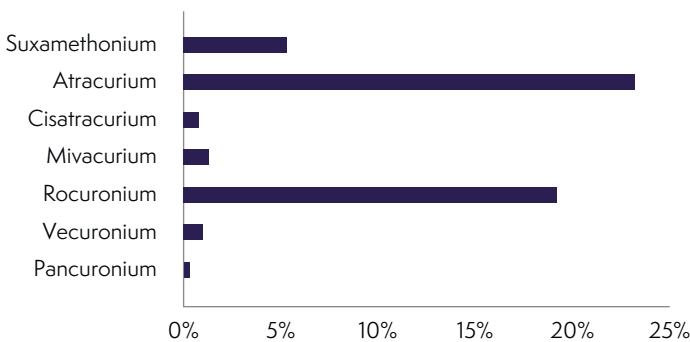
Within age groups, NMBAs were used in 23% of children, 49.6% of adults and 58.2% of elderly patients, and in almost all general anaesthetic caesarean sections (98.4%); distribution is shown in Figures 6 and 7. These figures are stable since NAP5.

Figure 6. Use of NMBAs by age group and in caesarean sections
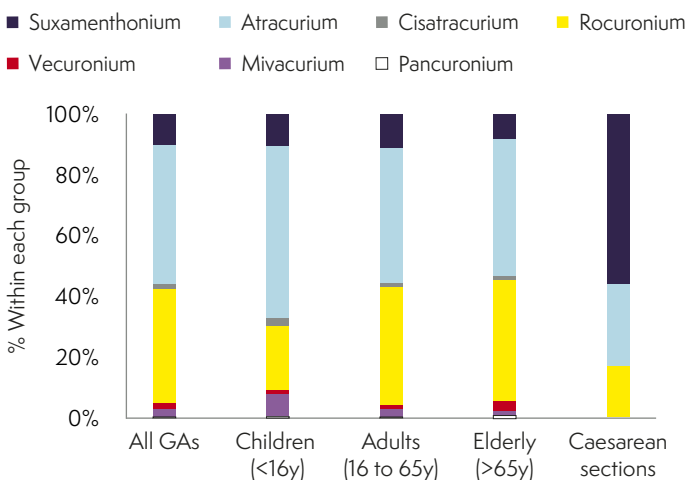
Figure 7. Use of NMBAs (by class) across different age groups and in caesarean sections
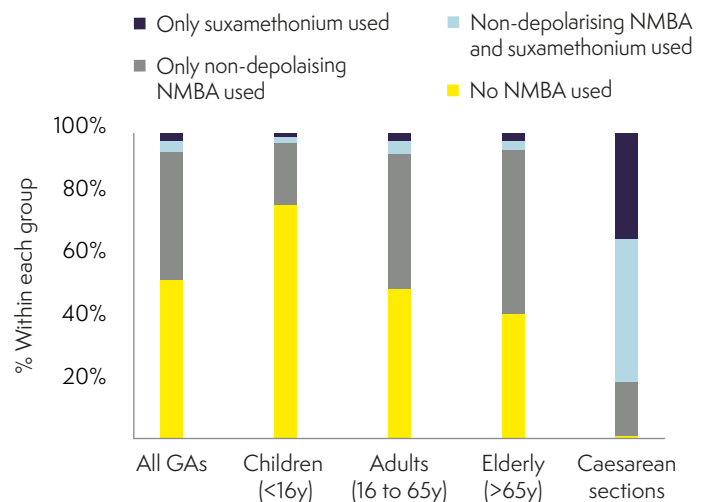
In most specialties atracurium and rocuronium were used predominantly, with the main exceptions being cardiac surgery, obstetrics and psychiatry. In cardiac surgery, pancuronium and vecuronium were used in 25.7% and 17.9% of cases respectively. All psychiatry cases received suxamethonium and 1.3% also received atracurium. The distribution of NMBAs in obstetrics was suxamethonium 72.5%, atracurium 35.2% and rocuronium 23.1%; 16.9% received only a non-depolarising NMBA.

Distribution of NMBA use by specialty and by clinical setting is shown in Figures 7-10.

Figure 8. Use of each NMBA by main surgical specialty
(*Note:* more than one NMBA may have been used in some procedures.)
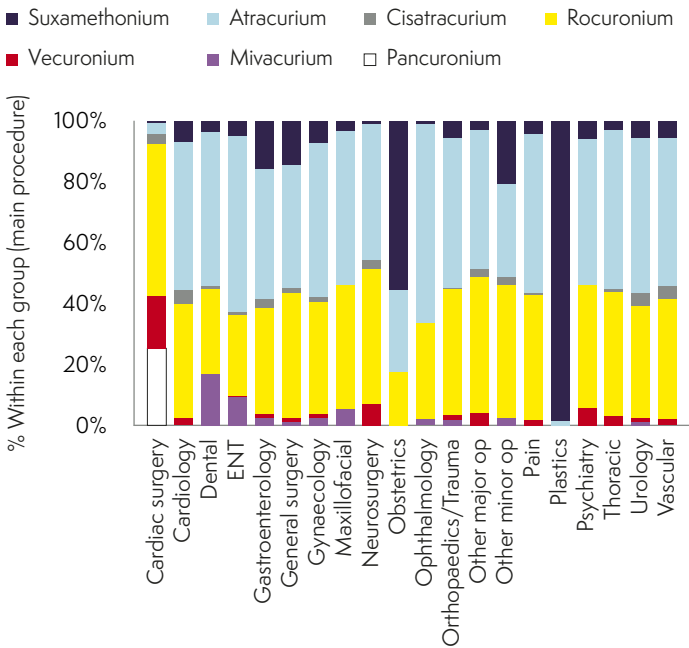
Figure 9. Use of NMBAs by admission type
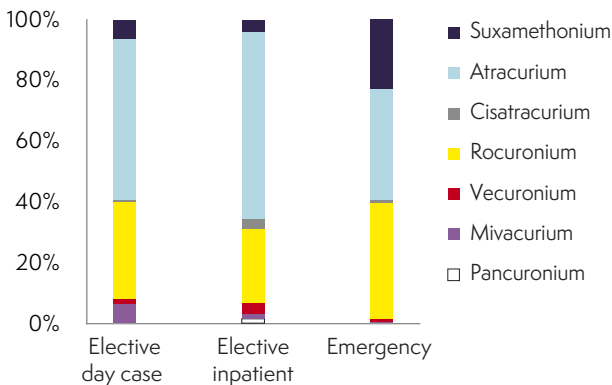
One notable finding is that in ICUs, suxamethonium use was absent and rocuronium was used more often (more than 50%) than in any other location. Conversely, in emergency departments suxamethonium was widely used and rocuronium notably less often (Figure 9).

Figure 10. Use of NMBAs by induction location
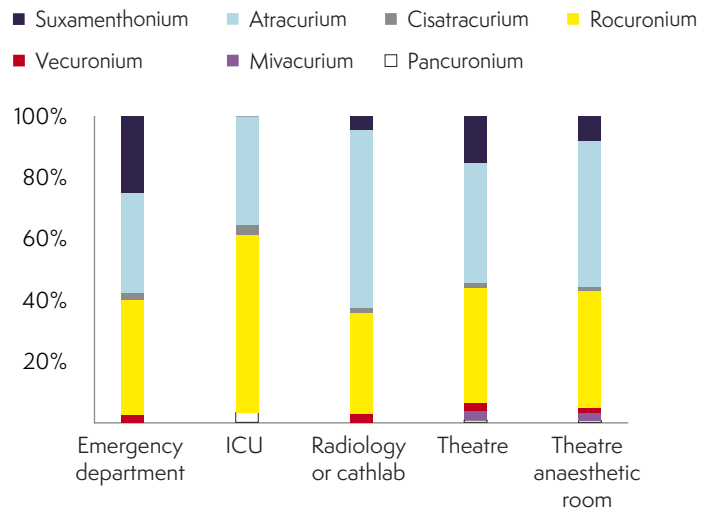
When suxamethonium was used, propofol was the induction agent in 73.6% of cases and thiopental in 22.4%, with other agents used rarely. Use of suxamethonium and rocuronium by age and NCEPOD priority is shown in Figure 11.

Figure 11. Use of suxamethonium and rocuronium by age groups (% within each group) and by NCEPOD priority (% within those GA cases receiving an NMBA, n=5,760)
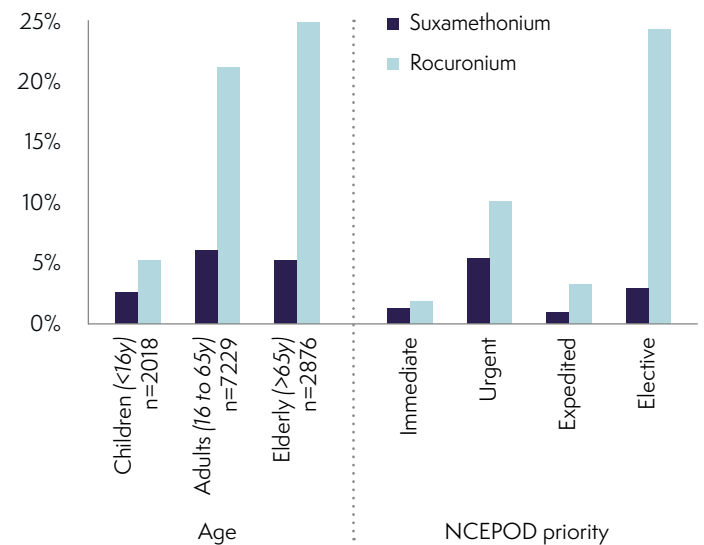
Reversal drugs

The pattern of use of reversal agents is described in Table 6. Sugammadex is now used in almost four times as many cases as in 2013 (2.2% of reversals) (Sury 2014).

Table 6. Use of reversal drugs and estimated annual caseload

	GA cases				
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all GAs	% of NMBA use	% of total drug group usage (sum of all; total > total no of cases)
At least one reversal drug used	**3,598**	**705,532**	**29.5%**	**62.5%**	**% of all reversal drug use**
Neostigmine	3,307	648,470	27.1%	57.4%	90.3%
Sugammadex	327	64,121	2.7%	5.7%	8.9%
Other	27	5,294	0.2%	0.5%	0.7%

Analgesics

Analgesics were used in 88.2% of all cases (any intended consciousness level); estimated annual caseload was 2,755,849. Opioids were used in 82.5% of all cases. Paracetamol was administered in 56.1% and a non-steroidal anti-inflammatory drug in 28.3% of cases.

Fentanyl was the most frequently used opioid, administered in 62% of cases, followed by morphine in 26.5% and remifentanil in 8.7% of cases. Diclofenac was the most commonly used NSAID, followed by parecoxib and ibuprofen. Clonidine was administered in 0.9% of cases. Use of each analgesic drug is illustrated in Figure 12 and estimated annual exposures in Table 7.

Figure 12. Use of analgesic agents in all cases

(use of each analgesic drug, whether in isolation or combined, n=15,776)

Table 7. Use of analgesic drugs and estimated annual exposures

	All cases				
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one analgesic used	**14,054**	**2,755,849**	**88.2%**	**–**	**–**
At least one opioid used	**13,145**	**2,577,603**	**82.5%**	**% of cases receiving opioid**	**% of all opioid use**
Alfentanil	1,095	214,719	6.9%	8.3%	5.9%
Fentanyl	9,822	1,925,996	61.6%	74.7%	52.9%
Remifentanil	1,385	271,585	8.7%	10.5%	7.5%
Diamorphine	1,412	276,879	8.9%	10.7%	7.6%
Morphine	4,162	816,127	26.1%	31.7%	22.4%
Codeine	146	28,629	0.9%	1.1%	0.8%
Dihydrocodeine	40	7,844	0.3%	0.3%	0.2%
Oxycodone	282	55,297	1.8%	2.1%	1.5%
Methadone	7	1,373	0.0%	0.1%	0.0%
Tramadol	215	42,159	1.3%	1.6%	1.2%
Clonidine	149	29,217	0.9%	–	–
Paracetamol	8,939	1,752,849	56.1%	–	–

Table 7. Use of analgesic drugs and estimated annual exposures *(continued)*

Individual drug/substance	All cases				
	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least 1 NSAID used (excludes paracetamol)	4,509	884,170	28.3%	% of cases receiving NSAID	% of all NSAID use
Parecoxib	905	177,461	5.7%	20.1%	19.9%
Ketorolac	468	91,770	2.9%	10.4%	10.3%
Diclofenac	2,317	454,341	14.5%	51.4%	50.9%
Ibuprofen	850	166,677	5.3%	18.9%	18.7%
Naproxen	16	3,137	0.1%	0.4%	0.4%
Other	240	47,062	1.5%	–	–

Opioids were used more frequently during general anaesthesia than in other cases. At least one opioid was used in 99.8% of GAs – fentanyl in 73.7%, morphine in 33.0%, remifentanil in 10.7%. Paracetamol was used in 67.5% of GA cases. The distribution of use of different analgesic drugs by intended consciousness level is illustrated in Figure 13.

Figure 13. Use of analgesic drugs by intended consciousness level

Antibiotics

Antibiotics were used in 57.2% of all cases, with an estimated 1,787,360 annual exposures. Gentamicin (19.7%), co-amoxiclav (17.0%) and cefuroxime (13.6%) were the three most commonly used antibiotics (Fig. 14), with estimated annual exposures of around a half a million for the former two and approximately 400,000 for the latter. Table 8 details antibiotics used and estimated annual exposures.

Figure 14. Use of antibiotics in all procedures (of each antibiotic, whether in isolation or combined, n=15,790.)

Table 8. Use of antibiotics and estimated annual caseload

Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one antibiotic used	9,115	1,787,360	57.2%	% of cases receiving antibiotic	% of all antibiotic use
Co-amoxiclav	2,716	532,580	17.0%	29.8%	21.6%
Flucloxacillin	1,081	211,973	6.8%	11.9%	8.6%
Piperacillin-tazobactam	144	28,237	0.9%	1.6%	1.1%
Other penicillin	248	48,630	1.6%	2.7%	2.0%
Metronidazole	1,388	272,173	8.7%	15.2%	11.0%
Teicoplanin	1,120	219,621	7.0%	12.3%	8.9%
Gentamicin	3,146	616,899	19.7%	34.5%	25.0%
Vancomycin	90	17,648	0.6%	1.0%	0.7%
Cefuroxime	2,163	424,143	13.6%	23.7%	17.2%
Other cephalosporin	135	26,472	0.8%	1.5%	1.1%
Other	364	71,377	2.3%	4.0%	2.9%

In a quarter of cases where teicoplanin or vancomycin were used (287/1120 and 23/90 cases, respectively), their choice was reported to have been influenced by past allergy history to an antibiotic (Figure 15).

Figure 15. Choice of antibiotics and past allergy history

Figure 16. Antibiotic use by specialty: (top) percentage of all surgical cases (bottom) percentage of cases in specialty receiving antibiotics

The greatest proportion of all antibiotics use by surgical specialty was in orthopaedics/trauma, accounting for 23.1%, followed by general surgery (14.4%), obstetrics (9.2%), urology (8.9%) and gynaecology (6.5%). The proportion of cases administered antibiotics by specialty was, in descending order, cardiac surgery 97.2%, neurosurgery 89.4%, urology 81.7%, thoracic surgery 80.9%, orthopaedics/trauma 69.9%, and general surgery 60.3% (Figure 16).

Co-amoxiclav was commonly used across most specialties. In ophthalmology, cefuroxime was the most common antibiotic used. In cardiac surgery and cardiology, the dominant antibiotic was gentamicin, with flucloxacillin, cefuroxime and teicoplanin also being frequently used (Fig. 19). Use of antibiotics in orthopaedics/trauma was almost evenly spread between gentamicin (32.7% of all orthopaedics/trauma procedures), teicoplanin (21.3%), flucloxacillin (18.2%) and cefuroxime (17.9%) (Figure 17).

Figure 17. Distribution of individual antibiotics use, by specialty

- Co-amoxiclav
- Flucloxacillin
- Piperacillin-tazobactam
- Other penicillin
- Metronidazole
- Teicoplanin
- Gentamicin
- Vancomycin
- Cefuroxime
- Other cephalosporin
- Other
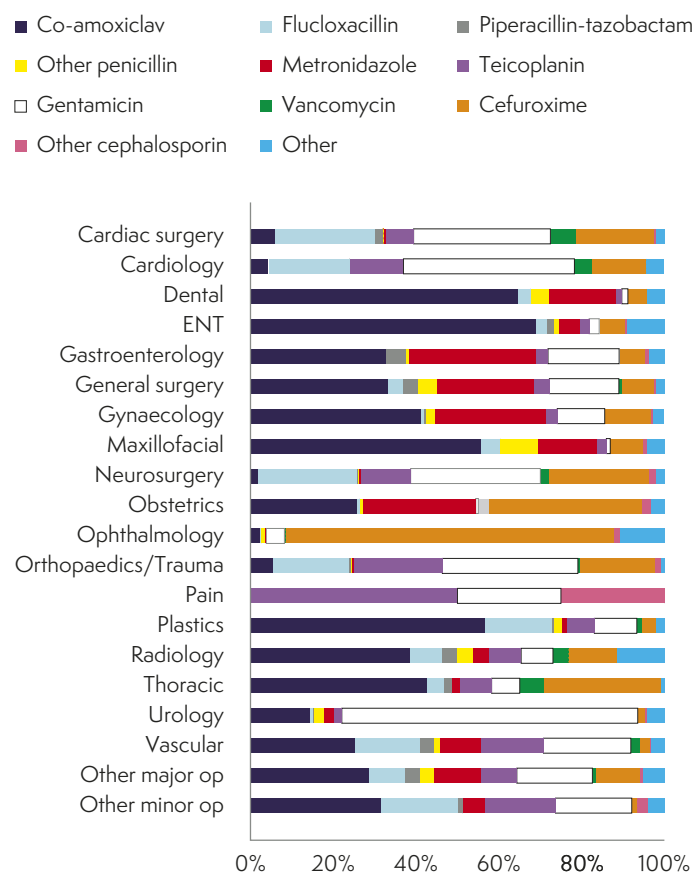
Co-amoxiclav

Co-amoxiclav was the most commonly used antibiotic: 21.6% of all antibiotic uses. It was regularly used in general surgery (27.5% of all cases receiving this drug), gynaecology (15.4%) and obstetrics (13.6%). When co-amoxiclav was used the choice of antibiotic was rarely affected by drug allergy (5.8%).

Teicoplanin

Teicoplanin accounted for 8.9% of all antibiotic administrations. It was used mainly in orthopaedics/trauma (17.5% of all cases receiving this drug), general surgery (16.9%) and gynaecology (10.8%). In 25.6% of cases receiving this antibiotic its choice was determined by previous history of antibiotic allergy.

Local anaesthetics

The pattern of use of local anaesthetics (LAs) is described in Table 9.

Use of LAs by consciousness level is detailed in Figure 18.

Figure 18. Use of local anaesthetics by intended consciousness level

- Lidocaine
- Levobupivacaine
- Bupivacaine
- Ropivacaine
- Prilocaine
- Other

% Within each group
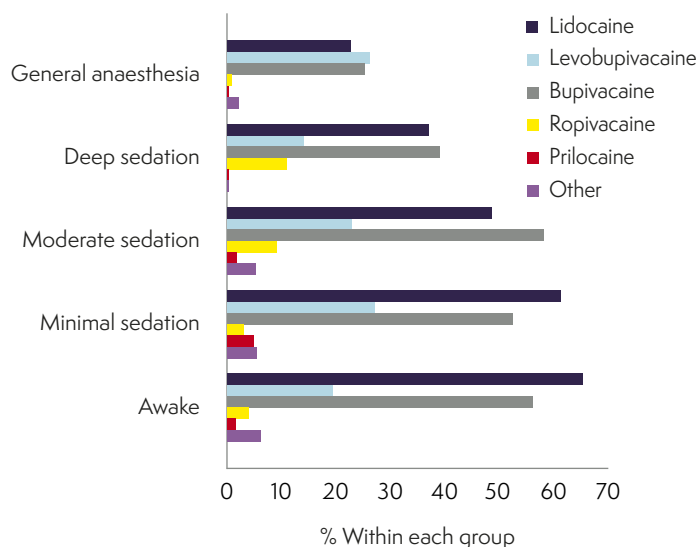
Table 9. Use of local anaesthetics and estimated annual exposures

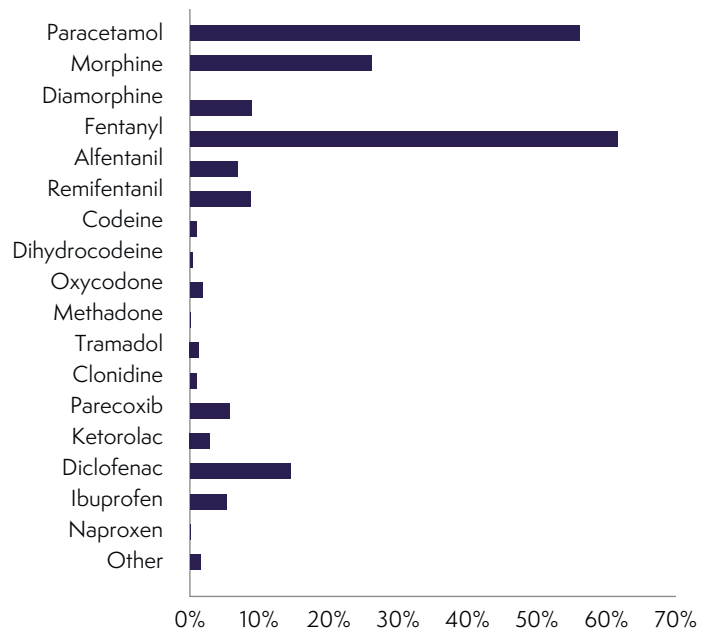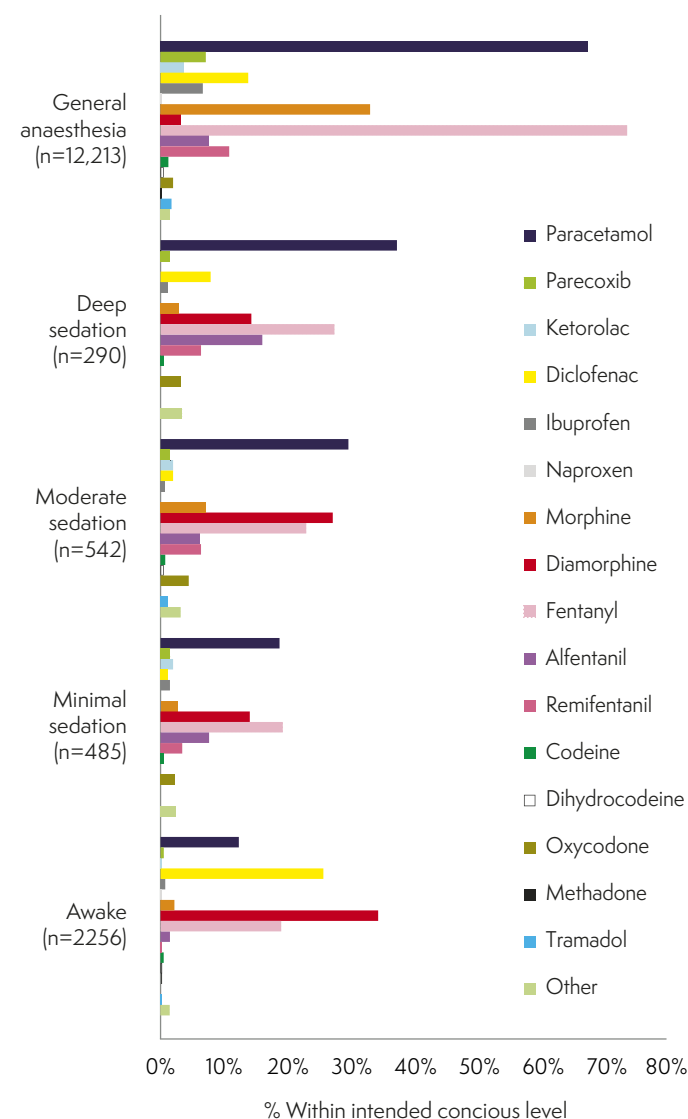|	All cases				
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one local anaesthetic used	11,831	2,319,941	74.2%	% of cases receiving LA	% of all LA use
Lidocaine	4,951	970,842	31.1%	41.8%	33.3%
Bupivacaine	5,092	998,490	31.9%	43.0%	34.2%
Levobupivacaine	3,954	775,340	24.8%	33.4%	26.6%
Ropivacaine	302	59,219	1.9%	2.6%	2.0%
Prilocaine	103	20,197	0.6%	0.9%	0.7%
Other	469	91,966	2.9%	4.0%	3.2%

Table 10. Use of anti-emetics and estimated annual exposures

Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
All cases					
At least one anti-emetic used	**11,655**	**2,285,429**	**73.1%**	% of cases receiving anti-emetic	% of all anti-emetic use
Ondansetron	10,456	2,050,317	65.6%	89.7%	52.6%
Dexamethasone	7,739	1,517,541	48.5%	66.4%	38.9%
Cyclizine	901	176,677	5.7%	7.7%	4.5%
Prochlorperazine	99	19,413	0.6%	0.8%	0.5%
Droperidol	267	52,356	1.7%	2.3%	1.3%
Metoclopramide	285	55,886	1.8%	2.4%	1.4%
Other	136	26,668	0.9%	1.2%	0.7%

Anti-emetics

Anti-emetics were used in 73.1% of all cases: ondansetron in 65.6% of all cases, dexamethasone in 48.5%, cyclizine in 5.7%, and all other anti-emetics less than 2% each (Table 10). During general anaesthesia anti-emetic use was higher: ondansetron 78.3% of cases and dexamethasone 60.4%. Ondansetron and dexamethasone were used in combination in 53.1% of all GA cases.

Intravenous colloids and blood products

Intravenous colloids and/or blood products were used in 4.2% of all cases. Gelatin-containing products (1.7%) and red blood cells (1.5%) were the most frequently used products. Starch or starch-containing products (0.2%), albumin (0.1%), platelets (0.4%), fresh frozen plasma (0.5%) and specific coagulation factors (0.2%), were used uncommonly (Table 11) The surgical specialties that used the greatest proportion of IV colloids or blood products were orthopaedics/ trauma, general surgery, cardiac surgery and obstetrics (1.0%, 0.8% and 0.5% each respectively of all cases). The specialties using IV colloids or blood products most frequently were cardiac surgery, other major operations and vascular surgery (56.6%, 16.7% and 13.6% respectively of cases within each specialty). Figure 19 details use of these substances by main procedure. There was no evidence that starch use was concentrated in a particular site or specialty.
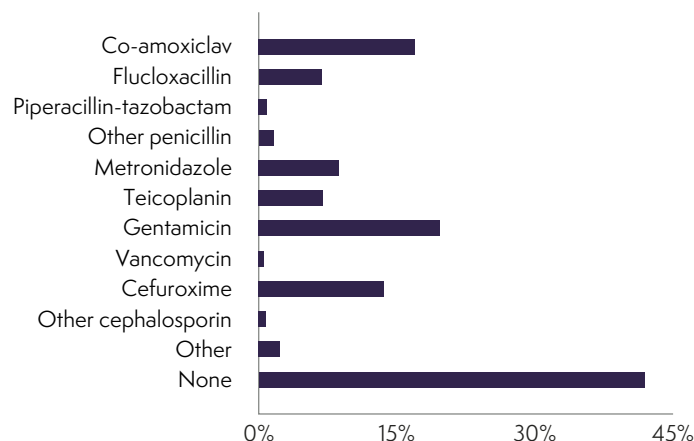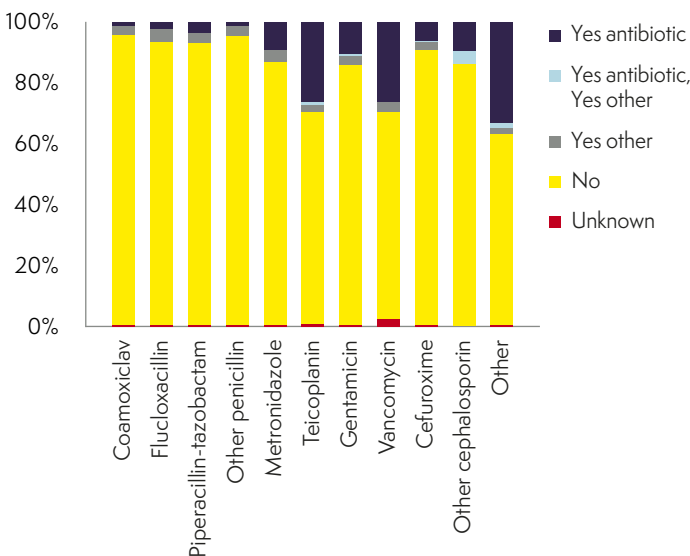
Table 11. Use of IV colloids and blood products and estimated annual caseload

Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
All cases			
At least one IV colloid/ blood product used	**668**	**130,988**	**4.2%**
Gelatin or gelatin-containing	266	52,160	1.7%
Starch or starch-containing	26	5,098	0.2%
Albumin (any concentration)	18	3,530	0.1%
Red cells	242	47,454	1.5%
Platelets	68	13,334	0.4%
Fresh frozen plasma	74	14,511	0.5%
Specific coagulation factors	28	5,491	0.2%
Other	156	30,590	1.0%

Figure 19. Use of IV colloids and blood products by main procedure
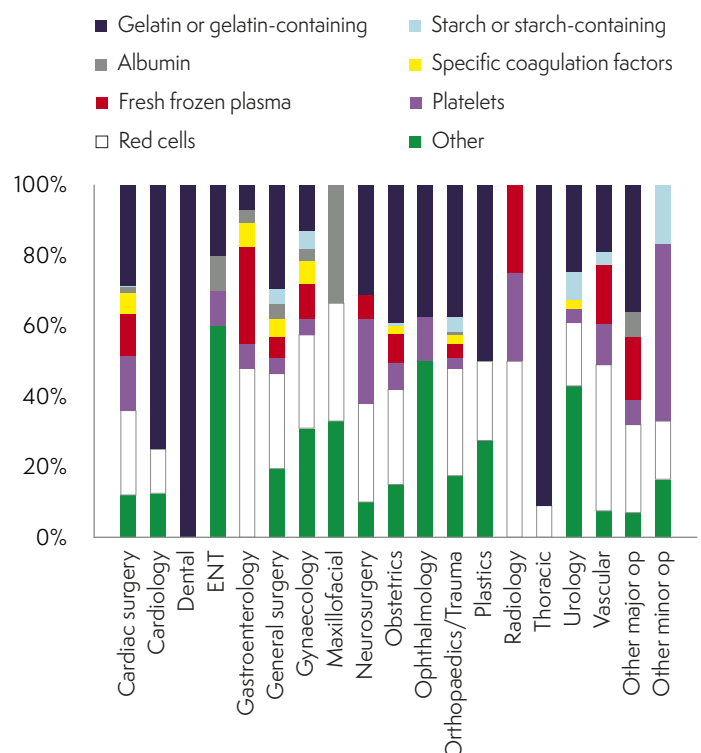
Drugs affecting coagulation

Drugs affecting coagulation were used in 8.3% of all cases. Tranexamic acid was the drug most commonly used (5.9% of all cases), followed by heparin (2.7%). Protamine, aprotinin, vitamin K and other coagulation drugs (not specified) were each used in less than 1% of all cases (Table 12). Use of these drugs was mostly concentrated in orthopaedics, cardiac and vascular surgery (52.2%, 25.4% and 10.9% respectively of all cases where a coagulation drug was used). Tranexamic acid was administered in 71% of cardiac surgery and 19% of orthopaedic operations.

Table 12. Use of coagulation drugs and estimated annual caseload

Individual drug/ substance	All cases		
	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
At least one coagulation drug used	1,319	258,643	8.3%
Heparin – any	435	85,299	2.7%
Tranexamic acid	940	184,325	5.9%
Aprotinin	12	2,353	0.1%
Protamine	139	27,257	0.9%
Vitamin K	27	5,294	0.2%
Other	45	8,824	0.3%
Specific coagulation factors	28	5,491	0.2%
Other	156	30,590	1.0%

Chlorhexidine

Chlorhexidine exposure was reported in 73.5% of all cases (Table 13), mostly via skin preparation by the anaesthetist (51.6% of all cases, accounting for 70.2% of all chlorhexidine-exposed cases) and/or the surgeon (44.7% of all cases, 60.7% of chlorhexidine-exposed cases). Very few cases were reported to be via urethral exposure (3.3% of all cases), coated/impregnated central venous catheter (CVC), surgical irrigation, or other exposure (0.6% of all cases each for the latter three routes). Exposure to this antiseptic was reported to be 'Unknown' in 0.9% of all cases and 23.6% of cases were reported to have no exposure. Chlorhexidine exposure was reported in more than two-thirds of cases for most surgical specialties (Figure 20).

Povidone-iodine

Povidone-iodine exposure was reported in 40.0% of all cases (Table 14), mostly via skin preparation by the surgeon (36.7% of all cases, accounting for 91.7% of all povidone-iodine-exposed cases) or by the anaesthetist (6.6% of all cases, 16.4% of povidone-iodine-exposed cases), with minor contributions by surgical irrigation (0.9% of all cases) or other routes (1.0% of all cases). A total of 54.6% of cases were reported to have had no exposure. Povidone-iodine was used in less than half of cases for all surgical specialties except for ophthalmology (where its use was almost ubiquitous at 95.6%), and neurosurgery, vascular surgery, general surgery and plastics, where it was used in more than half of the cases (Figure 20).

Table 13. Use of chlorhexidine and estimated annual exposures

Chlorhexidine exposure	All cases				
	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
Exposure – at least one route	11,722	2,298,567	73.5%	% of cases exposed to chlorhexidine	% of all chlorhexidine exposure
Coated/impregnated CVC	93	18,236	0.6%	0.8%	0.6%
Urethral	532	104,320	3.3%	4.5%	3.3%
Skin Prep – anaesthetist	8,232	1,614,213	51.6%	70.2%	50.9%
Skin Prep – surgeon	7,120	1,396,161	44.7%	60.7%	44.0%
Surgical irrigation	95	18,629	0.6%	0.8%	0.6%
Other	101	19,805	0.6%	0.9%	0.6%

Table 14. Use of povidone-iodine and estimated annual exposures

Povidone-iodine exposure	All cases				
	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
Exposure – at least one route	6,382	1,251,446	40.0%	% of cases exposed to povidone-iodine	% of all povidone-iodine exposure
Skin prep anaesthetist	1,047	205,306	6.6%	16.4%	14.6%
Skin prep surgeon	5,852	1,147,519	36.7%	91.7%	81.3%
Surgical irrigation	137	26,864	0.9%	2.1%	1.9%
Other	159	31,178	1.0%	2.5%	2.2%
Surgical irrigation	95	18,629	0.6%	0.8%	0.6%
Other	101	19,805	0.6%	0.9%	0.6%

Figure 20. Exposure to chlorhexidine and povidone-iodine, by main procedure
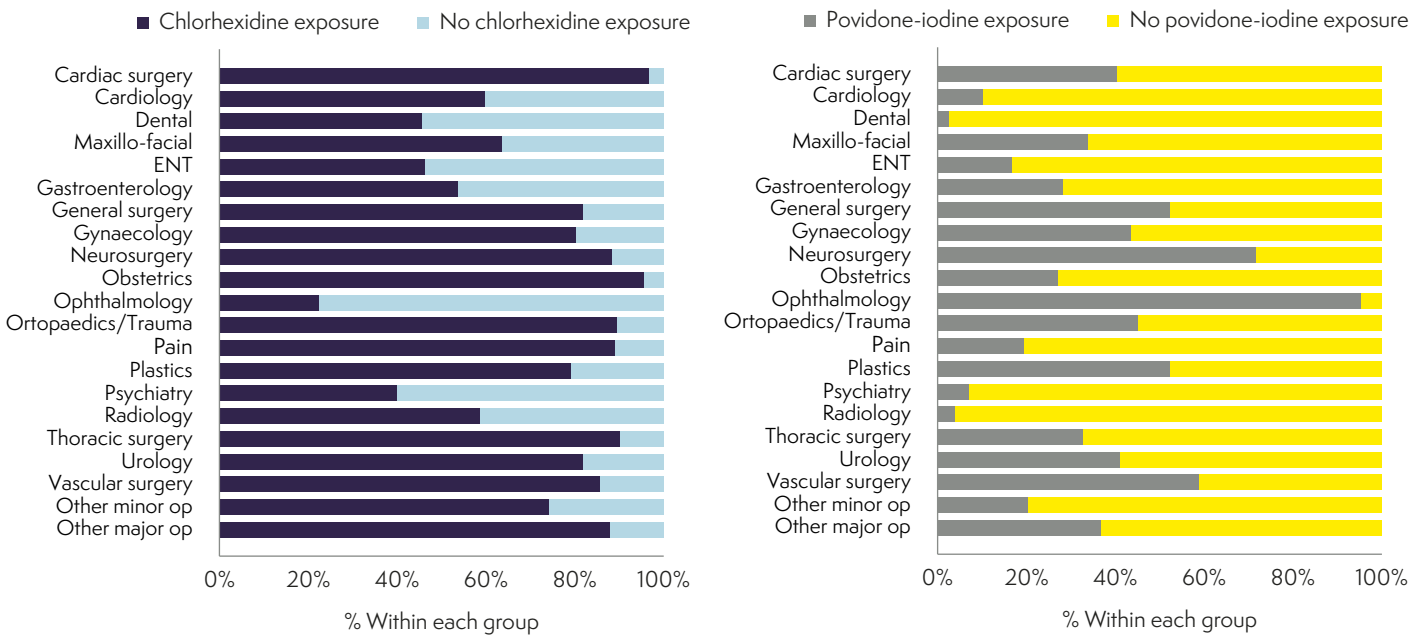
Table 15. Latex exposure and estimated annual caseload

	All cases				
Latex exposure	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
Exposure – at least one route	**11,119**	**2,180,325**	**69.7%**	% of cases exposed to latex	% of all latex exposure
Gloves	10,244	2,008,746	64.3%	92.1%	88.0%
Other	1,397	273,938	8.8%	12.6%	12.0%

Figure 21. Latex exposure, by main procedure
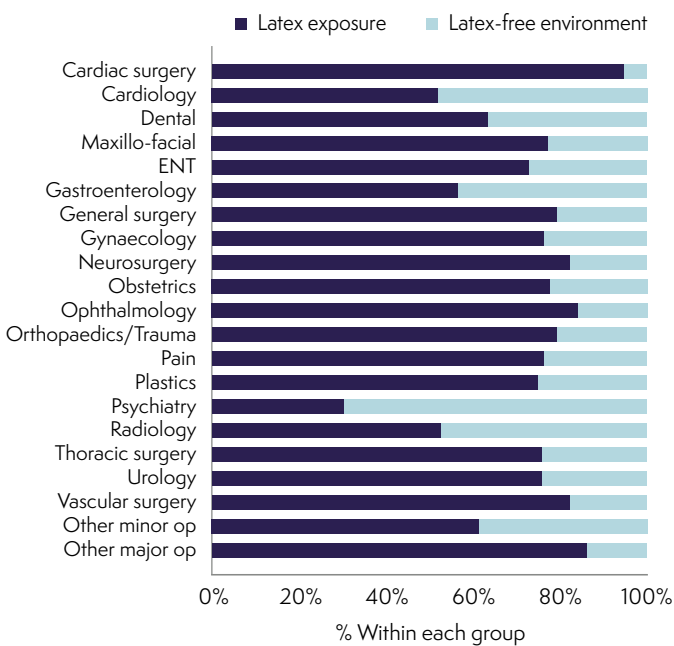
Latex

More than two-thirds of cases (69.7%) were reported to have been exposed to latex (Table 15), with the main route being latex gloves (64.3% of all cases, accounting for 92.1% of all latex-exposed cases). A latex-free environment was reported for 21.2% of all cases; latex exposure was 'Unknown' for 7.1%.

The specialty with the highest rate of latex exposure was cardiac surgery (94.8% of cases), and the lowest was psychiatry (30.8%) (Figure 21).

Miscellaneous drugs/substances

Bone cement was used in 2.6% of all cases and in 11.8% of orthopaedics/trauma cases, with an annual caseload of 78,240.

Blue dyes were used in 2.8% of all cases: Patent Blue in 2% and Methylene Blue in 0.9%. Both Patent Blue and Methylene Blue dyes were mostly used in general surgery: 29.8% and 35.3% respectively of all cases receiving these dyes, X-ray contrast was used in 1.7% of all cases, mostly in urology, radiology and orthopaedics: 24.5%, 22.3%, and 14.2% respectively of all cases receiving X-ray contrast.

Table 16 details use of the above substances and estimated annual exposures.

Table 16. Use of miscellaneous drugs/substances and estimated annual exposures

Individual drug/substance	All cases		
	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
Patent Blue dye	315	61,768	2.0%
Methylene Blue dye	139	27,257	0.9%
Bone cement	407	79,809	2.6%
X-ray contrast	274	53,729	1.7%

Discussion

This survey represents the most recent, comprehensive snapshot of anaesthetic activity and drug use in the United Kingdom. It provides unique, detailed insight into drug/substance exposure during anaesthetic activity in the perioperative period. In particular, compared with the equivalent Activity Survey performed in 2013 (Sury 2014), it provides considerably greater detail on use of analgesics, antibiotics, local anaesthetics, anti-emetics, intravenous colloids and blood products, as well as providing more information on all drugs assessed in that survey, enabling an examination of trends in practice. This survey also provides information on reported exposure to other substances, such as latex, antiseptics (chlorhexidine and povidone-iodine), radiocontrast media, dyes, and bone cement.

As not all drug use was studied in NAP5 we can only comment on changes in choice of induction and maintenance agents, and NMBAs and their reversal agents. We observed a substantial increase in the use of propofol for induction of anaesthesia for caesarean section and a reduction in the use of thiopental. NAP5 identified such surgery as particularly high risk for accidental awareness during general anaesthesia (AAGA) and thiopental was highlighted as a particular contributor to that (Pandit 2014, Cook 2014). We also saw a reduction (by about a third) of use of nitrous oxide in all age groups. We are aware that nitrous oxide may have become less popular after the publication of the ENIGMA (Myles 2007) study, and that some new hospital builds stopped including piped nitrous oxide to theatres. However the publication of ENIGMA-II has dispelled concerns about the safety of nitrous oxide, including safety in the elderly population (Myles 2014). A recent Canadian publication noted that ENIGMA had reduced use of nitrous oxide among anaesthesiologists, but that ENIGMA-II had not led to any recovery in usage (Jain 2018). Use of NMBAs has remained stable since the 2013 survey (Sury 2014), with almost half of patients undergoing general anaesthesia receiving NMBAs, and with stable distribution across age groups. Regarding choice of NMBA, use of suxamethonium appears to have declined slightly since 2013, both overall (5.3% vs 13% of cases in which an NMBA was used), and during caesarean section (81% vs 92%). Use of NMBA reversal agents has not increased overall, but the proportion of uses of sugammadex has increased four-fold. With the drug soon to come off patent a further increase might be anticipated. Overall, the static nature of NMBA use, the persistent underuse of reversal agents, and the underwhelming use

of neuromuscular monitoring reported in Chapter 8, Activity Survey, indicates no evidence of improvement in practice since increased vigilance in this area was recommended in NAP5 (Pandit 2014) and described as mandatory in the AAGBI minimum standards for monitoring document in 2015 (Checketts 2016).

This survey provides comprehensive and, to the best of our knowledge, previously unavailable data on the use of multiple drug classes, including analgesics, antibiotics, local anaesthetics, anti-emetics, drugs affecting coagulation, intravenous colloids and blood products. These data will be useful primarily in acting as a denominator for the wider NAP6 project, but we believe they will also have other uses.

Our data show that analgesics are used in ≈90% of all procedures involving an anaesthetist, and that opioids are used in virtually all general anaesthesia cases – a modest increase from NAP5 (92%). With increasing concerns about the use of opioids for reasons of both immune function and dependence potential (Brat 2018), the knowledge provided by this survey on proportional drug usage and allergenic potential, is useful, not only directly to inform practice, but also for the purpose of tracking usage changes over time. In total an estimated 3.6 million opioid drugs were administered in 3.1 million procedures, with fentanyl and morphine the dominant drugs, and oxycodone (about which some commentators have particular concerns) (Haffajee 2017) accounting for less than 2% of all opioid use and ranking as the fifth most frequently used opioid.

The widespread use of local anaesthetics, which were administered in three quarters of all cases, and the distribution of drugs used indicates that local and regional anaesthetic techniques were used in three quarters of cases, and with the previous results of NAP5, which indicated that neuraxial anaesthesia was being used for ≈30% of cases, suggests that most suitable cases are receiving neuraxial, peripheral nerve block or local anaesthesia infiltration, the first two of which are associated with improved patient reported satisfaction (Walker 2016). These data also provide numerator data – 2.3 million perioperative administrations of local anaesthetics – which may be of value when measuring the safety impact of non-Luer connectors on avoidance of wrong route errors (Cook 2012, NHS England 2016).

We have documented the use of anti-emetics in approximately three quarters of all cases, with dexamethasone now administered routinely (60%) during general anaesthesia. With concerns about the impact of dexamethasone on cancer recurrence (Singh 2014) and the relatively modest impact of this drug on postoperative nausea and vomiting (DREAMS trials collaborators 2017) this is also a notable finding.

Drugs affecting coagulation were used in ≈8% of all cases, with tranexamic acid used in ≈6% of all cases, in the majority of cardiac surgery cases, and in one in five orthopaedics/trauma operations. This is probably a relatively new phenomenon, but, with tranexamic acid now recommended for all patients undergoing surgery with anticipated blood loss greater than 500 mls (NICE 2016), our findings not only act as a benchmark, but also suggest that this recommendation may not be being widely applied.

The use of IV colloids is also of interest in relation both to blood-product use (one administration in every 37 cases) and to the use of synthetic colloids (less than 2% of cases). Among the synthetic colloids, the gelatins accounted for 90% of use, mostly during cardiac and vascular surgery. Starch-containing fluids are used in approximately 1 in 600 cases, and while there was no particular pattern to their use (surgical specialty, patient age, or ASA grade), it did include emergency cases and patients of ASA Grades 3–4. The 26 administrations of starch-containing fluids were reported from only 17 locations suggesting that perhaps the use is clustered in certain hospitals. The use of starch-containing fluid remains highly controversial, and the European Medicines Agency recently recommended their suspension from sale (EMA 2018). Based on our data this will have little impact on UK anaesthetic practice.

Amidst the current threat of increasing antibiotic resistance (WHO 2014 and 2017), our data provide detailed information on antibiotic usage, which was reported for more than half of the procedures and accounted for almost two million administrations annually. Gentamicin, co-amoxiclav and cefuroxime were the most commonly used drugs – each used for approximately 500,000 uses. Orthopaedics/trauma and general surgery are the main specialties using antibiotics, but cardiac and neurosurgery, urology and thoracic surgery are the specialties with the greatest proportion of cases receiving an antibiotic. The wide distribution of antibiotics used within specialties might perhaps hint at a lack of consistent application of best practice, but this would require further investigation.

The choice of drugs administered was reported to be influenced by allergy history in almost 10% of cases, and a history of antibiotic allergy influenced choice of teicoplanin or vancomycin in more than a quarter of cases when either of these antibiotics were used. We did not collect information on the specific antibiotic(s) that patients reported allergy to, but it is likely that a history of penicillin allergy was dominant, as these drugs are common substitutes for penicillins and penicillin allergy is reported in up to 10% of the general population and 20% of hospital in-patients (Weiss 2010, Lee 2000, Macy 2014a). Importantly more than 90% of patients with a history of penicillin allergy are deemed not allergic when investigated via skin and drug provocation tests (Macy 2015). The NAP6 baseline survey on anaesthetists' perspectives and experiences of perioperative anaphylaxis reported that penicillins were the drugs anaesthetists were most concerned about and avoided most often. Notably, teicoplanin, although it was prominent among suspected causative agents, was not frequently avoided (Kemp 2017). There is emerging evidence of teicoplanin as an important trigger of anaphylaxis events (Savic 2015), and it accounted for 28% of antibiotic-related anaphylaxis in one series (Chapter 8). A growing body of evidence has shown that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs with increased duration of treatment and hospital stay. They also, lead to higher rates of antibiotic resistance and infections, including methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile (C. diff) and vancomycin-resistant enterococcus (VRE) (Macy 2014b, Sade 2003, Solensky 2014). Our data provide additional evidence of use of second-line antibiotics, namely

teicoplanin, driven by drug allergy history, adding further strength to calls from the international allergy community for robust programmes to tackle the problem of inaccurate labels of antibiotic allergy, thus improving antibiotic stewardship (Macy 2014b, Sade 2003, Solensky 2014, Krishna 2017).

Chlorhexidine is a widely used antiseptic (Opstrup 2015) that has been increasingly reported as an emerging cause of allergy and of perioperative anaphylaxis in particular (Garvey 2007, Rutowski 2015, Nakonecha 2014, Mertes 2016, Egner 2017, Sharp 2016), although its use still appears to be under-recognised in the healthcare sector, especially in the perioperative setting, and its potential to cause allergic reactions seems to be underestimated by healthcare professionals (Totty 2017, Wittczak 2013, Faber 2012). Despite its known ubiquitous use in the hospital in accordance with infection prevention guidelines, our data reported chlorhexidine exposure in only ≈75% of all cases, mostly via skin preparation by the anaesthetist and/or the surgeon. Very few cases of exposure were reported via urethral exposure and coated/impregnated CVCs. National guidelines, such as NICE CG74 (NICE 2008), recommend use of chlorhexidine to prevent surgical site infections, and many local hospital guidelines advocate the use of chlorhexidine prior to venous cannulation. We suspect that our data may reflect under-reporting due to under-recognition of chlorhexidine exposure, for example, due to lack of awareness of chlorhexidine being present in many antiseptic alcohol wipes, urethral lubricants and CVCs. Conversely, it was unsurprising to find that povidone-iodine is used in about two fifths of cases and that exposure is mostly via skin prep by the surgeon.

Finally, our survey data suggest a latex-free environment was in place for only one fifth of cases.

This survey adopted similar methodology to that used for the NAP5 Activity Survey (Sury 2014). Discussion and details of the methodology used, in particular, the duration of the census over two days instead of a longer sampling time, the randomisation of specialist hospitals, and the extrapolation of sample data to estimate the annual workload, is already considered in Chapter 8. As also noted there, the large size of our sample data set means we can be confident that we have a true representation of the overall anaesthetic activity and allergen exposure in the UK, and that it is reasonable to scale-up the two-day sample data to estimate the annual data. However, where the sample size is small, variations in data captured or missed would have proportionately larger impacts on annual estimates, so these data should be treated more circumspectly.

This survey suggests an annual anaesthetic caseload of 3,126,067, which is a 15% reduction compared to that reported in NAP5 (3,685,800). We are not aware of any comparable data against which to benchmark. It should be noted that the NAP6 annual estimate of caesarean section caseload (171,579) is within 2% of that reported in NHS maternity data (174,720) (NHS Digital 2017b). We attempted to control for limitations in data collection by incorporating an estimated capture rate per hospital, by accounting for uninterpretable forms, and by calculating a scaling factor to allow for bank holidays. There are many factors that may have contributed to a fall in activity between 2013 and 2016,

and these are discussed in Chapter 8. However, the possibility also exists that we have missed a proportion of cases. If this is the case, we would have underestimated caseload, drug and allergen exposure, and activity by up to 15%. However, it would not impact on relative proportions and patterns of use/exposure within the dataset.

Overall this extensive national survey of anaesthetic practice in the United Kingdom provides new insights into drug uses and allergen exposures in UK 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.

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NAP6 Anaesthetic Activity/Allergen Exposure Survey

NAP6 Hospital Code: ☐☐☐　　**Date:** ☐☐/☐☐/☐☐ (dd/mm/yy)

PLEASE INDICATE ALL SPECIFIED DRUGS/SUBSTANCES THE PATIENT WAS EXPOSED TO DURING THE PERIOPERATIVE PERIOD (until patient discharged to the ward or HDU/ICU) *PLEASE SELECT ALL BOXES THAT APPLY IN EACH CATEGORY*

Theatre Number/Location: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐　**Actual List Order** (first patient is 01): ☐☐

Please complete this form for all patients where anaesthesia care is provided by an Anaesthetist during the two day survey period

---

Day of the Week
- ☐ Mon ☐ Tues ☐ Wed
- ☐ Thurs ☐ Fri ☐ Sat
- ☐ Sun

Admission Type
- ☐ Elective Day Case
- ☐ Elective Inpatient
- ☐ Emergency
- ☐ Other
- ☐ Unknown

Main Procedure
- ☐ Cardiac surgery
- ☐ Cardiology
- ☐ Dental
- ☐ Maxillo-facial
- ☐ ENT
- ☐ Gastroenterology
- ☐ General surgery
- ☐ Gynaecology
- ☐ Neurosurgery
- ☐ Obstetrics
- ☐ Ophthalmology
- ☐ Orthopaedics/Trauma
- ☐ Pain
- ☐ Plastics
- ☐ Psychiatry
- ☐ Radiology
- ☐ Thoracic
- ☐ Urology
- ☐ Vascular
- ☐ Other minor op
- ☐ Other major op

Either

NCEPOD Priority
- ☐ Immediate ☐ Urgent
- ☐ Expedited ☐ Elective
- ☐ Unknown

Or

Caesarean Category
- ☐ 1 ☐ 2
- ☐ 3 ☐ 4
- ☐ Unknown

Age of Patient (yrs)
- ☐ <1 ☐ 1-5
- ☐ 6-15 ☐ 16-25
- ☐ 26-35 ☐ 36-45
- ☐ 46-55 ☐ 56-65
- ☐ 66-75 ☐ 76-85
- ☐ >86 ☐ Unknown

Sex of Patient
- ☐ Male ☐ Female
- ☐ Unknown

ASA Grade
- ☐ 1 ☐ 2 ☐ 3
- ☐ 4 ☐ 5 ☐ 6
- ☐ Unknown

Body Habitus (BMI)
- ☐ Underweight (<18.5)
- ☐ Normal weight (18.5-24.9)
- ☐ Overweight (25-29.9)
- ☐ Obese (30-34.9)
- ☐ Morbidly obese (>35)
- ☐ Unknown

Ethnicity
- ☐ British (White)
- ☐ Irish (White)
- ☐ Any other White Background
- ☐ White and Black Caribbean (Mixed)
- ☐ White and Black African (Mixed)
- ☐ White and Asian (Mixed)
- ☐ Any other Mixed Background
- ☐ Indian (Asian or Asian British)
- ☐ Pakistani (Asian or Asian British)
- ☐ Bangladeshi (Asian or Asian British)
- ☐ Any Other Asian Background
- ☐ Caribbean (Black or Black British)
- ☐ African (Black or Black British)
- ☐ Any other Black Background
- ☐ Chinese
- ☐ Any Other Ethnic Group
- ☐ Unknown

Premed Given on the Ward
- ☐ Yes ☐ No ☐ Unknown

Induction Location
- ☐ Theatre anaesthetic room
- ☐ Theatre
- ☐ Radiology or Cath-lab
- ☐ ICU
- ☐ Emergency Department
- ☐ Other
- ☐ Unknown

Intended Conscious Level
- ☐ General anaesthesia
- ☐ Deep sedation
- ☐ Moderate sedation
- ☐ Minimal sedation
- ☐ Awake

Was Your Choice of Drugs Influenced By Previous Allergy History?
- ☐ No ☐ Yes - antibiotic
- ☐ Yes - other ☐ Unknown

Latex Exposure During This Case
- ☐ Yes (gloves)
- ☐ Yes (other latex)
- ☐ Latex-free environment
- ☐ Unknown

Povidone Iodine Exposure During This Case
- ☐ None
- ☐ Skin prep (anaesthetist)
- ☐ Skin prep (surgeon)
- ☐ Surgical irrigation
- ☐ Other
- ☐ Unknown

Chlorhexidine Exposure During This Case
- ☐ None
- ☐ Coated/impregnated CVC
- ☐ Urethral
- ☐ Skin prep (anaesthetist)
- ☐ Skin prep (surgeon)
- ☐ Surgical irrigation
- ☐ Other
- ☐ Unknown

Induction Agents
- ☐ None
- ☐ Propofol
- ☐ Thiopental
- ☐ Etomidate
- ☐ Midazolam
- ☐ Ketamine
- ☐ Sevoflurane
- ☐ Other volatile agent
- ☐ Other

Maintenance Agents
- ☐ None
- ☐ Sevoflurane
- ☐ Other volatile agent
- ☐ Nitrous oxide
- ☐ Propofol
- ☐ Other

Analgesics (any route)
- ☐ None
- ☐ Paracetamol
- ☐ Morphine
- ☐ Diamorphine
- ☐ Fentanyl
- ☐ Alfentanil
- ☐ Remifentanil
- ☐ Codeine
- ☐ Dihydrocodeine
- ☐ Oxycodone
- ☐ Methadone
- ☐ Tramadol
- ☐ Clonidine
- ☐ Parecoxib
- ☐ Ketorolac
- ☐ Diclofenac
- ☐ Ibuprofen
- ☐ Naproxen
- ☐ Other

Neuromuscular Blockers
- ☐ None
- ☐ Suxamethonium
- ☐ Atracurium
- ☐ Cisatracurium
- ☐ Mivacurium
- ☐ Rocuronium
- ☐ Vecuronium
- ☐ Pancuronium

Reversal Drugs
- ☐ None
- ☐ Neostigmine
- ☐ Sugammadex
- ☐ Other

Local Anaesthetics (any route)
- ☐ None
- ☐ Lidocaine
- ☐ Bupivacaine
- ☐ Levobupivacaine
- ☐ Ropivacaine
- ☐ Prilocaine
- ☐ Other

Was anaphylaxis (requiring urgent treatment) suspected during this case?
- ☐ Yes ☐ No

Antibiotics
- ☐ None
- ☐ Co-amoxiclav
- ☐ Flucloxacillin
- ☐ Tazocin
- ☐ Other penicillin
- ☐ Metronidazole
- ☐ Teicoplanin
- ☐ Gentamicin
- ☐ Vancomycin
- ☐ Cefuroxime
- ☐ Other Cephalosporin
- ☐ Other

IV Colloids/Blood Products
- ☐ None
- ☐ Gelatin or gelatin-containing
- ☐ Starch or starch-containing
- ☐ Albumin (any concentration)
- ☐ Red cells
- ☐ Platelets
- ☐ Fresh Frozen Plasma
- ☐ Specific coagulation factors
- ☐ Other

Anti-Emetics (any route)
- ☐ None
- ☐ Ondansetron
- ☐ Dexamethasone
- ☐ Cyclizine
- ☐ Prochlorperazine
- ☐ Metoclopramide
- ☐ Droperidol
- ☐ Other

Coagulation Drugs
- ☐ None
- ☐ Heparin (any)
- ☐ Tranexamic acid
- ☐ Aprotinin
- ☐ Protamine
- ☐ Vitamin K
- ☐ Other

Miscellaneous Exposure
- ☐ Patent blue dye
- ☐ Methylene blue dye
- ☐ Bone cement
- ☐ X-Ray contrast

Monitoring
- ☐ Depth of Anaesthesia
- ☐ Peripheral nerve stimulator
- ☐ Quantitative neuromuscular monitoring
- ☐ Cardiac output

Most Senior Anaesthetist Present
- ☐ Consultant
- ☐ Other career grade doctor
- ☐ ST4-7
- ☐ ST3/CT3
- ☐ CT2
- ☐ CT1
- ☐ Other (e.g. research fellow)
- ☐ Unknown

Appendix 2:

Calculation of Scaling Factor

Number of weeks in the year

It is not possible to multiply the weekly caseload by 52 due to bank holidays where activity will be reduced. Assuming activity on a bank holiday is similar to a weekend day the 'effective' number of weeks can be calculated. For 2016 the number of weeks used as a scaling factor to estimate annual activity was 50.6:

There were 366 days in 2016 (leap year), and 52.28 weeks (366/7 = 52.29).

Using the number of weekdays, a scaling a factor x, and y as the number of 'effective' weeks in 2016:

$5/7 * x = 52.29$ and $253/366 * x = y$

Therefore $x = 7 * 52.29/5 = y * 366/253$

And $y = (7 * 52.28 * 253) / (5 * 366) = 50.6$

Multiplication factor

Number of returns in a week = number of returned forms *3.5

Number of returns in a year (2016) = returned forms * 3.5 * 50.6

Estimated annual caseload = (returned forms * 3.5 * 50.6) / (proportion of interpretable forms * proportion of hospitals responding * individual site capture rate).

Multiplication factor = (3.5 * 50.6) / (0.98 * 0.96 * 0.96) = 196.09

10   Clinical features

K-L Kong

Surendra Karanam

Key findings

- Perioperative anaphylaxis is a clinical diagnosis, and presenting features may have many other causes that are more common than anaphylaxis. Despite this, early recognition and treatment of anaphylaxis during anaesthesia is key to avoiding harm.
- 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 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% of cases.
- 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, 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 <2% the presenting feature was delayed beyond 60 minutes.

- NMBA-induced anaphylaxis 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.

What we already know

Perioperative anaphylactic reactions may lead to substantial morbidity or mortality. Mertes and colleagues reported that 30–60% of anaphylactic reactions are due to IgE-mediated reactions with a 3.5–10% mortality rate (Mertes 2011a; Joint Task Force 2005).

International guidelines on the management of perioperative anaphylaxis emphasise the importance of early recognition and prompt treatment to avoid harm, which can include death or permanent disability (Krøigaard 2007; Harper 2009; Kolawole 2017). As these events occur rarely and randomly, regular education and training of anaesthetists and other members of the theatre team to recognise and treat anaphylaxis is needed (Simons 2014).

The diagnosis of perioperative anaphylaxis is a clinical one, and laboratory tests and biological markers are unhelpful at the time of presentation. A knowledge of the clinical features encountered during anaphylaxis, and a high index of suspicion by the anaesthetist is therefore essential.

Perioperative hypersensitivity reactions involve mainly the cardiovascular, respiratory and muco-cutaneous systems. However, reactions may present with isolated organ system involvement, including any of hypotension, tachycardia, bradycardia, bronchospasm, high airway pressure, oxygen desaturation, cutaneous flushing, urticaria, angioedema, itching, nausea and vomiting, and cardiac arrest (Mertes 2011b, Low 2016).

Clinical features consistent with perioperative anaphylaxis can be readily misinterpreted, as there are numerous possible causes for these signs. These include dose-related side effects of administered drugs, complications of the anaesthetic technique or surgery, and patient co-morbidities as well as hypersensitivity reaction. Unfortunately, the recognition of anaphylaxis is often delayed because key clinical features such as hypotension and bronchospasm more commonly have a non-allergic cause during the perioperative period. For example, severe hypotension after

induction of anaesthesia is not uncommon: clinically important hypotension occurring in 9% of patients within 10 minutes of induction according to one study (Reich 2005). Hypotension also occurs commonly during neuraxial blockade. Bronchospasm may be a more common feature of hypersensitivity in patients with pre-existing asthma, but non-hypersensitivity causes of bronchospasm are considerably more likely during anaesthesia. Widespread flushing or urticaria is seen in some patients with perioperative hypersensitivity reactions, but the absence of cutaneous signs does not exclude anaphylaxis.

The clinical features of perioperative anaphylaxis usually occur within a few minutes of exposure to the allergen, but may be delayed by up to an hour or longer. Reactions to neuromuscular blocking agents and intravenous antibiotics are usually rapid. Conversely, reactions to chlorhexidine, Patent Blue dye and intravenous colloids may be delayed, though this is not universal (Harper *et al* 2009).

Numerical Analysis

Grade of anaphylaxis

NAP6 inclusion criteria required Grade 3, 4 or 5 perioperative anaphylactic events: Grade 3 anaphylaxis is marked by life-threatening hypotension and/or severe bronchospasm, Grade 4 requires CPR and Grade 5 is fatal (see Chapter 5, Methods).

Grades of all events as determined by the review panel were:

- Grade 3: 136 (51%)
- Grade 4: 120 (45%)
- Grade 5: 10 (3.8%).

Grade 5 reactions were more common in patients with a higher ASA (Figure 1) and this is discussed in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Figure 1. Grade of anaphylaxis and ASA status
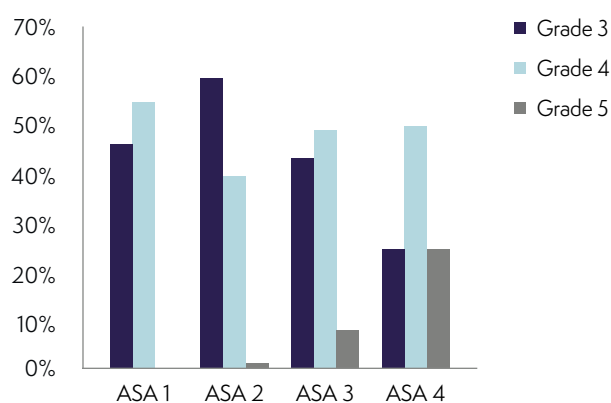
Gender

There were more reports of anaphylaxis in women (n=150; 58%) than men (n=108; 42%) (Figure 2), but this matched proportions of women and men undergoing procedures, as measured in the NAP6 Activity Survey (8,965, 58% females and 6,488, 42% males) (Chapter 8, Activity Survey).

Figure 2. Anaphylactic reactions by gender (numbers)
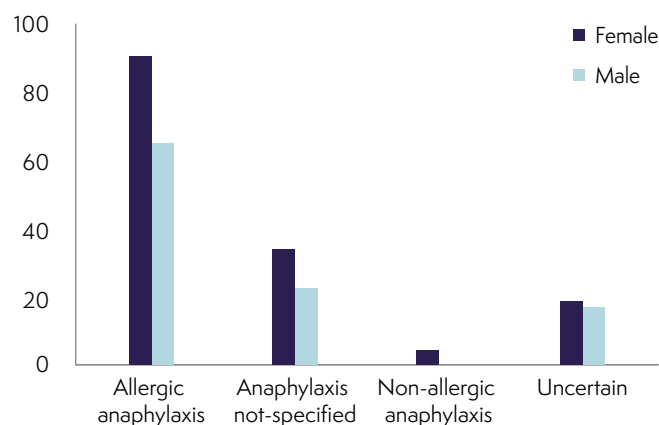
Presenting feature

The commonest presenting feature of perioperative anaphylaxis by far was hypotension (accounting for 46%), followed by bronchospasm/high airway pressure (18%), tachycardia (9.8%), flushing/non-urticarial rash 6.6% and cyanosis/oxygen desaturation (4.7%). A reduced or absent capnography trace was the seventh commonest presenting feature (2.3%). Three patients presented with cardiac arrest (1.2%).

This pattern of presenting feature was very similar in the subgroup of patients subsequently diagnosed as having an allergic anaphylactic reaction (Figure 3). Urticaria was not a common presenting feature or clinical feature during anaphylaxis, even in patients with a history of pre-existing urticaria. This was particularly so in severe cases, and in some cases skin signs only became evident after resuscitation (also see Chapter 12, Deaths, cardiac arrest and profound hypotension).

Figure 3. Presenting features of perioperative anaphylaxis
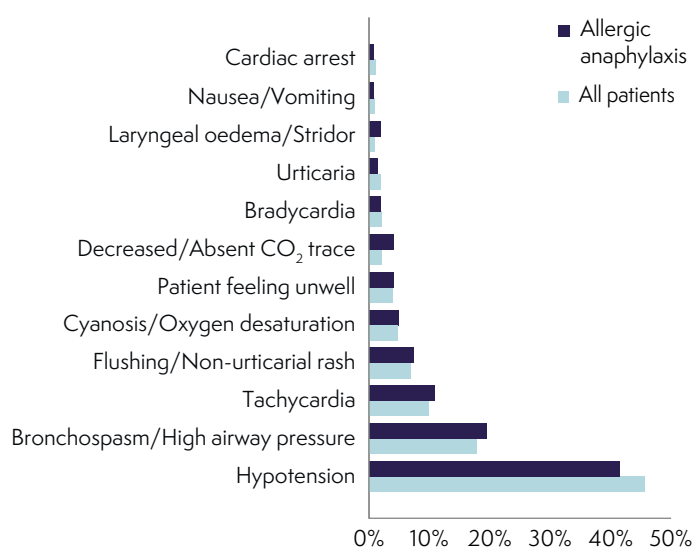
All clinical features during anaphylactic event

Hypotension was also the commonest clinical feature throughout the anaphylactic episode, occurring in all patients. This was followed by flushing/non-urticarial rash in 56%, bronchospasm/high airway pressure in 49%, tachycardia in 46%, cyanosis/oxygen desaturation in 41% and a reduced or absent capnograph trace in 30%. Again, this clinical pattern was very similar in the subgroup of allergic anaphylaxis patients (Figure 4).

> A healthy patient scheduled for elective day-case surgery, became hypotensive (systolic blood pressure <50 mmHg) with reduced capnography trace and oxygen desaturation within five minutes of induction. Over the next 20 minutes the patient received multiple doses of metaraminol, followed by a metaraminol infusion and also boluses of ephedrine before the possibility of anaphylaxis was considered and treated with adrenaline. No flushing of urticarial rash was seen at any point during the event. Subsequent investigations confirmed allergic anaphylaxis.

Figure 4. Clinical features present at any time during an episode of perioperative anaphylaxis
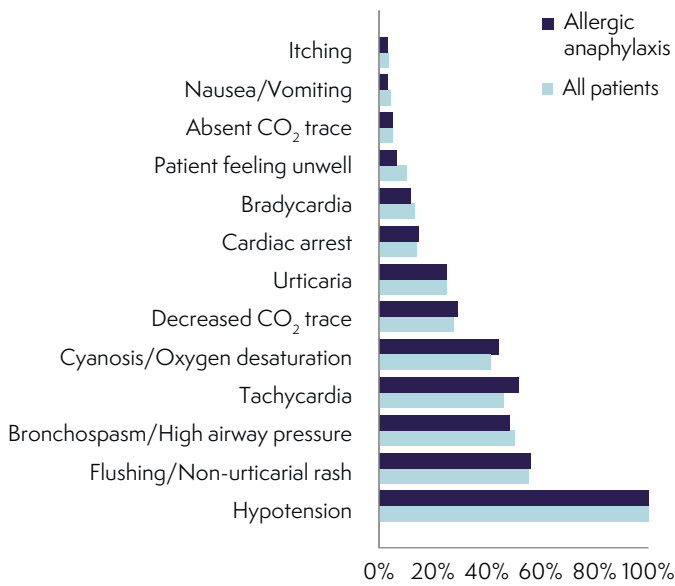
Isolated organ system involvement

Fifteen (5.6%) patients presented with isolated cardiovascular features and four (1.5%) with isolated respiratory features.

History of asthma

In patients with a history of asthma, bronchospasm/high airway pressures were proportionately more common, both as first presenting features and as clinical features occurring at any point during the anaphylaxis episode (Figure 5). This was true even when the condition was well controlled preoperatively.

Figure 5. Presenting features of perioperative anaphylaxis in patients with and without asthma
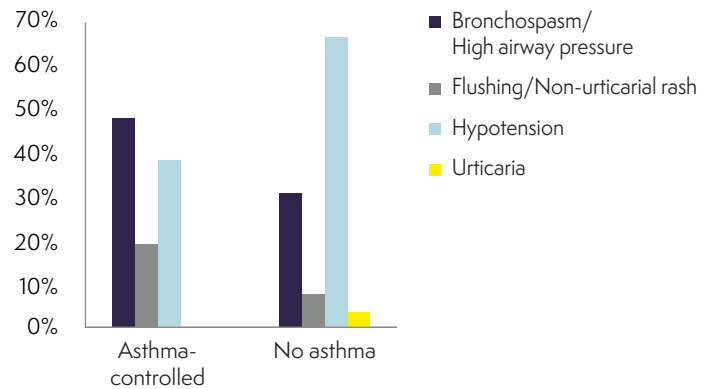
History of coronary artery disease

In contrast to asthma, there was no important difference in first presenting feature or clinical features during the anaphylactic episode in patients with or without a history of coronary artery disease. However, patients with coronary artery disease were more likely to experience fatal events (see Chapter 12).

Patients taking beta-blockers

Tachycardia was infrequent in these patients, either as a presenting feature or as one occurring during the episode (Figure 6). Bronchospasm was also proportionately less likely to occur during the event. These patients generally had higher-grade events and this is discussed in Chapter 12.

Figure 6. Presenting features in patients taking beta-blocker medication
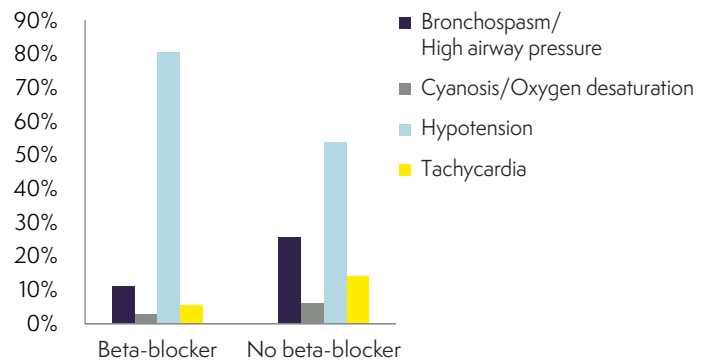
Patients taking an ACE inhibitor

In patients taking an ACE inhibitor, hypotension was a main presenting feature and was common during anaphylaxis (Figure 7). These patients generally had higher-grade events, and this is discussed in Chapter 12.

Figure 7. Presenting features in patients taking ACE inhibitor medication
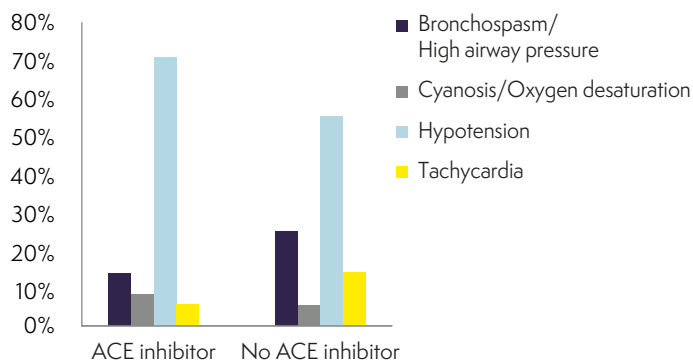
Body habitus

Bronchospasm and high airway pressure was the presenting feature in 34% of obese and morbidly obese patients, and 15% of non-obese patients (Figure 8).

Figure 8. Presenting features according to body habitus
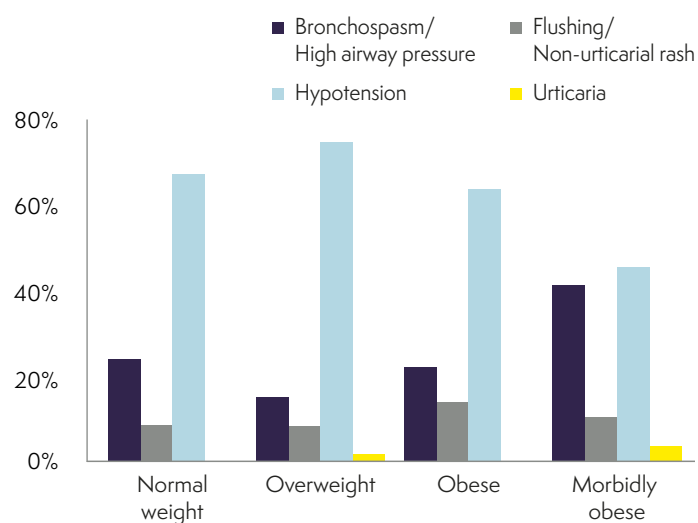
Influence of gender on presenting feature

In terms of presenting features, hypotension was slightly more common in men and bronchospasm slightly more common in women (Figure 9). This may be explained by differences between the genders in rates of coronary artery disease (men 23.7% vs women 8.4%) and use of beta-blockers and ACEI medication (26.7% vs 11.2% and 21.2% vs 15.2% respectively), whereas more women than men had asthma (25% vs 15.5%). Similar proportions of either gender were obese (38% vs 39%).

Figure 9. Presenting features of perioperative anaphylaxis in male and female patients
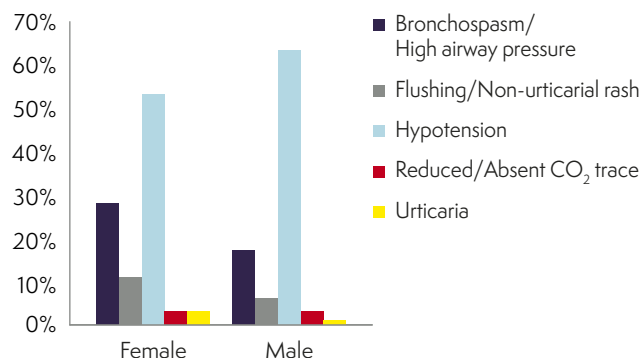
Culprit Agent

Neuromuscular blocking agents (NMBAs)

Although the numbers were small, we noted differences in the presenting features amongst different NMBAs responsible for anaphylaxis: atracurium was more commonly associated with hypotension and suxamethonium with bronchospasm/high airway pressure. Rocuronium was associated with both bronchospasm and hypotension in approximately equal measure (Figure 10).

However, taking all clinical features that occurred during anaphylaxis into account, the commonest clinical feature was hypotension for all three NMBAs.

Figure 10. Presenting features of NMBA anaphylaxis
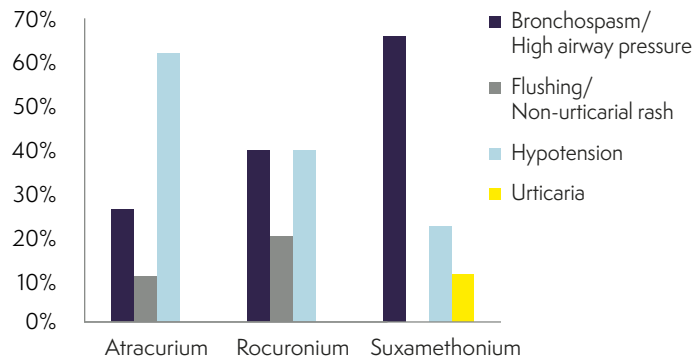
Amongst patients with anaphylaxis to NMBAs, women were relatively over-represented: 46 women and 19 men.

Antibiotics

Cardiovascular features (hypotension and tachycardia) were the predominant presenting features in patients with antibiotic-induced anaphylaxis. During teicoplanin anaphylaxis, hypotension was a dominant presenting feature with bronchospasm uncommon (Figure 11).

Figure 11. Presenting features of co-amoxiclav and teicoplanin anaphylaxis

- Bronchospasm/High airway pressure
- Flushing/Non-urticarial rash
- Hypotension
- Reduced/Absent CO_2 trace
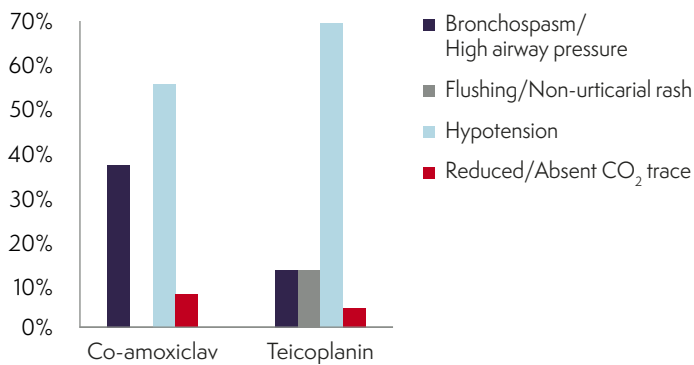
Chlorhexidine and Patent Blue dye

Hypotension was the commonest presenting feature in chlorhexidine and Patent Blue anaphylaxis (Figure 12). Of 18 patients with chlorhexidine anaphylaxis, there were 15 men and two women (gender not specified for one patient). All patients with Patent Blue dye anaphylaxis were women undergoing breast or gynaecological surgery.

Figure 12. Presenting features of chlorhexidine and Patent Blue anaphylaxis

- Cyanosis/Oxygen desaturation
- Flushing/Non-urticarial rash
- Hypotension
- Laryngeal oedema/Stridor
- Tachycardia
- Urticaria
- Other
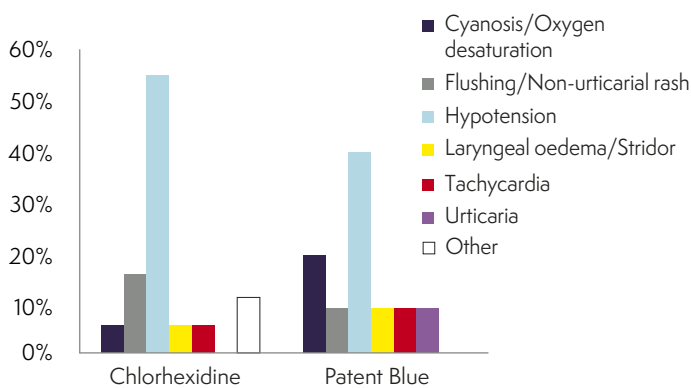
Time from exposure to presenting feature

In the majority of anaphylactic events (83%), the presenting feature appeared within 10 minutes of exposure to the culprit agent.

In only 5 cases (1.9%) was appearance of the presenting feature delayed beyond 60 minutes (Table 1).

Table 1. Time from exposure to presenting feature

Time from exposure to presenting feature	Number (percentage) of patients
0 - 5 mins	176 (66.2%)
6 - 10 mins	44 (16.5%)
11 - 15 mins	13 (4.9%)
16 - 30 mins	19 (7.1%)
31 - 60 mins	7 (2.6%)
61 - 120 mins	3 (1.1%)
>120 mins	2 (0.75%)
Blank	2

Time from exposure to presenting feature by culprit agent

When the culprit agent was an NMBA presentation was rapid, in all but one case (98%) presentation occurred in <30 minutes, and for all cases related to rocuronium, suxamethonium and mivacurium (Figure 13) presentation was in <10 minutes. An isolated case of atracurium anaphylaxis presenting at >120 minutes after exposure may have been a data-entry error.

Figure 13. Time from exposure to presentation: NMBA-induced anaphylaxis

- Atracurium
- Mivacurium
- Rocuronium
- Suxamethonium
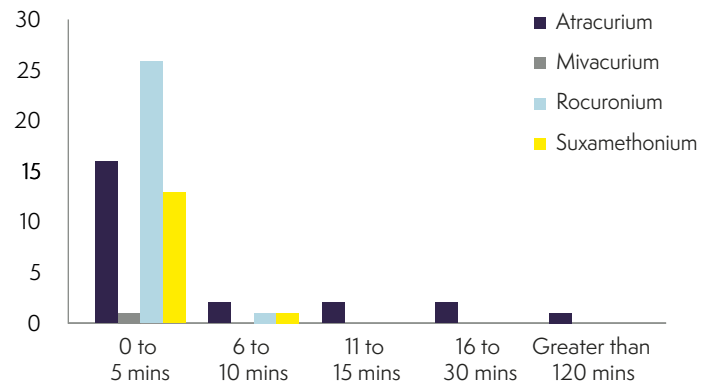
Similarly, when the culprit agent was an antibiotic, the presenting feature occurred rapidly – in <15 minutes in 97% of cases and in <30 minutes in all cases. (Figure 14).

Figure 14. Time from exposure to presentation: antibiotic-induced anaphylaxis

- 0 to 5 mins
- 6 to 10 mins
- 11 to 15 mins
- 16 to 30 mins
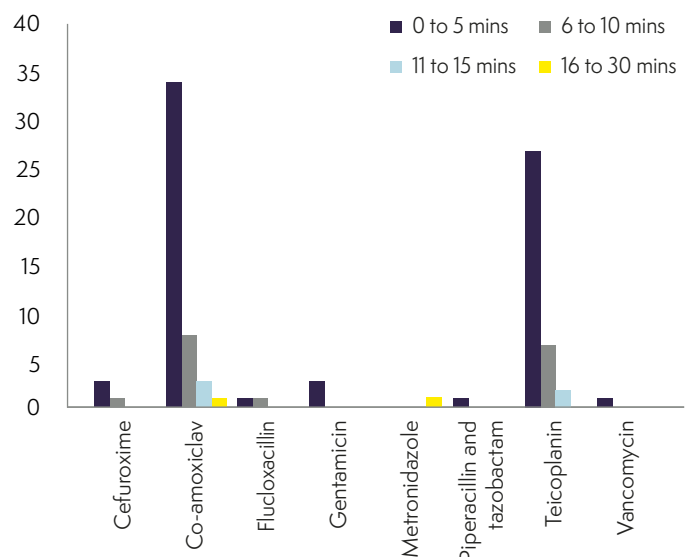
Some slower reactions were seen when the culprit agent was chlorhexidine or Patent Blue dye, frequently at >10 minutes and some at >120 minutes (Figure 15), and in reactions to orally administered drugs.

Figure 15. Time from exposure to presentation: chlorhexidine and Patent Blue dye induced anaphylaxis

Legend:
- 0 to 5 mins
- 6 to 10 mins
- 11 to 15 mins
- 16 to 30 mins
- 31 to 60 mins
- 61 to 120 mins
- Greater than 120 mins
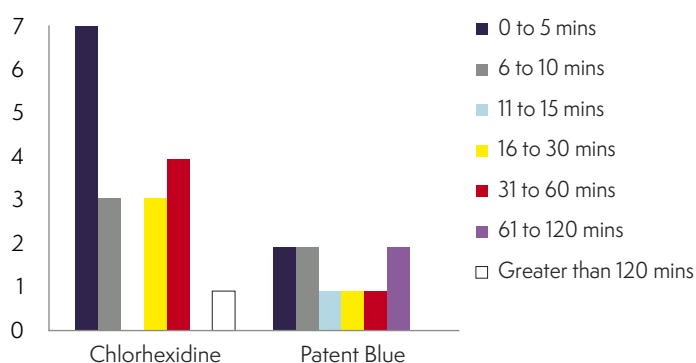
Time to suspect and treat anaphylaxis

The time interval between exposure to the suspected agent and the anaesthetist suspecting and treating anaphylaxis is reported in Chapter 11, Immediate management. Here we note that speed of response may vary according to presenting feature. Response was always <10 minutes when the presenting feature was cardiac arrest, bradycardia, reduced/absent capnograph trace, and laryngeal oedema. However, longer delays (up to 60 minutes) occurred when the presenting feature was hypotension, bronchospasm/ high airway pressure, cyanosis/oxygen desaturation, non-specific flushing, and reports of an awake patient feeling unwell.

Reduced capnography trace and grade of reaction

During the anaphylactic event, a reduced or absent capnograph trace was recorded in 80 (30%) of 266 cases. There was no clear correlation with grade of reaction (Table 2).

Table 2. Patients with reduced capnograph trace and grade of reaction

Grade of reaction	All patients n=266	Patients with reduced or absent capnograph trace. n=80	Percentage of cases in that grade
3	136	34	25%
4	120	43	36%
5	10	3	30%

Unrecordably low oxygen saturation

A total of 31 cases reported an unrecordably low oxygen saturation at some point during the anaphylactic event. When compared to the entire group of patients with anaphylaxis, this subgroup of patients were more likely to experience a Grade 4 or 5 reaction. These patients were also more likely to exhibit respiratory features or cardiac arrest/profound hypotension. This group of patients tended to have rapid onset anaphylaxis (exposure to presentation <5 minutes in 84%), and anaesthetists were prompt in suspecting and treating anaphylaxis.

Discussion

Several publications have suggested that a higher proportion of perioperative anaphylactic reactions occur in women, possibly related to sex hormones (Mertes 2003; Harboe 2005; Chen 2008; Leysen 2013). Our data indicate that the higher number of female patients with perioperative anaphylaxis was proportional to the higher number of female patients undergoing surgery and anaesthesia in general. Nevertheless, subgroup analyses revealed twice as many women as men when the culprit agent was an NMBA and a preponderance of male patients when the culprit agent was chlorhexidine. This is consistent with published data to date (Light 2006; Egner 2017) although differences in gender-based baseline exposure to these triggering agents is unclear.

Under-diagnosis of anaphylaxis is common, especially when there is a lack of cutaneous involvement in presentation. Our data indicate that although presenting features may vary, hypotension is universal during perioperative anaphylaxis (see also Chapter 12, Death, cardiac arrest and profound hypotension). Unexplained perioperative hypotension should prompt anaesthetists to consider anaphylaxis as a differential diagnosis in this setting. Muco-cutaneous signs are often absent at presentation, particularly in the more severe events.

It is well recognised that perioperative anaphylaxis can present as isolated organ system involvement and this was seen in a small minority of patients, even amongst the cohort of Grade 3 to 5 reactions that were the subject of NAP6. Other features such as itching, urticarial rash, or tissue swelling may be absent or masked either by general anaesthesia or as a consequence of the severity of the reaction (see also Chapter 12, Death, cardiac arrest and profound hypotension). Anaesthetists must therefore exercise a high index of suspicion in recognising perioperative anaphylaxis, as not all patients present with the 'full-blown' picture with involvement of the cardiovascular, respiratory and muco-cutaneous systems.

We noted some differing patterns in presentation depending on the trigger agent and patient co-morbidities. Amongst the NMBAs, hypotension was the commonest presenting feature in atracurium anaphylaxis, and bronchospasm/high airway pressure in suxamethonium anaphylaxis. Hypotension was also the commonest presenting feature in anaphylaxis due to chlorhexidine, Patent Blue dye and antimicrobials. As expected, hypotension was a common presenting clinical feature in patients taking beta-blockers or ACE inhibitors.

In the vast majority of cases, and for most culprit agents, presentation was within 10 minutes of exposure. This might be expected, as almost all drugs are delivered intravenously in the perioperative setting. The exceptions to this were chlorhexidine and Patent Blue dye, where presentation was more likely to be modestly (>10 minutes) or significantly (>30 minutes) delayed. This was also observed in reactions to drugs administered orally. This delay is probably due to the time lag in absorption of the allergen through skin, mucosal surfaces and/or soft tissues, and this is discussed further in Chapter 17, Chlorhexidine and Chapter 18 Patent Blue dye.

Some clinical features are clearly of immediate concern to the anaesthetist or are often associated with anaphylaxis, and these appeared to prompt the anaesthetist to suspect anaphylaxis and to start anaphylaxis-specific treatment swiftly. These clinical features included cardiac arrest, reduced or absent capnograph trace, and laryngeal oedema. Other clinical features, in particular hypotension, occur relatively frequently during anaesthesia, and causes unrelated to anaphylaxis are far more common: these confounding issues may cause a delay in the recognition and treatment of anaphylaxis. Though perioperative anaphylaxis is relatively rare, it should be high in the differential diagnosis of unexplained or severe hypotension during anaesthesia. Considering the diagnosis is the first step to recognising it.

Although bronchospasm and high airway pressures are commonly associated with exacerbation of asthma or airway stimulation, it may be a presenting feature of anaphylaxis and this is particularly the case in patients with pre-existing asthma, including patients with pre-existing good control. Assuming that all bronchospasm in asthmatics is caused by poor asthma control risks delaying or missing a diagnosis of anaphylaxis. Anaesthetists should therefore exercise caution in attributing bronchospasm or high airway pressures in the perioperative period solely to exacerbation of asthma.

A recent publication suggested that an end-tidal carbon dioxide value below 2.6 kPa is a useful independent marker of a severe anaphylactic reaction (Gouel-Cheron 2017). Capnography is readily and continuously measured throughout routine general anaesthesia, and a sudden reduction in the end-tidal carbon dioxide concentration could prompt early diagnosis and management of anaphylaxis. The NAP6 data, from cases of severe anaphylaxis, has not strongly confirmed this finding. While we did not ask reporters to report end-tidal carbon dioxide values, we did ask whether a reduced or absent capnograph trace was present. This was only reported in 30% of all patients. Whether this casts doubt on the previous findings or indicates failure to recognise or report this change is uncertain. Further examination of this observation is merited but it has not been confirmed in this study.

We found that patients who had an unrecordably low oxygen saturation at some point during the anaphylactic event experienced severe reactions. These cases were severe reactions with either prominent respiratory features or cardiac arrest/ profound hypotension. These cases were recognised and managed promptly by the anaesthetist, and this may be a useful sign in recognising severe anaphylaxis.

Our data indicate that patients with higher ASA, with a history of coronary artery disease and those taking beta-blocker medication or ACE inhibitors were more likely to have profound hypotension and poor outcomes – this is discussed further in Chapter 12, Deaths, cardiac arrest and profound hypotension. Vasopressin and glucagon were rarely administered in this setting, and this is discussed in Chapter 11, Immediate management and departmental organisation.

Recommendations

Institutional

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

Individual

- 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

- 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

- 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

- During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1 mg should be considered, repeated as necessary.

Research

- 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

- 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.

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Key findings

- All patients were resuscitated by an anaesthetist of appropriate grade and recognition of a critical event was prompt.

- The first clinical feature of anaphylaxis appeared in <5 minutes in 66% of cases, in <10 minutes in 83%, in <15 minutes in 88% and after >30 minutes in 4.6%.

- Recognition of a critical event and of anaphylaxis was generally very prompt.

- There was delay in starting anaphylaxis-specific treatment in 25% of cases, illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis.

- Airway management was generally uncomplicated and without difficulty. A single front of neck airway was judged the only case of airway morbidity associated with anaphylaxis.

- When cardiac compressions were indicated there was delay starting them in more than half of cases.

- Vasopressin and glucagon were very rarely used.

- Fluid administration was frequently judged to be insufficient and was inappropriate in 19%.

- The review panel judged management to be 'good' or 'good and poor' in 85% of cases.

- Careful examination of the role of antihistamines found no evidence of harm or benefit.

- More than half of patients required admission to critical care: of these 70% required level 3 care and most required catecholamine infusions after admission.

- Six per cent of survivors underwent surgery between the index event and the patient being seen in clinic. This was uneventful in every case.

What we already know

Recognition of perioperative anaphylaxis

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

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

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

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

Pharmacological management

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

Adrenaline

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

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

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

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

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

Metaraminol

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

Vasopressin

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

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

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

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

Glucagon

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

Corticosteroids

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

Antihistamine drugs

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

Sugammadex

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

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

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

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

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

Intravenous fluids

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

Numerical Analysis

Organisational preparedness for perioperative anaphylaxis

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

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

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

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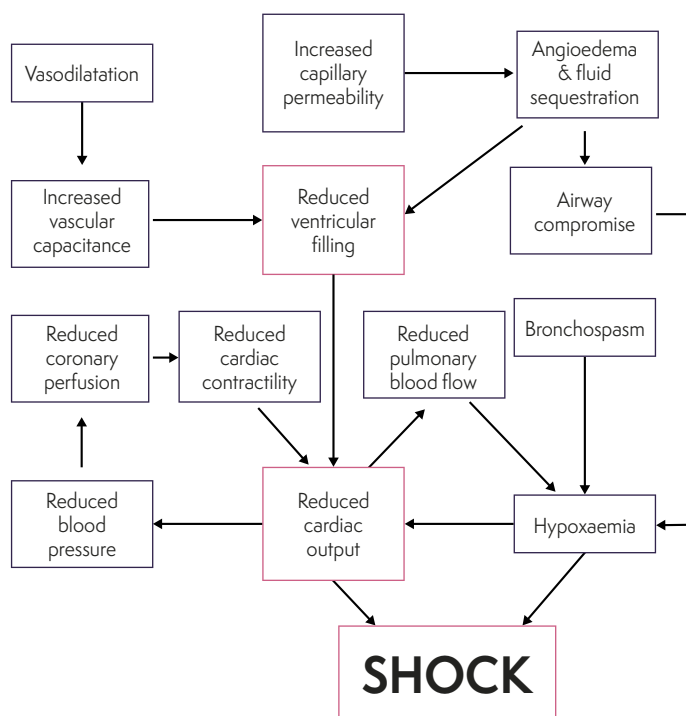
The number of consultant, non-consultant career grade and trainee anaesthetists varied widely from 1-150 (median 32), 0-40 (median 7) and 0-77 (median 19) respectively. Overall medical staffing numbers ranged from 1-228 (median 77).

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

Immediate management of perioperative anaphylaxis

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

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

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

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

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

Overall initial clinical management by the anaesthetist

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

Figure 2. Quality of the overall initial clinical management by the anaesthetist as judged by the review panel
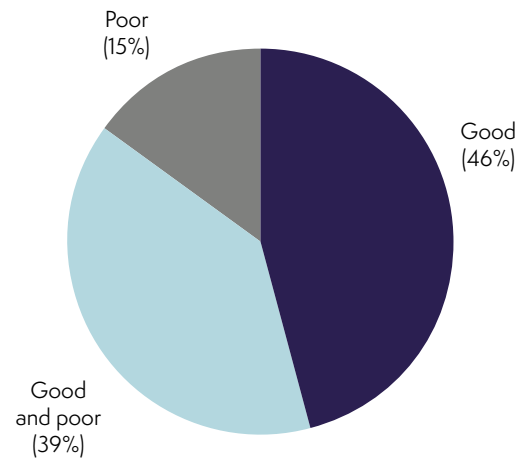
Recognition of the critical incident, recognising anaphylaxis, and starting specific treatment

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

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

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

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

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

Figure 3. Elapsed time (minutes) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis (number of cases)
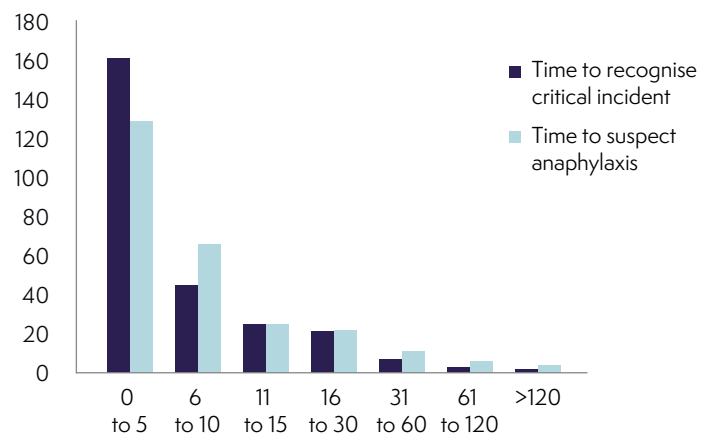
Once the first clinical feature of anaphylaxis had appeared, specific treatment for anaphylaxis was started in <5 minutes in 64% of cases and <10 minutes in 83%. (Figure 4). Reported reasons for delay included confounding differential diagnoses such as pulmonary embolism, tension pneumothorax, gas embolism during abdominal endoscopy, primary cardiac events, surgical haemorrhage, and neuraxial blockade-associated hypotension.

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

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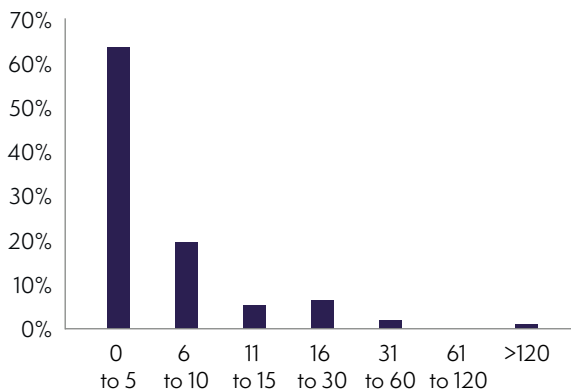
Airway management

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

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

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

Cardiac compressions

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

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

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

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

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

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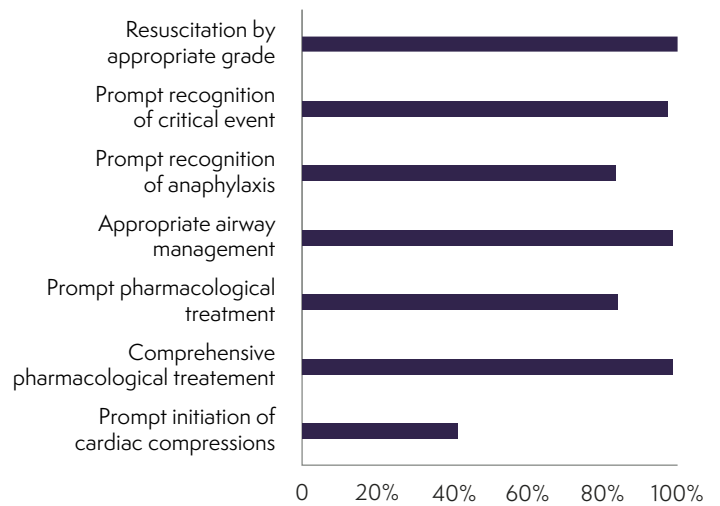
Use of guidelines and algorithms

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

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

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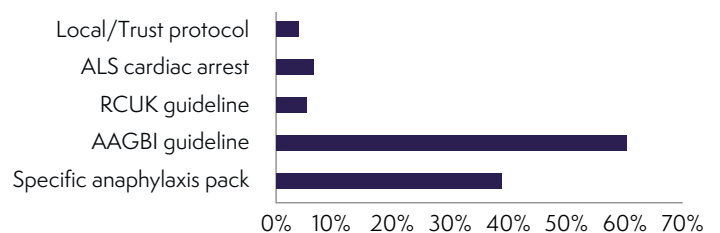
Teamwork

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

Vasoactive drugs

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

Figure 7. Vasoactive drugs administration during initial management of perioperative anaphylaxis (%)
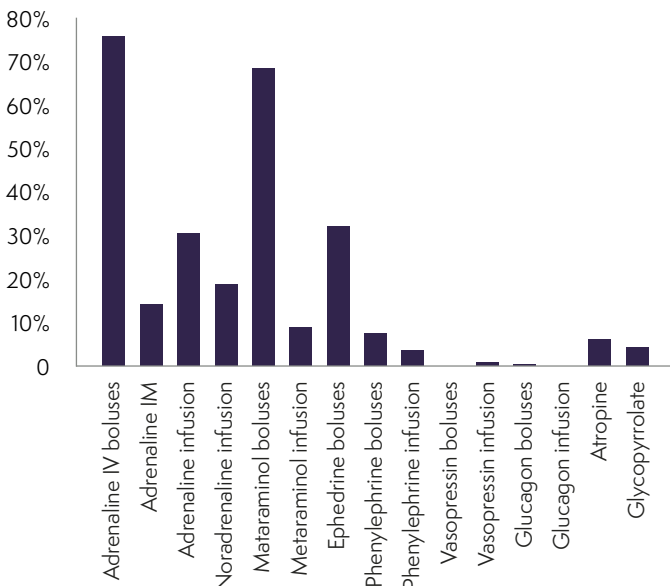
The dose of IV adrenaline was related to the severity of the anaphylactic event. The median total dose was 0.2 mg, 0.5 mg and 4 mg in severity Grades 3, 4 and 5 respectively (Figure 8).

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

Figure 8. Proportion of patients (%) receiving IV adrenaline boluses by grade of event in 261 cases with data available (%)
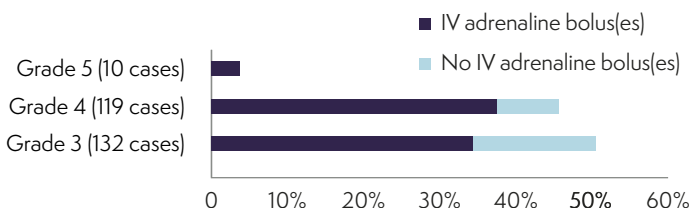
Adrenaline was judged not to have been given when indicated in 19.4% of cases – either not administered (11%) or administered late (8.4%).

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

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

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

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

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

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

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

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

Corticosteroids and antihistamines

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

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

Figure 9. Administration of corticosteroids and antihistamines after the anaphylactic event (% of cases)
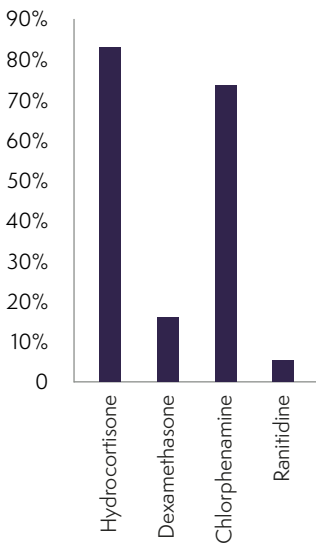
Table 3. ASA grade, level of care and outcomes in patients receiving chlorphenamine or no chlorphenamine for Grade 3-5 perioperative anaphylaxis *physical harm was based on 138 cases and 40 cases with this information available who did or did not receive chlorphenamine, respectively

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

In view of the current interest in, and uncertainty about, the possible benefits or harm of antihistamines during treatment of anaphylaxis, we performed further analysis using a logistic regression model. Variables included: the initial resuscitation drugs (adrenaline bolus, corticosteroids, metaraminol, ephedrine and chlorphenamine), patient factors (age-group intervals excluding children and over 75s due to small numbers), and ASA status (excluding ASA 5 due to small numbers). Outcome was level of harm (no harm, low, moderate/severe harm or death). Despite the univariate findings, in the logistic regression chlorphenamine administration was associated with an increased probability of no harm (odds ratio 2.20; 95% CI 1.05-4.58) and reduced probability

of moderate/severe harm or death (odds ratio 0.41; 0.18-0.91). The odds ratios had wide confidence intervals. In order to exclude the possibility that administration of chlorphenamine was simply a surrogate for good (as opposed to 'poor' or 'good and poor') clinical management (noting that chlorphenamine administration was not used as a measure of quality of care during panel discussions) we performed a Fisher exact test. This confirmed a significant association between administration of chlorphenamine and care being judged as good (P<0.005). Thus, it was not possible to extricate any potential benefits of chlorphenamine from the presumed benefits of good care.

Bronchodilator drugs

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

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

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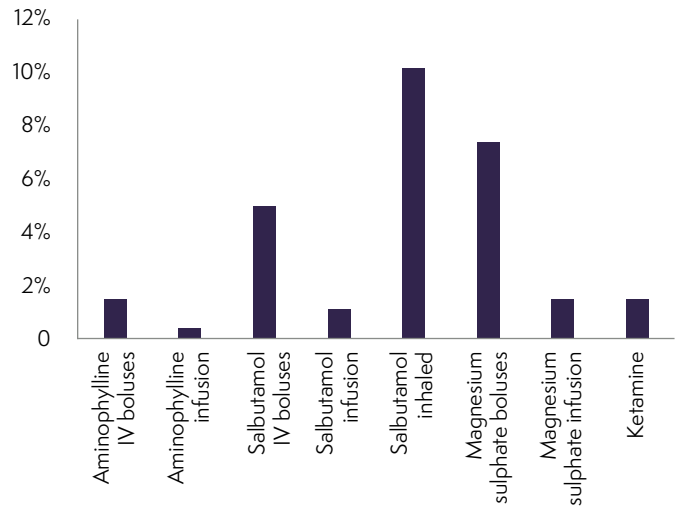
Sugammadex

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

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

Miscellaneous drugs

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

Fluid management

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

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

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

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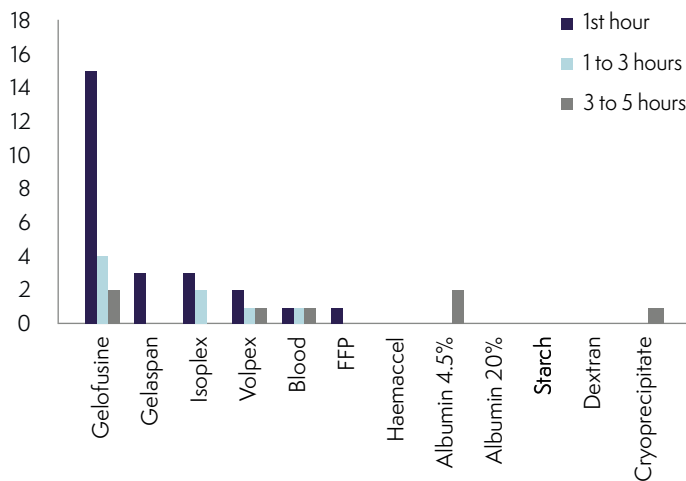
Discontinuation of the trigger agent

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

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

Impact of anaphylaxis on the interventional procedure

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

Figure 12. Outcome of the intervention or surgical procedure
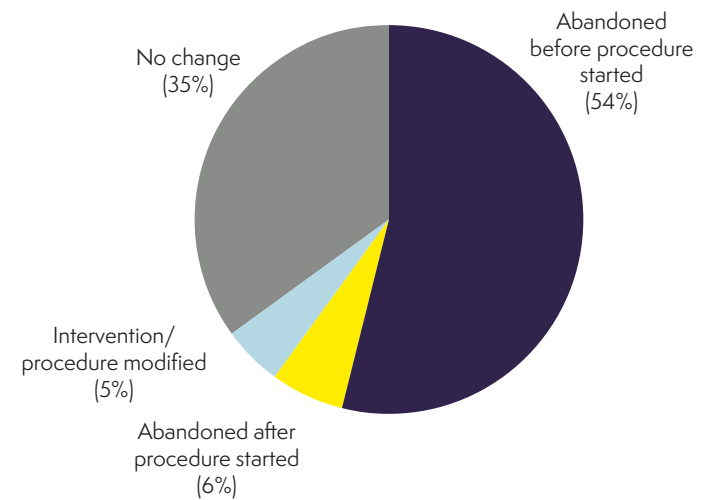
In 14% of cases in which the procedure was abandoned it was decided not to re-schedule surgery.

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

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

Unplanned hospital stay and critical care admission

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

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

Discussion

Departmental organisation

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

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

Immediate management

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

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

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

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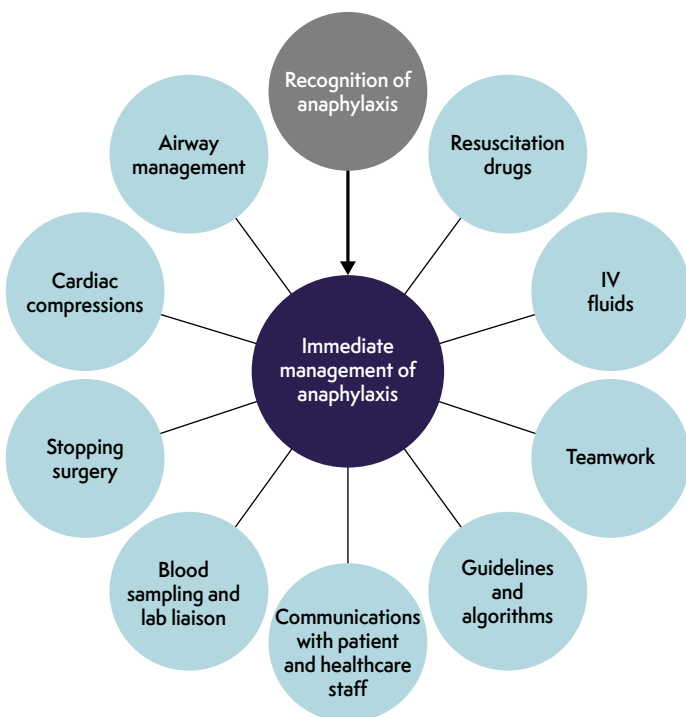
Recognition of Anaphylaxis

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

With the exception of rash, urticaria and angioedema, the individual clinical features of perioperative anaphylaxis are not specific diagnostic 'pointers', and therefore the diagnosis will be

delayed in some cases. It is probable that the late onset (or late recognition) of rash was partially responsible for delaying the diagnosis of anaphylaxis in some cases. Rash was never the first feature in cases where there was a delay in making the diagnosis, although it was the first clinical feature in 46 cases (17.3%) where the diagnosis was not delayed. Several anaesthetists made the observation that rash was noticed only when the surgical drapes were removed at the end of the case.

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

> The patient felt unwell and complained of facial tingling after a regional block with local anaesthetic. These symptoms were followed by cardiovascular collapse. The differential diagnosis included local anaesthetic toxicity, for which the patient initially received treatment.
>
> Hypotension did not respond to the usual treatment. A rash was noticed only when the level of lighting was increased in theatre at the end of surgery.
>
> A rash was only noticed when the surgical drapes were removed. The blood pressure had been low throughout surgery.
>
> An awake patient developed hypotension during an obstetric procedure. Anaphylaxis was suspected only when she complained of cutaneous symptoms.

Airway management

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

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

Cardiac Compressions

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

Guidelines and anaesthesia anaphylaxis packs

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

We recommend two sorts of specific Anaesthetic anaphylaxis packs:

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

Pharmacological management

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

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

Examination of NAP6 narratives suggests that anaesthetists may be reluctant to administer adrenaline in the presence of known coronary artery disease, cardiac valvular disease, or in the presence of cardiac arrhythmias. There is no published evidence on which to base this decision, but it is known that rapidly-administered or large doses of IV adrenaline can precipitate cardiac ischaemia and arrhythmias (Hoshino 2015). However, as patients with cardiac disease appeared more likely to have a poor outcome in NAP6 (see Chapter 12) and we saw very few complications of adrenaline administration (arrhythmias and cardiac ischaemia at any point

in the event both occurred in <2% of cases) our findings do not support delaying the administration of adrenaline. It is not known whether a particular patient will respond without adrenaline, and valuable time will be lost due to procrastination. Harm from adrenaline is unlikely.

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

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

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

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

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

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

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

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

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

Noradrenaline

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

Glucagon

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

Vasopressin

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

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

Corticosteroids

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

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

Antihistamines

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

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

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

Bronchodilator drugs

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

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

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

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

Sugammadex

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

Intravenous fluid management

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

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

Discontinuation of the trigger agent

In a minority of cases it would have been possible to prevent further trigger exposure. This included two cases of chlorhexidine-induced anaphylaxis where a chlorhexidine-coated central venous catheter remained in place. It is frequently impossible for the anaesthetist to identify the culprit and, in order to avoid re-exposure or continuing exposure, all drugs or other substances administered during the hour before the anaphylactic event should not be re-administered. Potentially-cross-reacting drugs

should also be avoided and, if an NMBA was been administered prior to the event, no further muscle relaxant drug should be administered. Chlorhexidine-coated central venous catheters present a considerable problem. Despite MHRA recommendations (Medicines and Healthcare products Regulatory Agency 2012), labelling of chlorhexidine-coated central venous catheters is not always prominent and the risk may remain unnoticed (see also Chapter 17, Chlorhexidine).

Outcome of the interventional procedure

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

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

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

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

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

Hospital stay and critical care admission

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

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

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

Chapter appendices

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

Appendix A: Anaesthetic anaphylaxis treatment packs.

Appendix B: Anaesthetic anaphylaxis investigation packs.

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

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

Recommendations

National

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

Institutional

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

- There should be a departmental lead for perioperative anaphylaxis in each department of anaesthesia (see Chapter 11, Appendix D). This role should be supported by appropriate time and DCC/SPA allocation

- Department leads and their local allergy clinic should liaise directly to ensure current phone numbers and email contacts for the clinic are readily available to anaesthetists in their department, and kept up to date

- Departments of anaesthesia should have protocols for the detection, management and referral for investigation of perioperative anaphylaxis. These should be readily accessible to all departmental members, widely disseminated and kept up to date

- Clinical Directors of anaesthetic departments should ensure their anaesthetists have been trained in the management of perioperative anaphylaxis

- Perioperative anaphylaxis guidelines and/or a management algorithm should be immediately available wherever anaesthesia is administered

- Anaesthesia anaphylaxis treatment packs, including an anaphylaxis management algorithm, adrenaline pre-filled syringes suitable for IV administration, hydrocortisone and details of the location of glucagon and vasopressin should be immediately available wherever anaesthesia is administered

- Anaesthesia anaphylaxis investigation packs should be available in all theatre suites, including tryptase sampling tubes and paperwork that describes:
    a. Details of blood tests required and their timing
    b. Instructions on referral for further investigation and allergy clinic details
    c. Documentation for the patient

- Vasopressin and glucagon for the management of intractable perioperative anaphylaxis should be available within 10 minutes wherever anaesthesia is administered

- Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the patient's medication and the event, and timings of all drugs administered prior to the event. A standardised form (the NAP6 or AAGBI pro-forma) should accompany the referral

- Investigation of perioperative anaphylaxis should include follow-up, either in hospital or in primary care, to detect adverse sequelae, such as new anxiety, impairment of cognition or activities of daily living or deterioration in cardiorespiratory or renal function. The anaesthetic department lead should coordinate this.

Individual

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

- Adrenaline is the primary treatment of anaphylaxis and should be administered immediately anaphylaxis is suspected. In the perioperative setting this will usually be IV

- Where a critical perioperative hypotensive event occurs and perioperative anaphylaxis is one of several differential diagnoses, treatment for anaphylaxis should start promptly as there is little to be lost and much to be gained

- If IV access is not immediately available, intramuscular or intraosseous routes should be used promptly, until IV access is established

- A rapid IV crystalloid (not colloid) fluid challenge of 20 ml/kg should be given immediately. This should be repeated several times if necessary

- During anaphylaxis with a systolic blood pressure <50 mmHg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with adrenaline and liberal IV fluid administration

- If an IV colloid is being administered at the time of the anaphylactic event, it should be discontinued, and the IV administration set replaced

- Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory

- During perioperative anaphylaxis in patients taking beta-blockers, early administration of IV glucagon 1 mg should be considered, repeated as necessary

- When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one

- A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis

- Chlorphenamine may be given as part of the resuscitation process, but NAP6 found no evidence of either benefit or harm. It may reduce angioedema and urticaria

- Blood samples for mast cell tryptase should be taken in accordance with national guidelines:
    - 1st sample as soon as the patient is stable
    - 2nd sample as close to 1-2 hours as possible after the event
    - 3rd (baseline) at least 24 hours after the event

- All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event, ie. the consultant anaesthetising or supervising the case

- Where a trainee refers a patient to an allergy clinic the contact details of a consultant anaesthetist should be included in the referral

- If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice, as well as making a written referral

- Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules (see Appendix C).

Research

- There remains uncertainty about the benefits or potential harm of administering antihistamine drugs during resuscitation of perioperative anaphylaxis. Clinical trials would provide valuable evidence

- There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium-induced anaphylaxis specifically. Clinical trials would provide valuable evidence

- Research would be of value to investigate the effect of corticosteroids, both given prior to anaphylaxis and for its treatment.
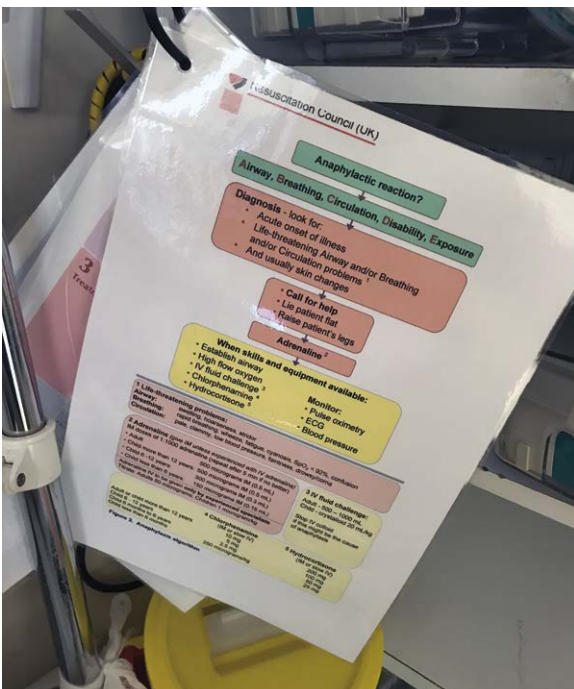
Laminated copies of guidelines can assist management

Airway problems were notably uncommon in NAP6

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Appendix A:

ANAESTHETIC ANAPHYLAXIS **TREATMENT** PACK

Suggested contents

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

- Hydrocortisone 100 mg x2.

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

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

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

  Or

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

  Or

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

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

Appendix B:

ANAESTHETIC ANAPHYLAXIS INVESTIGATION PACK CHECKLIST

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

MAST CELL TRYPTASE SAMPLES

- It is the anaesthetist's responsibility to ensure the samples are taken, including the 24-hour sample.

- Use tubes for serum sample, eg. electrolytes (colour coding varies between hospitals). Ensure you date and time the tubes. There is no need to refrigerate the samples.
  - 1st sample – as soon as the patient is stable. (Ideally less than 30 mins)
  - 2nd sample – as close to 1–2 hours as possible after the event. (No more than 6 h)
  - 3rd (baseline) – at least 24 hours after the event.

- Phone your local lab (usually Immunology) when you have taken the 2nd sample so they expect a group of 3 samples.

COMMUNICATION AND FOLLOW-UP

- Refer to critical care for continuing care of the patient.

- Record full details of the anaphylaxis and resuscitation in the patient's medical record.

- Explain to the patient what has happened as soon as practicable and record your conversation in the medical record. Give the patient the completed **Patient Letter**.

- Ensure the event is reported to your local incident reporting system.

- Contact your Departmental Lead for Perioperative Anaphylaxis for advice.

- If postponed surgery is urgent, refer to the **Urgent Surgery Management Plan.**

- Complete all parts of the **Allergy Clinic Referral Form** and send *together with photocopies of anaesthetic record and other relevant documentation*.

- Inform the patient's GP using the **GP Letter**.

- Ensure the event is reported to the MHRA through the Yellow Card system and keep a note of the MHRA Reference Number to update with the Allergy Clinic diagnosis.

- Ensure the patient is followed up for adverse physical and/or psychological effects.

Appendix B2:

LETTER TO THE PATIENT FOLLOWING PERIOPERATIVE ANAPHYLAXIS

[Hospital header]   Date …………………..

Patient's name ....

Patient's address ....

Medical record number ……………………………….

NHS Number …………………………….……....

Dear ....

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

....

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

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

1) Latex

2) Chlorhexidine, including medical, dental and household products

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

                                         ……………………………………..

                                         ……………………………………..

                                         ……………………………………..

                                         ……………………………………

                                         ……………………………………..

4) Antibiotics (SPECIFY)   ……………………………………..

                                         ……………………………………..

5) Analgesics (SPECIFY)   ……………………………………..

                                         ……………………………………..

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

                                         ……………………………………..

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

I will write to your GP with this information.

Yours sincerely,

Consultant Anaesthetist   Contact phone number……………….…………………

Appendix B3:

LETTER TO PATIENT'S GP FOLLOWING PERIOPERATIVE ANAPHYLAXIS

[Hospital header]   Date …………………..

[GP's Name and Address …….]

Dear Dr ……………………

Your patient ……………………………

Address ………………………………

MRN …………………………………

NHS Number ……………………………………

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

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

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

1) Latex ………………………

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

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

4) Antibiotics (SPECIFY)   ………………………………………..
                                                            ………………………………………..

5) Analgesics (SPECIFY)   ………………………………………..
                                                            ………………………………………..

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

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

Yours sincerely,

Consultant Anaesthetist

Contact phone number………………………………….

Appendix B4:

NAP6 ANAESTHETIC ANAPHYLAXIS REFERRAL FORM (4 pages)

Patient details

Name……………………………………………………….......................................

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

Address ………………………………………………….......................................

………………………………………………… Telephone ……………..............

Referring consultant anaesthetist (for clinic correspondence)

Name……………………………………………………….......................................

Address……………………………………………………………………………….

……………………………………………………………...…………………………

Telephone……………………….. Secure Email ………………………………

Patient's GP (for clinic correspondence)

Name……………………………………………………….......................................

Address……………………………………………………………………………….

……………………………………………………………………………………….

Telephone…………………… Secure Email ………………………………

Surgeon (for clinic correspondence)

Name……………………………………………………….......................................

Address………………..…………………………………………………………….

……………………………………………………………………………………….

Telephone…………………… Secure Email ……………...…………………

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

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

1) ………………….......... 2) ……………..........……… 3) ……………….........…..…

Proposed surgery or other procedure : ……………………………………………

Was surgery/procedure completed? Yes ☐ No ☐

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

Urgency/Date of future surgery……………………………………………………...

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

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

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

1 …………………   _____:_____   2 ………….….…   _____:_____
3 …………………..   _____:_____   4 ……………………   _____:_____

Neuraxial blockade   Spinal ☐ Epidural ☐ CSE ☐

Drug/Procedure	Time (24 hr clock)	Route

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

Drug	Time (24 hr clock)	Route

Latex free environment?   Yes ☐   No ☐

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

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

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

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

Drugs and IV fluids given to treat the reaction

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

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

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

Investigations performed before referral (please give results)

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

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

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

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

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

Other bloods tests:

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

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

Case discussed at a multidisciplinary meeting?   Yes ☐   No ☐

Reported to the MHRA   Yes ☐   No ☐

By whom? ……………………………………

MHRA Reference Number ....

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

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

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

Appendix C:

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

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

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

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

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

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

- Assume that the patient previously received an antibiotic. Antibiotics are the most common cause of perioperative anaphylaxis in the UK. Discuss antibiotic prophylaxis with a microbiologist beforehand
- Assume that the patient was previously exposed to propofol, morphine, chlorhexidine, latex, IV colloid, and an NMBA
- If possible, use local or regional anaesthesia in patients who have had a previous suspected anaphylactic event during general anaesthesia, and vice versa

Appendix D:

ANAESTHETIC DEPARTMENTAL ANAPHYLAXIS LEAD:
ROLES AND RESPONSIBILITIES

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

- Lead on anaphylaxis education and training in the department.

- Disseminate relevant updates as necessary.

- Engage with the local specialist allergy clinic and ensure up to date contact details (named contact, direct phone number and email).

- Act as a reference point for anaesthetists in the department who encounter perioperative anaphylaxis.

- Provide advice on referring patients for specialist investigation.

- Ensure that the patient and the GP have been given adequate, timely information in each case.

- Ensure that cases have been reported to the trust or board (Scotland) incident reporting system.

- Ensure that cases have been reported to the MHRA and that after investigation the data held by the MHRA is updated and accurate (using MHRA reference number)

- Coordinate, with primary care, appropriate follow-up of patients who have experienced perioperative anaphylaxis to identify physical or psychological adverse sequelae. This will usually take place in an outpatient setting. Refer onwards for specialist management if appropriate.

- Liaise with the hospital resuscitation team where appropriate

- Maintain a record of cases (within data protection regulations), and carry out annual audit and quality improvement as appropriate.

- Ensure that anaphylaxis guidelines are present at all sites where anaesthetics are given.

- Ensure the introduction of:
  - anaesthesia anaphylaxis treatment packs
  - anaesthesia anaphylaxis investigation packs.

- Ensure that cases are presented at departmental meetings, and that learning points are acted upon and audited if appropriate.

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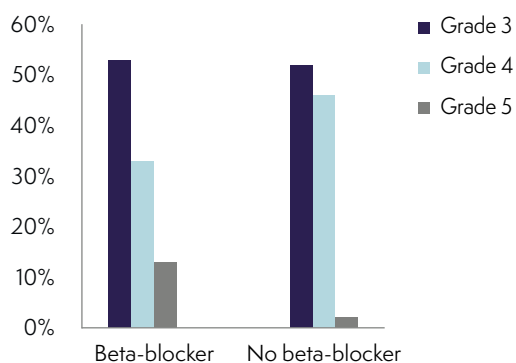
Characteristics of patients who survived or died after perioperative anaphylaxis are compared in Table 1.

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
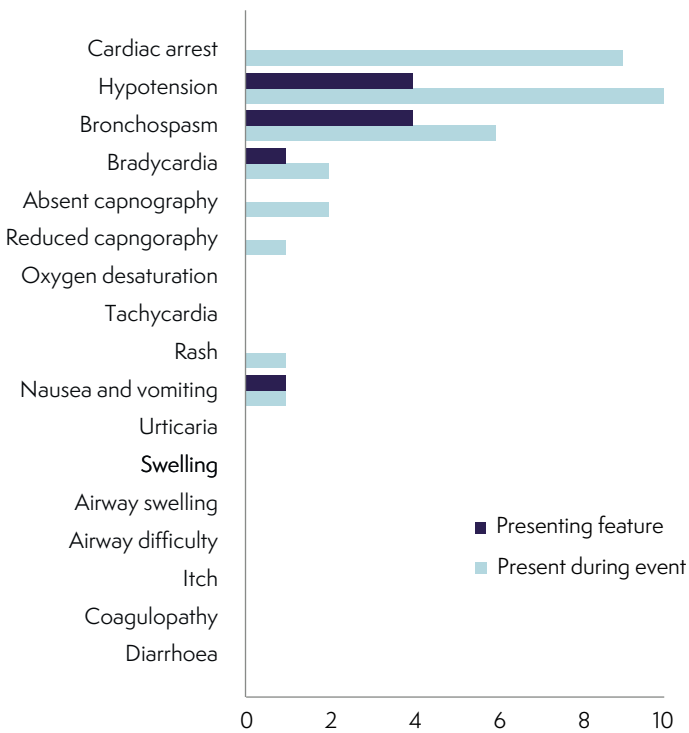
Nine of ten patients experienced cardiac arrest at the time of the event, and the final patient was established on cardiopulmonary bypass as part of resuscitation. There were no significant arrhythmias preceding the nine cardiac arrests. Cardiac arrest was preceeded by prolonged hypotension in four cases 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
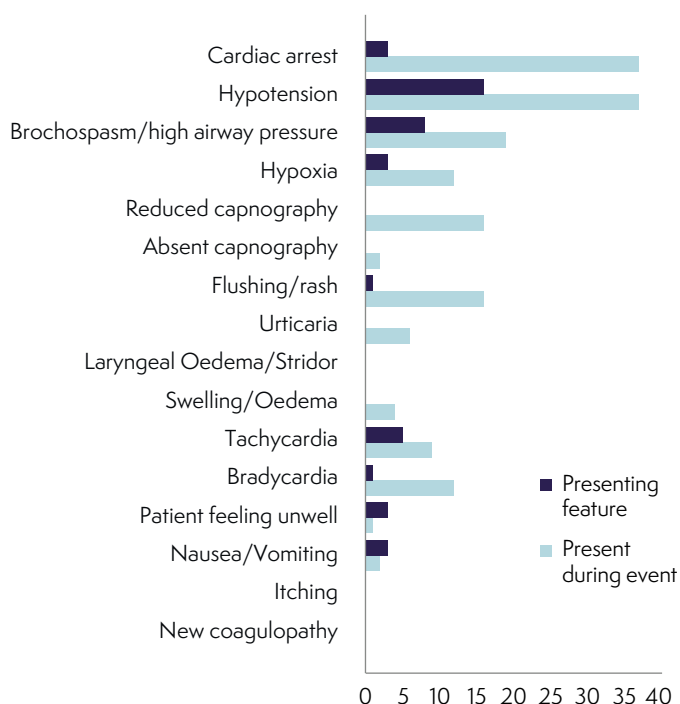
Hypoxia in the hour after the event was common (75%), and was more common than in patients who did not arrest (40%).

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). Resuscitation 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
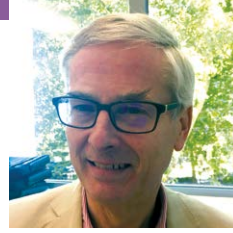
William Egner   Tim Cook   Nigel Harper   Tomaz Garcez

Key findings

- We describe self-declared provision and practice of specialist perioperative allergy services in the UK and compare this to national recommendations.
- An on line questionnaire was distributed to providers of allergy services in the UK in 2016.
- Over 1200 patients were investigated in 44 centres annually.
- 21 adult centres saw >20 patient per year, twelve <20 adults and eleven only children.
- Variation in workload, waiting times, access, staffing, and diagnostic approach was noted. Geographical variation was marked.
- Paediatric centres reported the longest routine waiting times (most wait >13 weeks) in contrast to adult centres (most <12 weeks).
- Service leads are allergists/immunologists (91%) or anaesthetists (7%).
- Potentially important differences were seen in:
  - Testing repertoire [10/44 (23%) lacked BSACI-compliant NMBA 'panels'
  - 17/44 (39%) lacked a NAP6 defined minimum NMBA panel
  - 19/44 (43%) failed to screen all cases for chlorhexidine
  - 21/44 (48%) failed to screen all cases for latex
  - 26/44 (59%) had specialist nurses
  - 18/44 (41%) clinics included an anaesthetist
  - 18/44 (41%) gave immediate information to patients in clinic, and 5/44 (11%) on support groups.
- Diagnostic testing is not harmonised, with marked variability in the NMBA panels used to identify safe alternatives.
- Poor access to services and patient information provision require attention.
- Harmonisation of diagnostic approach is desirable, particularly with regard to a minimum NMBA panel for identification of safe alternatives.
- These baseline data provide a valuable resource for comparision to data collected during the NAP6 project

Introduction

National Guidelines exist for the investigation and management of drug allergy, including in the perioperative setting (Ewan 2010, Harper 2009, NICE 2014). The incidence of perioperative anaesthetic anaphylaxis is uncertain, and access to specialist allergy services in the UK outside of London and the South East of England has been noted to be patchy and poorly harmonised in the approach to diagnosis and management (Finlay 2014). There are also NHS national specialist services definitions for allergy B09 and E09 (NHS Commissioning Board 2013a, NHS Commissioning Board 2013b). This survey of the provision of specialist perioperative allergy centres was conducted as part of NAP6 studying perioperative anaphylaxis. It aims to describe the self-reported provision and practice of specialist allergy services for perioperative anaphylaxis in the UK.

Methods

A SurveyMonkey™ questionnaire to ascertain availability, workload and practice in centres providing the specialist assessment of perioperative allergy in the UK was devised (Appendix 1) and distributed to all potential providers of perioperative allergy services in the UK. Sixty-five potential providers were contacted through triangulation of clinic lists from the British Society for Clinical Immunology and Allergy (BSACI), the British Society for Immunology (BSI), Allergy UK, the Anaphylaxis Campaign, Royal Colleges of Pathologists and Physicians and the professional networks known to the panel and the UK Immunology and Allergy Nursing Group. Of these, 44 separate centres declared such activity, and there are no other known UK specialist clinics with a significant workload who have not responded yet are known to the panel. This survey was distributed between December 2015 and April 2016, and services were asked to provide data relating to the previous 12 months. Where discrepancies or uncertainties were identified in the data, the centres were contacted again for clarification by email.

The SurveyMonkey™ data was exported to a spread sheet for descriptive analysis. No formal statistical analysis was undertaken.

Based on responses, adherence to recommendations derived from the BSACI (Ewan 2010), the Association of Anaesthetists of Great Britain and Ireland (Harper 2009), and the National Institute for Health and Care Excellence CG183 (NICE 2014) guidance was assessed as follows:

National Institute for Health and Care Excellence (NICE) CG183 recommendations (N)

N1   Allergy specialists should give the following written information to people who have undergone specialist drug-allergy investigation:

   N1.1   the diagnosis – whether they had an allergic or non-allergic reaction

   N1.2   the drug name and a description of their reaction

   N1.3   the investigations used to confirm or exclude the diagnosis

   N1.4   drugs or drug classes to avoid in future

   N1.5   any safe alternative drugs that may be used.

N2   Providing information and support to patients:

   N2.1   provide structured written information on person's suspected drug allergy.

British Society for Clinical Immunology and Allergy (BSACI) recommendations (B)

B1   Referral should be made to a major allergy centre with expertise in drug allergy and high throughput of anaesthetic anaphylaxis because of the need for experience in interpreting tests and the serious consequences of diagnostic error.

B2   The centre should be able to investigate all potential causes. This involves a range of drug classes/substances, including:

   B2.1   neuromuscular blocking agents (NMBAs)

   B2.2   intravenous (IV) anaesthetics

   B2.3   antibiotics

   B2.4   opioid analgesics

   B2.5   non-steroidal anti-inflammatory drugs (NSAIDs)

   B2.6   local anaesthetics (LAs)

   B2.7   latex

   B2.8   skin antiseptics (we used chlorhexidine as a surrogate for this).

B3   Investigation should be in a dedicated drug-allergy clinic.

B4   Stepwise investigation is necessary and depends on the likely cause, but a suspected IgE-mediated reaction (eg. NMBAs, IV anaesthetics, antibiotics, latex) requires:

   B4.1   skin testing and

   B4.1   in some cases, drug challenge.

B5   The aim of the investigation should be to identify the cause of anaphylaxis and to recommend a range of drugs/agents likely to be safe for future use.

B6   The allergist is responsible for a detailed report to the referring doctor and GP, and a shorter report and provision of 'medical alert' wording to the patient.

B7   Role of the anaesthetist – Report to Medicines and Healthcare products Regulatory Agency (MHRA).

B8   Role of the allergist.

   B8.1   Identify the cause of the reaction

   B8.2   Identify drugs likely to be safe for future anaesthesia

   B8.3   Provide a written report to referring consultant, copied to GP and surgeon

   B8.4   Provide patient with a brief 'to whom it may concern' letter (listing the above)

   B8.5   Provide patient with an 'Alert' application and the specific wording to be inscribed

   B8.6   Report to MHRA.

B9   The presence of a clinic nurse with specialist allergy experience.

Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommendations (A)

A1 Cases of anaphylaxis occurring during anaesthesia should be reported to the Medicines Control Agency (Note: MHRA has now superseded the Medicines Control Agency (MCA)).

We arbitrarily defined 'larger' adult centres as those seeing ≥20 patients referred for investigation of perioperative hypersensitivity per year, and 'smaller' centres as those seeing <20, to examine whether there were any differences in the services provided that clearly correlated with workload for standard B1.

Some of the text of the guideline recommendations above are open to interpretation. The guidelines state that the clinic should be able to investigate all causes, but are not specific about whether testing should occur in all cases to demonstrate lack of sensitisation or detect potential hidden exposure. Therefore, the NAP6 panel agreed that for antiseptics (chlorhexidine in most cases) the compliant clinic would be able to test, but we have also noted where the testing was applied to all, or only selected cases since this is often a hidden allergen. The same approach was used for latex testing. We have noted where centres were able to test to B2.1–2.8 inclusively as evidence of full repertoire testing.

Similarly, where NMBA use was assessed (standard B2.1), the centre was deemed compliant where the ability to test for NMBAs was offered, and we separately assessed if panels of NMBAs included all of the following (the agreed NAP6 minimum NMBA panel (see below) and referenced to standard N1.4, N1.5, B2.1, B5, B8.2).

The 'NAP6 minimum NMBA panel' was defined as: the suspected NMBA, at least one alternative in the same class, inclusion of suxamethonium and rocuronium (to identify a safe agent for rapid sequence induction), and inclusion of atracurium or cisatracurium. If the suspected culprit drug is one of those agents, then the minimum panel would consist of four agents. Vecuronium, pancuronium and mivacurium have either not been available at times during the survey period or are so infrequently used that their use was not deemed mandatory for compliance with the 'NAP6 minimum NMBA panel.'

For MDT related data (mandated in the National Specialist Services Contracts for Allergy B9 and E9) (NHS Commissioning Board 2013a, NHS Commissioning Board 2013b), we defined an MDT as a face-to-face or telephonic/video-conferenced multidisciplinary meeting with at least two medical and/or nursing specialties present. We did not count clinics where two or more specialties were present but where the respondents did not report an MDT in the MDT specific question.

Results

We identified approximately 50 centres providing adult, paediatric or mixed perioperative allergy testing services. The survey was sent to all centres and 47 evaluable responses were received. One respondent submitted no data so was excluded from analysis, and two other services submitted duplicate entries which were excluded, leaving 44 evaluable responses. Eleven services provided paediatric services alone. Adult services were available in 33 centres, of which five also saw a small number of children.

Workload

Sixteen adult centres and two paediatric centres reported actual numbers of patients seen, and other centres estimated activity for the previous twelve months.

Adult Centre Workload

The 33 adult centres evaluated an estimated 1271 adult patients in the previous twelve months. Of these, 21 (64%) investigated ≥20 patients per year (range 21–136, median 57 cases), and twelve (36%) saw <20 (median 10). Eleven (33%) adult centres saw ≥50 patients per year. Ninety per cent (1,149/1,271) of adult cases were investigated in larger centres (>20) and 10% (122/1,237) in smaller centres (<20).

Paediatric Centre Workload

All paediatric centres saw <20 patients per year, with a median of 4 (range 1-9). Fifty-three children were investigated for suspected perioperative anaphylaxis over the previous twelve months; 46 in specialist paediatric centres and seven in the five combined adult/paediatric centres.

Access

Considerable geographical variability in distribution of services is shown in Figure 1.
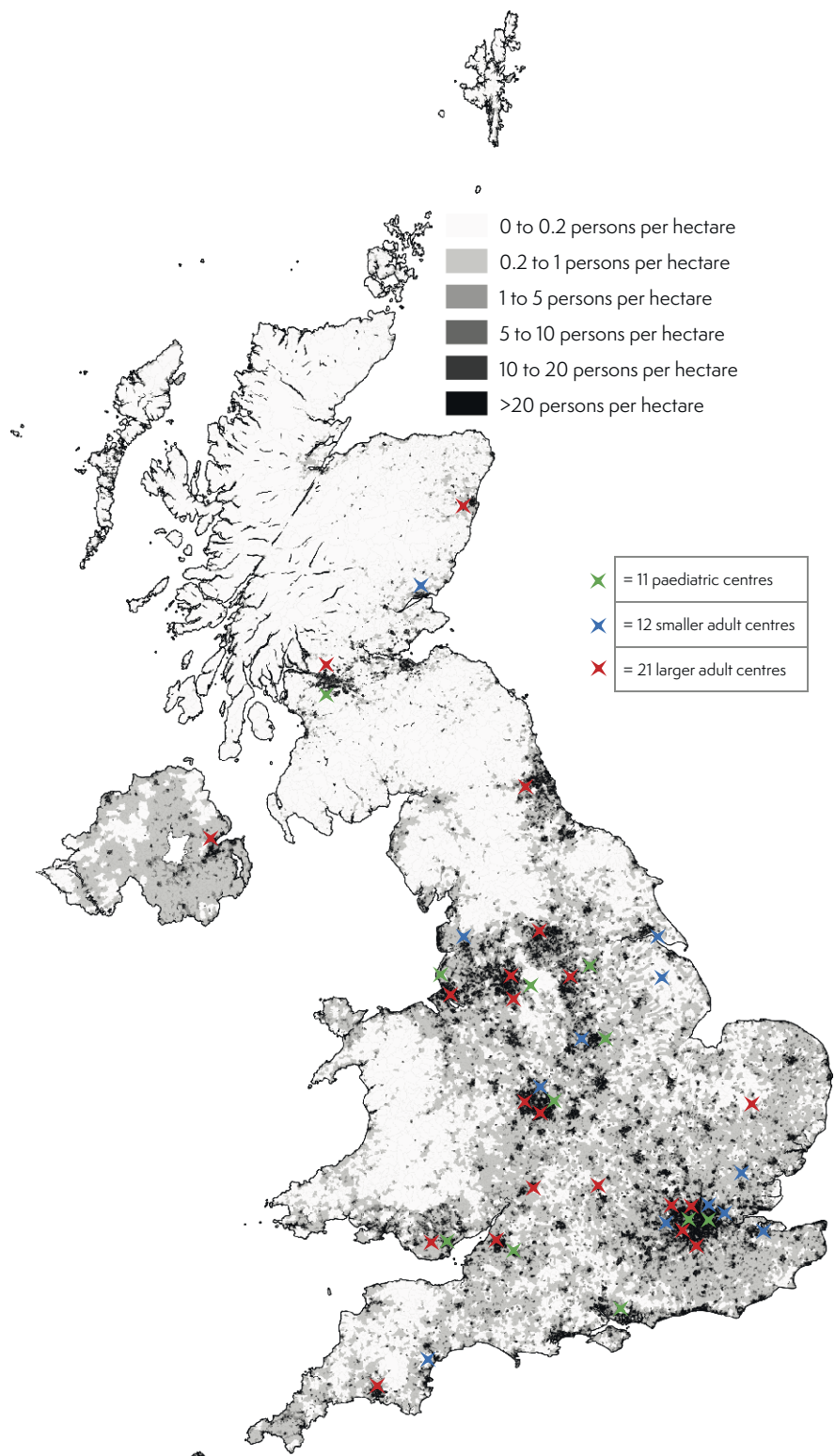
Figure 1a. Geographical distribution of centres providing specialist assessment of perioperative allergy in the UK
This map is modified from https://commons.wikimedia.org/wiki/File%3APopulation_density_UK_2011_census.png By Skate Teir CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0) under the GNU Free Document Licence http://www.gnu.org/copyleft/fdl.html The original data is from the ONS: Office for national statistics licensed under the Open Government Licence v3.0

Figure 1b. Regional variation in the number of services and referral patterns related to population size and density

(Note that the longer bars to the left of 1.0 are the smallest values, but to the right are larger values. Case/pop million = survey-reported cases per million of population in the 2011 UK Census data. Case/pop dens = survey-reported cases divided by the population density per km² in the 2011 UK census data.)
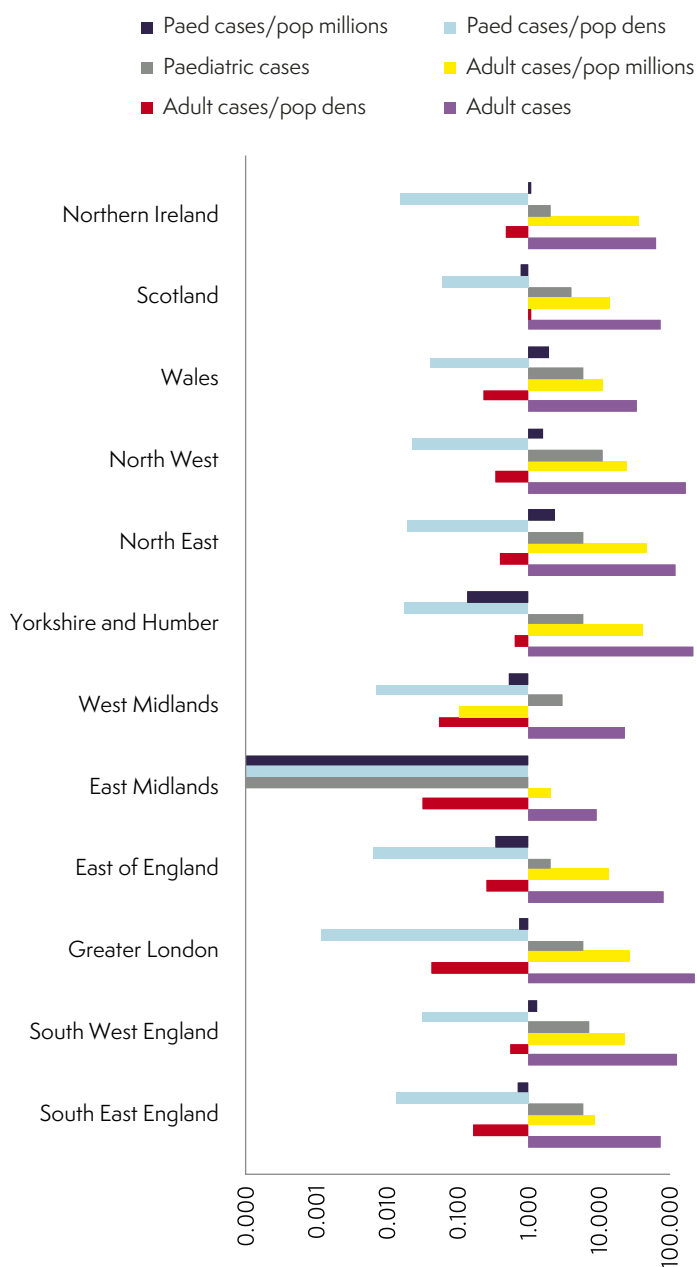
Compliance with standards

Compliance with published standards for each aspect of patient care is presented in (Figures 2a–c). Overall the results showed little difference in compliance between larger, smaller or paediatric centres (Figures 2a–c) for most elements, but notable differences in approach to paediatric cases due to a perception of rarity of neuromuscular blocking agent (NMBA) allergy in paediatric cases in some, or a wish to avoid or limit distressing testing (like IDT (intradermal testing)) in most. As a result, few paediatric

centres would strictly meet the BSACI standard of investigating all administered drugs or identifying several or a range of (herein assumed to be at least 2) alternatives.

Figure 2a. Clinic adherence to BSACI guidance (%)
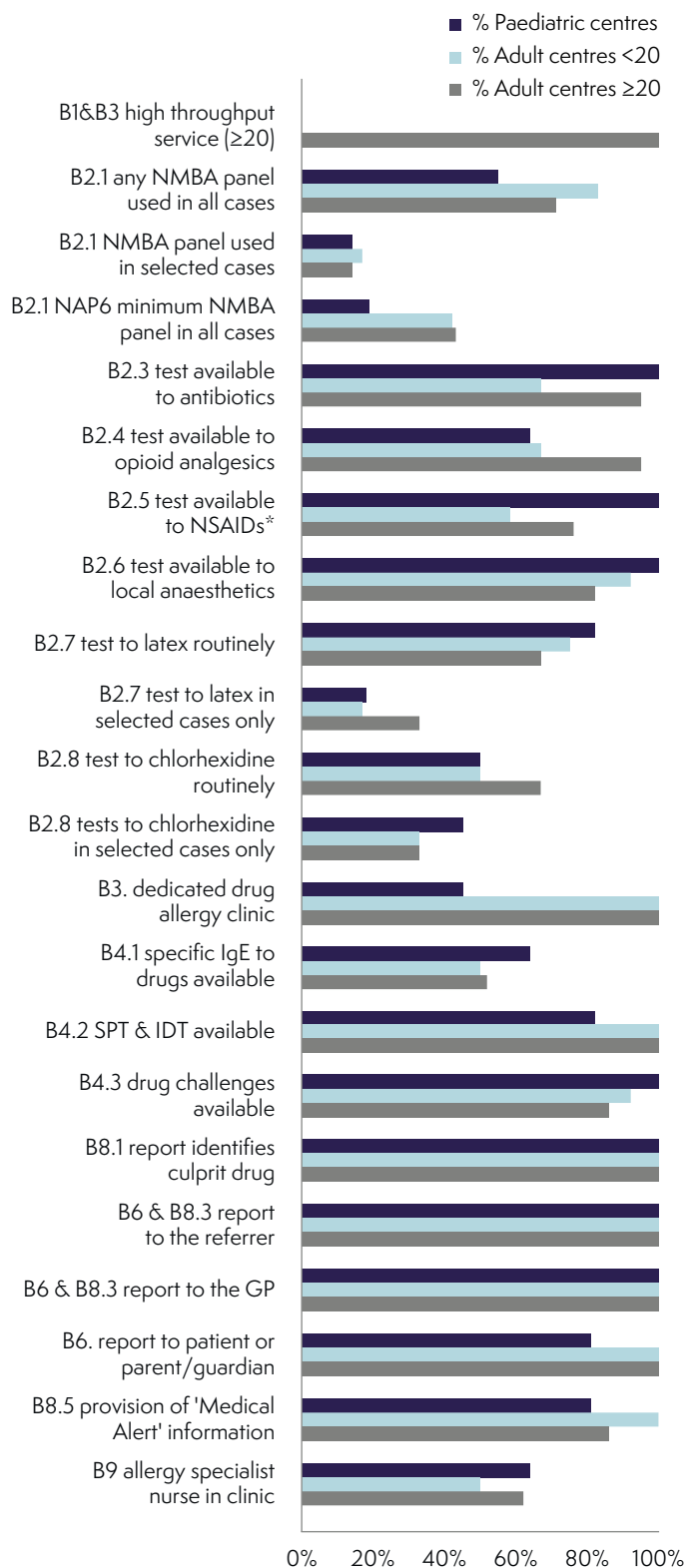
Figure 2b. Adherence to NICE CG 183 and BSACI communication guidance (%)

Standards with greatest variations in practice were the use of NMBA panels and anaesthetists in paediatric clinics, issuing of written and verbal information at the clinic visit, provision of information on patient support groups, availability of blood testing for drug-specific IgE, routine use of testing to latex or chlorhexidine and direct reporting to MHRA by the clinic.

Waiting times

Waiting times are shown in Figures 3a–c.

Adult centres

Urgent appointments were available to most within five weeks (Figures 3a & b). Most adults were seen within 12 weeks routinely. Two centres breached current national waiting time targets of 18 weeks – both were larger centres.

There were no major differences in waiting times between larger and smaller centres.

Figure 3a. Outpatient waiting times in 12 smaller adult centres

Figure 2c. Compliance with AAGBI guidance on MHRA reporting by clinic and anaesthetist
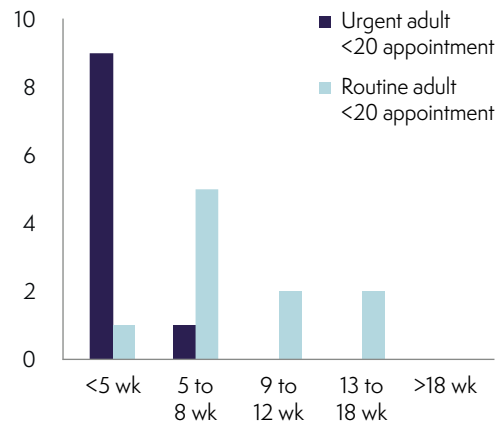
Figure 3b. Outpatient waiting times in 21 larger adult centres

Figures 2a–c show clinic compliance with the standards assessed. For NMBA compliance we have shown those centres which routinely use a panel in all vs those which use panels in selected cases only; both would be deemed complaint with BSACI guidance as written (since stepwise investigation is allowed). Compliance with NAP6 minimum NMBA panel specification is also shown in contrast to those who routinely use panels. The availability of all routine test modalities – sIgE (specific IgE blood test), SPT (skin prick testing), IDT is also shown, as these are required both for expert allergy centre status and to meet the requirements of BSACI guidance.

Paediatric centres

Urgent appointments were available to most within eight weeks. Routine paediatric appointment waiting times were longer than adults, with most waiting >13 weeks (Figure 3c).

One centre breached current national targets with a wait of >18 weeks.

Figure 3c. Outpatient waiting times for children in 11 paediatric centres
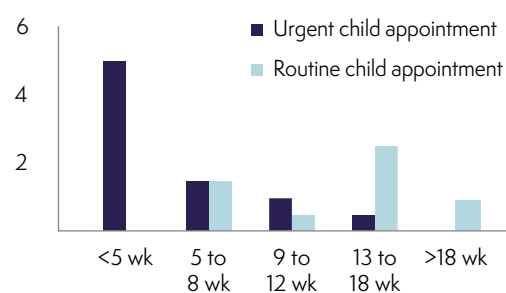
Staffing and leadership

Leadership

Adult centres

The majority of services (28/33) are led by an allergist or immunologist, with three led by an anaesthetist, one by a respiratory physician and one did not declare a specialty lead.

Of the 21 larger adult centres, 18 were allergist/immunologist-led, and three led by an anaesthetist with drug allergy experience. Of the 12 smaller adult centres, nine are allergist/immunologist-led, one led by an anaesthetist with allergy experience, and one by a respiratory physician experienced in allergy and one did not declare a specialty lead.

Paediatric centres

All eleven centres are led by a paediatric allergist.

Involvement of an anaesthetist

Adult centres

Nine of 21 larger centres and five of 12 smaller centres reported involvement of an allergy-experienced anaesthetist in the clinic. A total of 675/1,271 (53%) adults were seen in a clinic including an allergy-experienced anaesthetist, of whom 626 (93%) were seen in the nine larger centres. Two further centres (both larger centres) had an anaesthetist without extensive anaphylaxis experience and one reported both.

Paediatric centres

One of eleven paediatric centres reported the involvement of an allergy-experienced anaesthetist.

Overall, eighteen of 44 (41%) centres can be deemed to have appropriate anaesthetist involvement.

Involvement of a nurse with drug allergy experience

Sixty per cent of all centres (26/44) had at least one nurse with drug allergy experience.

Adult centres

Thirteen of 21 larger adult and six of twelve smaller adult centres had a drug allergy-experienced nurse.

Paediatric centres

Seven of eleven paediatric centres had a drug allergy-experienced nurse.

Involvement of a pharmacist to prepare drug dilutions

Four centres reported the availability of pharmacy-led drug preparation for clinical investigations; in three larger adult centres and one paediatric centre.

Operation of the service

Adult centres

Face-to-face multi-disciplinary team meetings (MDTs) were more common in larger centres (12/21, 57%) than smaller centres (4/12, 33%). Two centres (one larger, one smaller) had an alternative arrangement to ensure MDT discussion (eg. a telephone MDT before, during or after the clinic). Three larger and one smaller adult centres reported presence of an anaesthetist in clinic, but no formal MDT.

While 55% complied with a face-to-face or telephone MDT, if the presence of two specialties in a clinic is judged to be equivalent to an MDT then overall provision rises to 67%.

Paediatric centres

Five paediatric centres had a face-to-face MDT arrangement (5/11, 45%). Two additional services performed clinics jointly with a paediatric allergist. Only one clinic was staffed by an anaesthetist experienced in drug allergy.

Overall compliance with a face-to-face MDT standard in paediatric clinics was 45% and if the presence of two specialties in a clinic is judged to be equivalent to an MDT then overall compliance rises to 64%.

Clinic assessment

Most adult patients (1,262/1,271, 99%) and all 53 paediatric cases were assessed by face-to-face clinic visits. Some larger centres offered additional remote diagnostic interpretation and triaging of cases. Two larger adult centres reported additional initial laboratory interpretative investigation of acute reactions for 203 patients, some of whom may have subsequently been triaged to face-to-face clinic visits (information not available).

Database

Sixty-four per cent of all centres reported keeping a database of anaesthetic adverse reaction cases: thirteen larger adult centres (62%), eight smaller adult centres (67%) and seven paediatric centres (64%).

Referral pathways

All but one clinic reported that they accept consultant-to-consultant referrals to enable rapid and direct assessment.

Investigations

Considerable variation in practice was revealed both in the repertoire and testing modalities across the survey centres. Centres should be able to investigate all potential culprits in line with the standards above.

Pholcodine testing

Six larger adult centres, one smaller centre and one paediatric centre routinely query pholcodine exposure (8/44, 18%). There is no specific standard for testing against pholcodine, but it would be expected to be part of an expert centre's repertoire.

Chlorhexidine testing

Fifty-seven per cent (25/44) of centres reported testing for chlorhexidine in all cases. A further 16 (36%) reported testing only those with known exposure. Thus, 93% were compliant with the guidance for being able to assess this antiseptic. Compliance is summarised in Figure 2.

Fourteen (67%) larger adult centres routinely tested for chlorhexidine and seven in selected cases only. Six smaller (50%) adult centres routinely tested for chlorhexidine and four in selected cases only. Five (45%) paediatric centres routinely tested and five only in selected cases.

Reported testing protocols (Figure 4) varied. Skin prick testing (SPT) was the most common first-line test (26/44) followed by serum specific immunoglobulin E (sIgE) (9/44), with intradermal testing (IDT) or sIgE commonly used for second-line testing in adults (IDT was rarely used in children). One centre reported performing chlorhexidine challenges. Nine centres reported the use of chlorhexidine sIgE blood tests as a first-line test (seven of which would then do SPT as a second-line test). Only one larger adult clinic used IDT as a first-line test (with sIgE test as a second-line test).

Latex

Twenty-three adult centres (14 larger; nine smaller, 70% overall) reported always testing for latex, and nine more in selected cases. SPT was the preferred first test for 20 (16 larger,; four smaller) and sIgE for five (three larger; two smaller) centres. Secondary testing was predominantly sIgE (eight centres) and IDT (three centres). Only larger adult centres used IDT for latex. Compliance is summarised in Figure 2.

Figure 4. Testing sequence for chlorhexidine
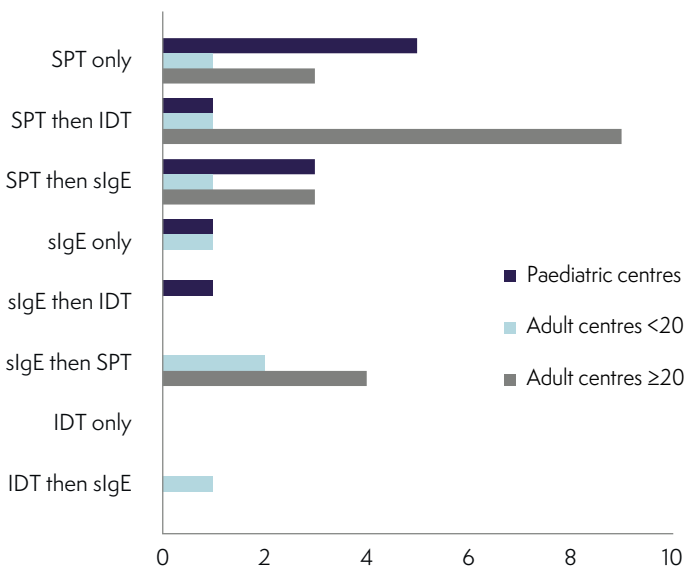
Nine of eleven paediatric centres reported that they always test for latex and two in selected cases. Ten reported using SPT as first line testing, six reported using sIgE as a second line test and none reported using IDT. Five apparently only use a single modality of testing (four SPT, one sIgE) (Figure 5).

Figure 5. Testing sequence for latex
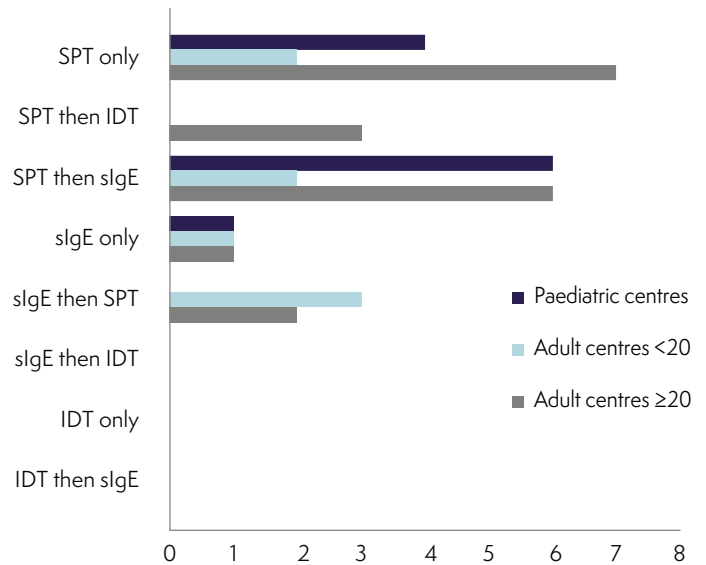
Neuromuscular blocking agents (NMBA)

Panel testing and safe identification of alternative NMBA

Practice was highly variable. Compliance is summarised in Figure 2 and Table 1.

Table 1. Comprehensive panels of NMBA are not used in all centres *Any use of an NMBA Panel initially or sequentially. Two additional centres said that cisatracurium would be tested but only where it had been administered at time of the reaction. **Panel including suxamethonium, rocuronium and either atracurium or cisatracurium as defined by NAP6 (see Methods)

Panels which include this drug(s) routinely	Larger adult centres ≥20 n=21 (%)	Smaller adult centres <20 n=12 (%)	Paediatric centres n=11 (%)
Compliant with BSACI NMBA panel*	**13 (62%)**	**5 (43%)**	**2 (18%)**
Compliant with NAP6 minimum NMBA panel**	**9 (43%)**	**5 (43%)**	**2 (18%)**
Atracurium	15 (71%)	10 (83%)	6 (54%)
Cisatracurium*	12 (57%)	5 (42%)	2 (18%)
Mivacurium	10 (48%)	7 (58%)	4 (36%)
Pancuronium	10 (48%)	5 (42%)	3 (27%)
Suxamethonium	14 (67%)	8 (83%)	5 (46%)
Vecuronium	14 (67%)	9 (75%)	5 (46%)
Rocuronium	9 (43%)	4 (33%)	3 (27%)

Adult centres

Most adult centres (32/33) reported using a 'panel' of agents containing many of the routinely available drugs when testing for NMBA allergy (Table 1), but the majority would only do so where the suspected NMBA was positive in initial skin testing. There is no definition of an appropriate panel in existing guidance, but the NAP6 panel agreed a harmonised NAP6 minimum NMBA panel definition to meet the requirement of safe identification of alternative agents (see methods).

Compliance is summarised in Figure 2 and Table 1. Most adult centres initially test to the suspected culprit agent only, and all reported use of a panel of NMBAs, however one specifically would only test to a couple of alternatives rather than the full panel or the NAP6 minimum panel. A small number of larger centres reported that they routinely test extended NMBA panels in all, but most appeared to only use the panel where one of the suspected culprits was positive on initial screening.

Paediatric centres

Five of eleven paediatric centres initially test to the suspected culprit agent only, while six reported use of a limited panel of NMBAs sequentially, of which only two included rocuronium and suxamethonium routinely. However, all would only proceed to use the panel where the initial test was positive, and one centre specifically stated that NMBA was rarely tested in children. Compliance is summarised in Figure 2a.

Suxamethonium was routinely used in panels by five paediatric centres, but another commented that suxamethonium is rarely used in children and is therefore rarely part of the panel (Table 1).

Testing strategies appeared consistent for NMBAs, with most reporting use of SPT first and then IDT if negative; two specified SPT only (Figure 6). Several centres noted the need to minimise distressing IDT testing in children. Few centres used sIgE to thiocholine, suxamethonium, and quaternary ammonium groups. One centre reported using sIgE followed by sequential SPT and IDT.

Drug challenges

No centre performed challenges to NMBAs. Twenty-five of 44 (57%) centres perform challenges to anti-emetics, eleven (25%) to hypnotics, 24 (55%) to anxiolytics, 34 (77%) to NSAIDs, 29 (66%) to opioids, and 41 (93%) to local anaesthetics.

Other challenges on offer include: heparin, latex, chlorhexidine, and paracetamol.

All paediatric centres offered NSAID and local anaesthetic challenges.

Antibiotic challenges

Forty centres (91%) provide antibiotic challenges (20/21 larger adults centres, 8/12 smaller centres, 11/11 paediatric centres).

Waiting times for antibiotic challenges were reported to be under nine weeks for 21/44 (48%), more than three months in 12/43 (28%) of centres and were similar in all types of centre (Figure 7).

Figure 6. Testing sequence for NMBAs
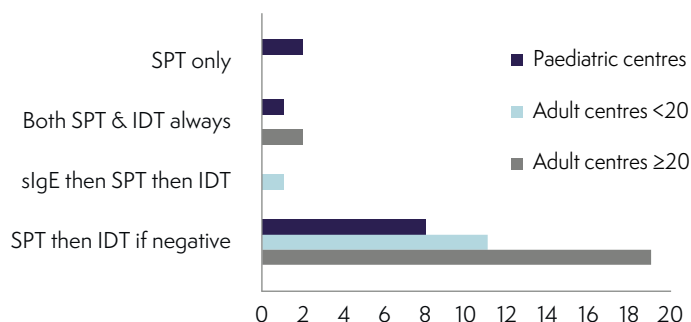
Information

Adherence to relevant guidelines is shown in Figure 2a.

Only half of adult centres give immediate information to the patient (10/21 larger, 5/12 smaller and 3/11 paediatric centres). All centres, however, stated that the patient receives a copy of the clinic letter. Only five of 44 centres (11%) reported giving additional information on patient support groups (two smaller adult centres and three larger ones).

Thirty-nine (89%) centres (19/21 larger adult, 11/12 smaller adult, 9/11 paediatric) issued Medical alert/hazard warning information to the patient.

All adult and paediatric centres sent a clinic letter to the referring clinician, and all also sent this to the general practitioner.

Copy letters to the surgeon where applicable (Figure 2a) were sent by 36 (82%) centres (18/21 larger, 10/11 smaller, 8/11 paediatric centres).

All centres reported that the clinic letter identified the culprit drug when found and all but one identified the nature of the reaction (Figure 2a and 2b). Two (5%) centres did not routinely describe the clinical features of the reaction or the clinical tests performed in the clinic letters (Figure 2b).

All adult clinic centres reported identifying the drugs or drug groups to avoid and suitable alternatives.

Only six centres reported that they provide details of the alternative diagnosis where IgE-mediated allergy was excluded (Figure 2b).

Medicines and Healthcare products Regulatory Agency (MHRA) reporting

Eleven (25%) centres overall (5/21 larger adult, 3/12 smaller adult and 3/11 paediatric) reported directly to MHRA, the rest relying on the referring clinician to do this (Figure 2c).

Discussion

This is the first UK survey of specialist allergy centres evaluating perioperative anaphylaxis and provides important information on the availability and self-reported practice in these services, prior to NAP6 case data collection. Where possible, practice has been mapped to UK recommendations (Ewan 2010, Harper 2009, NICE 2014). Most activity occurred in adult centres, but we do not know if this reflects differences in adult or paediatric referral patterns or incidence of anaphylaxis or surgery. Future analysis of cases reported to NAP6 will provide data on this.

Figure 7. Waiting times for antibiotic challenge
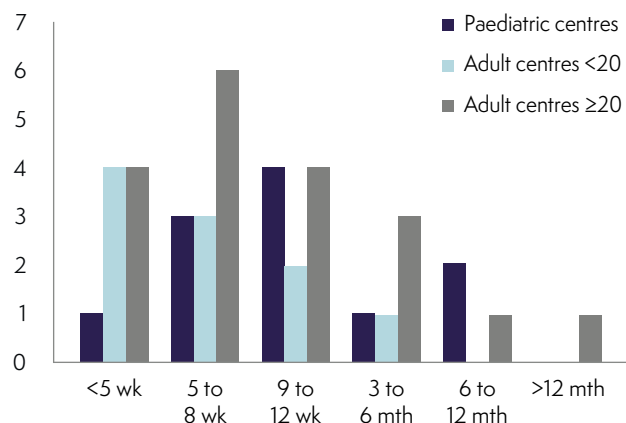
Forty-four widely distributed UK centres (33 adult and 11 paediatric) were identified, of which 21 saw more than 20 adult patients per year, but paediatric services were small and inequitably distributed. Two smaller adult centres subsequently ceased providing service in 2017 due to staff retirements (workload approximately 30 patients per annum) and one more may also have ceased operation. There was wide variation in the number of cases seen in each region with respect to total regional population and population density (Figure 1).

London and the Midlands have the greatest concentration of services and, in contrast to many other reports on allergy services, the urban areas of northern England appear to be well served.

Provision of services is limited in Northern Ireland, Wales, Scotland, the East of England, the South West, the South East of England and the West Midlands. Scotland has three adult centres and Wales and Northern Ireland only one each. Wales and Scotland appear to have only one paediatric centre and Northern Ireland none. No services submitted paediatric returns from the South West or East of England.

Paediatric centres and a few larger adult centres reported the greatest problems with access waiting times, and therefore the relationship of staffing and resources appropriate to the workload may need to be explored further. Two thirds of children had to wait more than twelve weeks to be seen, while more than half of adults waited more than eight weeks to be seen, which may impact on test sensitivity. Drug sensitisation to chlorhexidine is known to be transient (Opstrup 2016), so these delays in assessment run the risk of missing important sensitisations and compromising the diagnostic algorithm.

Access to drug challenge services was also poor, with fewer than half the centres able to challenge to antibiotics within eight weeks.

Both BSACI and AAGBI guidance strongly recommend a sufficient workload to maintain expertise and 20 cases was designated by our NAP6 panel to be a reasonable minimum to achieve this (Ewan 2010, Harper 2009). Future guidelines should agree a definition of the minimum workload. Our pragmatic definition enabled a review of compliance with recommendations by workload. Only one third of centres see more than 50 patients each year. No paediatric service saw more than ten cases in a year. Of note, we found no clear evidence that self-reported compliance with published

guidance varied markedly between adult centres with larger and smaller workload except for the less frequent use of extended NMBA panels, or between adult and paediatric centres, with the exception of the provision of more limited range of testing in smaller centres and the fact that testing is limited in children to minimise painful investigations like IDT, as well as the perception that NMBA allergy is rare in children. NAP6 minumum NMBA panel use is the exception rather than the rule. Separate paediatric guidance may be needed in future, since most centres would therefore not be adherent to the suggested NAP6 minimum NMBA panel.

The NHS England National Specialist Service Definitions for allergy (B09 and E09) mandate hub and spoke networking, accreditation and working to NICE, BSACI, RCPCH and AAGBI guidance. Smaller clinics and all paediatric clinics might benefit from being part of these governance networks where this is not already the case.

As almost two thirds of centres already keep a record of their cases in a spreadsheet or database (a requirement of the Specialist Allergy Service Specifications), this provides the opportunity to support research in allergy. A minimum dataset could usefully be defined by professional societies. Improved coordination of data collected would offer the opportunity of improved research in specialist allergy.

Adherence to guidelines for testing modalities appears good overall in adults and most services appeared comprehensive in repertoire, consistent with current recommendations. However, there was room for harmonisation of approach to NMBA, latex and chlorhexidine testing, and better patient information. The current guidelines are not very specific regarding minimal acceptable test repertoire and the authors analysed several additional requirements (NAP6 minimum NMBA panel and routinely testing for chlorhexidine) specifically to enable robust evaluation. Future iterations of guidelines should consider being more specific to advance harmonisation of practice.

The purpose of perioperative drug allergy testing is to identify the culprit drug, plus any cross-reacting drugs to which the patient may also be allergic, thereby to identify safe drugs, particularly when several drugs were co-administered. This should enable the centre to provide a list of drugs to avoid, a list of safe alternatives and a list of drugs that have been excluded as the cause of the allergic reaction. Not all centres used harmonised protocols for NMBA and routine testing for chlorhexidine and latex, but paediatric centres may have some valid reasons for differences.

We noted marked variability in the adequacy of the NMBA panels used (Ewan 2010, Harper 2009, NICE 2014) when judged against the NAP6 minimum NMBA panel suggestions and this may raise concerns about adequacy of testing – especially the identification of safe alternative NMBAs for rapid sequence induction of anaesthesia. Most centres reported they would only test an extended panel if the putative culprit was positive, consistent with current guidance, but this may create a risk of failure to identify NMBA allergy through false negative testing should all other culprits be negative, or if the clinical picture was highly suspicious for NMBA allergy. It was not clear if all would proceed to panel testing if the original suspected culprit was negative, but several centres specifically commented that they would do so in those circumstances.

Half of the centres apparently omitted some common drugs (particularly cisatracurium and suxamethonium). This could be a risk to patients, since not testing prevents detection of relevant sensitisations or cross-reactivity to select safe alternatives, or restricts future anaesthetic options for rapid sequence induction. Practice in children may however be different for practical reasons, and separate guidance may be needed.

It is likely that specific guidance on this matter would be of benefit in future for adults too. The NAP6 panel developed a minimum NMBA panel that met the requirements of safe future anaesthesia in all circumstances. Only 20 to 43% of centres met the NAP6 minimum NMBA panel definition. This panel could be considered for future adoption (potential culprit, an NMBA from a different class, and two agents with specific utility: rocuronium and suxamethonium). Auditing and understanding the best diagnostic algorithm will require harmonised practice in future.

Communication with colleagues appears generally good. Communication with patients may be less good. Most centres reported that they were fully compliant with the recommendations of NICE CG183 regarding specific written information, however supply of immediate information to patients, written information to patients and information on patient support groups was incomplete on their returns (Figure 2b).

Reporting of allergy testing results to the MHRA by clinics is rare and this is usually deferred to the anaesthetist (Figure 2c).

While MDT working is not in guidelines it is a national specialist commissioning standard. Only half of the services had a face-to-face MDT to discuss cases. Of concern, anaesthetists were involved in fewer than half of the specialist centres and very rarely in paediatric clinics. Three adult services were led by anaesthetists. Anaesthetists have a key role in detecting non-allergic causes for the clinical presentations, understanding the normal adverse event profile of the drugs given, the confounding effects of polypharmacy and patient co-morbidity, advising on suitable future strategies for anaesthesia and ensuring that all likely causes have been considered (Harper 2009). More anaesthetists with an interest in allergy are needed to promote learning and enhance service quality. Networking arrangements could be used to ensure anaesthetist involvement in MDT case discussions.

The staffing of clinic services was very variable and may not meet specialist service recommendations and guidance. Specialist nurses with allergy experience were missing in 36–50% of clinics. Pharmacist involvement in preparation of drug dilutions for skin tests or challenges was very infrequent, but would be desirable.

Diagnostic testing practice must be harmonised. Definitive and translatable predictive values for any testing strategy or sequence remain unknown. Skin prick testing remains the initial test of choice for most centres, but follow-up testing and the indications to do so are variable. Intradermal testing appears to be under-used in comparison to international recommendations overall (Ewan 2010, Opstrup 2014, Simon 2014) and this was particularly so in paediatric centres.

Chlorhexidine appeared to be under-investigated and not part of routine testing in many centres, in spite of its ubiquitous (and at times unrecognised) presence in the perioperative environment. Despite many publications and a suspicion of increasing prevalence of this potentially hidden allergen, many centres did not screen routinely, although all claimed to assess potential exposures. No guideline explicitly states that chlorhexidine testing is mandatory in the investigation of perioperative anaphylaxis, but the variability in testing and the ubiquity of chlorhexidine make this worthy of consideration. In contrast, latex allergy may be becoming less prevalent, yet is still routinely included by most.

From a patient's and clinician's perspective, variability of care is a concern. Our patient representative authors were concerned about low-volume services that rarely see this type of event, or services that do not have harmonised protocols in place for testing of culprit agents and safe alternatives.

It was reassuring that no major differences were noted that obviously correlated with service size other than breadth of NMBA panel and fewer MDT discussions. However, this survey did not evaluate differences in the diagnostic accuracy or quality of advice provided by centres, more data on this will be available through NAP6 data analysis. Therefore, the recommendations regarding hub and spoke networking to improve harmonisation and quality assurance merit consideration. As recommended in NICE CG183 (NICE 2014), it was noted that consultant-to-consultant referrals remain an important source of referral.

This survey provides an important snapshot of UK provision and practice in perioperative allergy testing before the main phases of NAP6.

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The Survey Questions

Q1 Please enter the full name of the hospital Trust where the allergy clinic is situated:

Q2 Please enter the postcode of your Trust:

Q3 Please enter the email address of the person completing the Survey:

Q4 How many cases of suspected perioperative anaphylaxis has your clinic investigated in the past 12 months?

Q5 Is this figure: Estimate or Actual?

Q6 How many cases do you see by each of the methods below?

Please provide the number of cases for each method in the past 12 months:

- Face to face clinic appointment
- Laboratory investigation only
- Other - please specify the method and number of cases

Q7 Is this figure: Estimate or Actual?

Q8 What is the current perioperative allergy clinic waiting time for:

- for CHILDREN
- An URGENT clinic
- A ROUTINE clinic
- for ADULTS
- An URGENT clinic
- A ROUTINE clinic
- Choices
- <5 weeks
- 5-8 weeks
- 9-12 weeks
- 13-18 weeks
- 18 weeks
- N/A (laboratory only service)

Q9 How is your perioperative allergy clinic normally staffed and supported? Please include all staff who are routinely involved in the clinic. Please tick all options that apply:

- Allergist or immunologist in clinic
- Anaesthetist with drug allergy experience in clinic
- Anaesthetist without specific drug allergy experience in clinic
- Nurse with drug allergy experience in clinic
- Pharmacy drug preparation for clinic
- Face to face multidisciplinary team meeting pre/post clinic
- Telephone multidisciplinary team meeting pre/during/post clinic
- Other (please specify)

Q10 Do you have a spreadsheet or database of the cases seen in your suspected perioperative allergy clinic?

- Yes or No

Q11 Do you routinely ask about exposure to pholcodine?

- Yes or No

Q12 Which of these are tested as part of your routine panel for perioperative allergy?

- Chlorhexidine
- Latex
- Other

Frequency?

- Never
- Always
- Selected cases

Initial test

- Skin Prick Test
- Intradermal Skin Test
- Allergen Specific IgE
- N/A

Subsequent test

- Skin Prick Test
- Intradermal Skin Test
- Allergen Specific IgE
- N/A

Q13 When investigating Neuromuscular Blockade (NMB) anaphylaxis, what is your testing pathway?

- Skin Prick Test only
- Intradermal Skin Test only
- Skin prick Test first and Intradermal Skin Test if negative
- Both Skin Prick Test and Intradermal Skin Test, regardless of either result
- Other (please specify)

Q14 Do you test for the suspected culprit only or alternatively a panel of NMBs?

- Culprit (if you select this option please progress to Q16 - please skip Q15)
- Panel (if you select this option please complete Q15 onwards)

Q15 Which of the following drugs are in your panel?
Please tick all that apply:

- Atracurium
- Cistatracurium
- Mivacurium
- Pancuronium
- Suxamethonium
- Vecuronium
- Other (please specify)

Q16 Do you provide a challenge testing service for the following?
Please tick all that apply:

- Antibiotic
- Antiemetic
- Hypnotic (excluding benzodiazepines)
- Anxiolytic
- Muscle relaxants
- NSAID
- Opioids
- Local anaesthetic
- Other

Q17 If an antibiotic is suspected and initial tests are negative, what is the average additional time to complete the challenge testing?

- Less than 5 weeks
- 5-8 weeks
- 9-12 weeks
- 3-6 months
- 6-12 months
- Greater than 12 months

Q18 What information do you provide to the PATIENT following the assessment and diagnosis of perioperative anaphylaxis? Please tick all that apply:

- Immediate written information
- Information regarding patient support groups
- Clinic letter
- Written information as per NICE guidance (NICE GC183 – https://www.nice.org.uk/guidance/cg183)
- Medical alert application
- Other (please specify)

Q19 What information do you provide to REFERRERS/OTHERS following the assessment and diagnosis of perioperative anaphylaxis? Please tick all that apply:

- Clinic letter to referrer
- Clinic letter to GP
- Clinic letter to Surgeon (if applicable)
- Other (please specify)

Q20 What information do you include in the clinic letter/ documentation to the referrer and patient? Please tick all that apply:

- Name of culprit agent
- Nature of reaction (allergic versus non-allergic)
- Clinical features of reaction
- Details of tests performed
- Drugs/groups to avoid
- Suitable/safer alternatives
- Details if allergy excluded
- Other (please specify)

Q21 Reporting to the MHRA – who does this?

- Us – the suspected perioperative anaphylaxis clinic
- The referrer/anaesthetist – we remind them to do it
- Not us – we leave this at the discretion of the referrer/ anaesthetist involved at the event

Q22 Do you accept consultant to consultant referrals for perioperative anaphylaxis?

- Yes
- No, referral must come from GP

William Egner

Key findings

- 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. Twenty-three per cent 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 sampes met BSACI guidance for 'immediate' sampling, and 76% met ANZAAG 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 x1.2) +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 culprit agents and poor communication.

- All potential culprit agents had been adequately investigated in only 27% of cases.

- Ten per cent of assessments were judged as good, 49% good and poor, 41% poor.

- Despite limitations of testing in 88% of cases the same trigger was identified by the clinic and the panel.

- Seventy-four percent of triggers were correctly predicted by the anaesthetist.

- NAP6 shows that adherence to existing guidelines is poor and confirms 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 culprits 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 communication of results: to anaesthetists, general practitioners and patients.

Introduction

The 2016 NAP6 allergy baseline survey showed that UK specialist perioperative allergy clinics are few and distributed unequally (Egner 2017a and Chapter 13). It also recorded self-reported clinical activity and perceived adherence to national guidance from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (Harper 2009), the British Society for Allergy and Clinical Immunology (BSACI) guideline on investigation of anaphylaxis during general anaesthesia (Ewan 2010) and the National Institute for Health and Care Excellence CG183 'Drug allergy: diagnosis and management of drug allergy in adults, children and young people' (NICE 2014).

We examined all cases reported to NAP6 and performed either a full (184 cases) or short (82 cases) review of care (Chapter 5). This included classifying the nature of the reported reaction, identifying the trigger agent where possible and assessing the completeness and quality of allergy clinic investigation, judged both against prevailing standards and with the performance claimed in the NAP6 baseline survey.

What we already know

Tryptase release is seen in most but not all cases of perioperative anaphylaxis, most commonly in the higher grades of reaction (Grade 3–5) (Scolaro 2017, Egner 2016, Low 2016, Mertes 2003, Mertes 2011, Sprung 2015, Dybendal 2003).

There is a poor correlation between mast cell tryptase (MCT) levels and reaction grade individually but the median values are higher in more severe reactions (Egner 2016). Tryptase levels plateau between 30 and 90 minutes after the reaction (Sainte-Laudy 1998). Using the identification of a dynamic change in tryptase values may identify mediator release in more cases than using fixed thresholds of 11.4 or 14 mcg/L (ie, 95% and 99% upper limits of normal values) (Egner 2016, Baretto 2010).

Exposure to opioids like pholcodine may correlate with neuromuscular blocking agent (NMBA) anaphylaxis, because Denmark, where it is banned, rarely diagnose NMBA anaphylaxis, unlike Norway (until recently) and the UK (de Pater 2017, Brusch 2014) (See also Chapter 16, NMBAs)

Basal tryptase levels may correlate with severity of anaphylaxis in non-perioperative settings such as sting anaphylaxis (Rueff 2009).

The incidence of latex allergy is probably decreasing (Low 2016, Harper 2009, Kolawole 2017).

Rocuronium may now be a leading cause of NMBA reactions (Sadleir 2013).

Chlorhexidine and teicoplanin are increasingly identified as triggers (Low 2016, Harper 2009, Kemp 2017, Garvey 2016, Egner 2017b, Savic 2015). There is considerable variation in skin testing and no consensus on the best panel and sequence of testing.

Methods

Reports were assessed by the panel in a Bayesian-type expert consensus analysis of imputability (Agbabiaka 2008) as described in the NAP6 methods paper (Cook 2018 and Chapter 5).

Clinic assessment and referral was graded by the panel as 'good' (no deviation from guidance), 'good and poor' (minor deviation unlikely to affect diagnosis) and 'poor' (major deviation likely to affect future risk).

The non-parametric Kruskall-Wallis test was used to compare median MCT levels using the statistical package 'Analyse-IT and SPSS'. $P < 0.05$ was used to indicate statistical significance.

Numerical analysis

Number of cases

Of 504 submitted reports, 266 met inclusion criteria.

Tryptase sampling

Peak tryptases (Tp) above 14 mcg/ml were seen in 71% of cases.

Number and timing of samples

At least three MCT samples were available in 178/266 (67%) of cases, two in 51 (19%) and one in 22 (8%). In 8 (3%) samples were taken but not received/reported and 7 (3%) had no samples taken.

Eighty-one per cent of 184 reviewed cases had interpretable dynamic MCT samples (≥2 samples within 6 hours of the reaction) (Egner 2016, 2017c, Cook 2018).

First tryptase (T1)

Forty-five per cent of cases met BSACI guidance for 'immediate' sampling, 45 (17%) at <15 minutes post-reaction, 64 (28%) at 16–30 minutes. A total of 175 (76%) were taken within the hour, consistent with the ANZAAG guidelines (Figure 1). (Egner 2017a, 2017c, Kolawole 2017, Cook 2018, Ewan 2010).

Figure 1. Timing and levels of first tryptase (T1) (minutes) (number of cases)
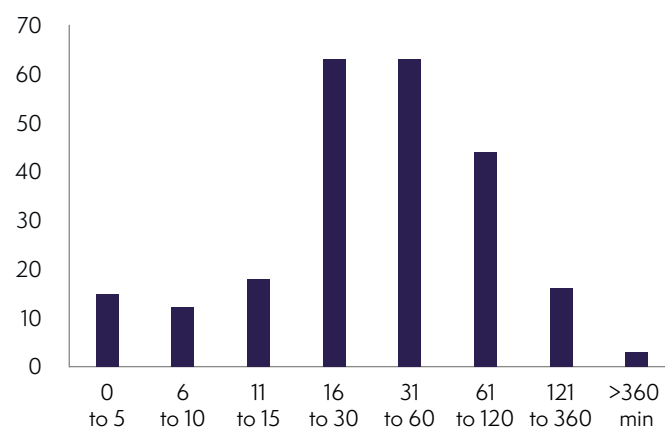
Second tryptase (T2)

Twenty-three (10%) samples were taken within 60 minutes and 74 (32%) within 120 minutes, consistent with BSACI guidance, rising to 43% within 3 hours and 71% within 6 hours.

Third tryptase (T3)

One hundred and sixty eight (73%) patients had satisfactory >24 hour baseline samples, 12% were too early, taken less than 20 hours after the event.

Tryptase levels

Basal tryptase (Tb)

Basal Tb were not significantly different in reaction Grade 3 (4.0 mcg/L) and Grade 4 (5.0 mcg/L) (Figure 2). 10% had raised basal tryptase (24 samples 15.4–54.2 mcg/L, plus one at 153 mcg/L).

Figure 2. Basal tryptase results by grade of reaction

Grade 3 reactions: Basal tryptase Median 4, 95% CI 4.3–6 mcg/L

Basal tryptase (mcg/L)
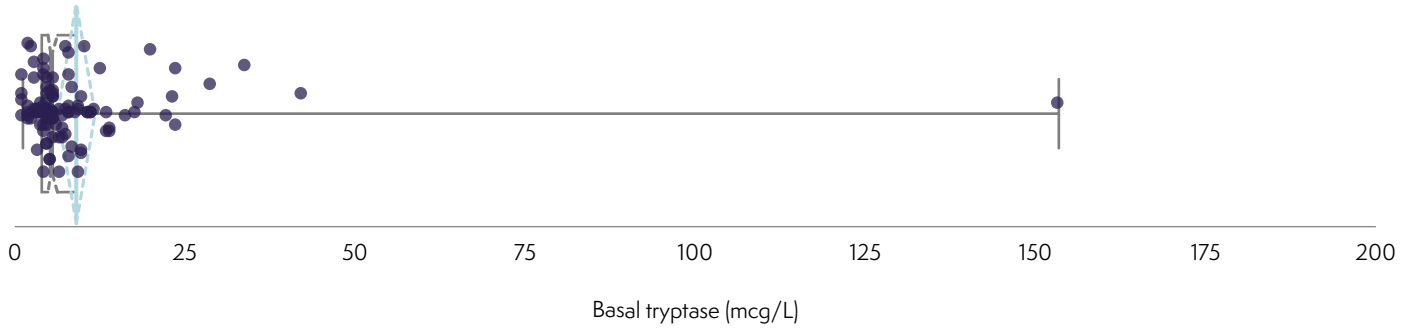
Grade 4 reactions: Basal tryptase Median 5, 95% CI 3.9–5.3 mcg/L

Basal tryptase (mcg/L)
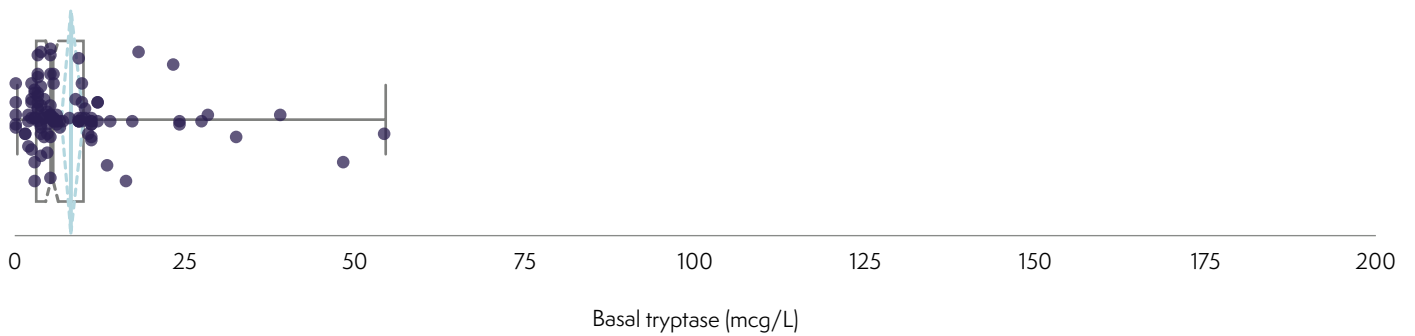
Key: Dots represent individual measurements. The black bar is the median and the box the 25th and 75th centiles.
Dotted indents represent the 95% confidence intervals of mean and median. Horizontal bar = max–minimum range.

Peak tryptase (Tp)

Tryptase values generally peaked at the first sample (T1):
T1 includes all single samples (Figure 3).

Figure 3. Timings of first (T1) and peak (Tp) tryptase samples

Peak tryptase (maximum value in series, all grades) n=229. Median 25.7 (95% CI 19–37), range 1–576

Peak tryptase Tp (mcg/L)
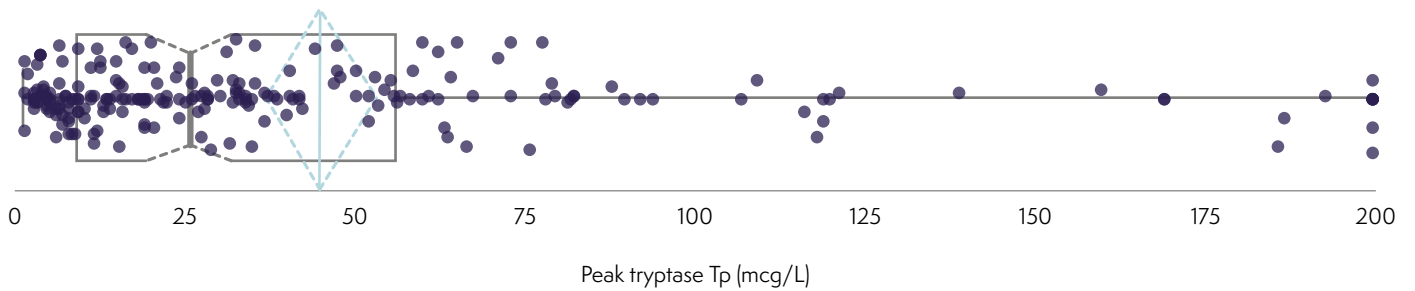
T1 tryptase (first value in series, all grades) n=245. Median 21.9 (95% CI 18–29), range 0.1–576

Tryptase T1 (mcg/L)
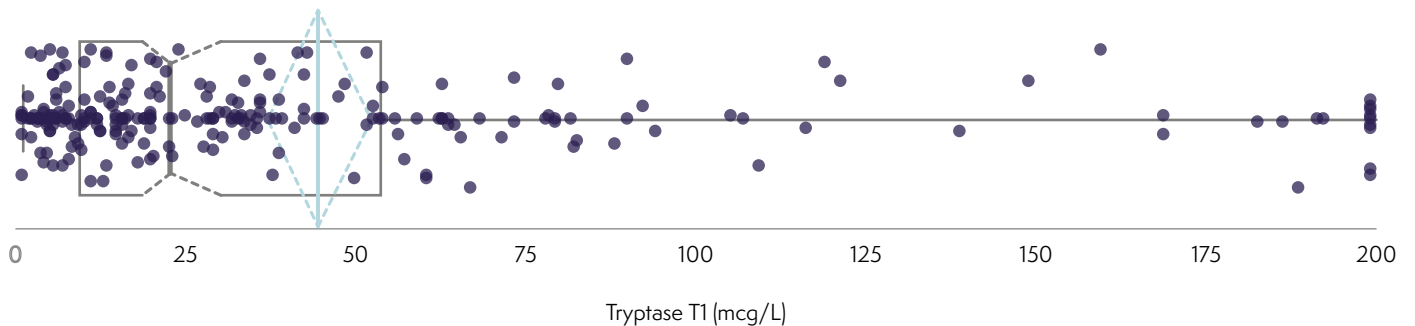
Tryptase and culprit agents

The median Tp/T1 appeared lowest for chlorhexidine and highest for suxamethonium (Figure 4, Supplementary material B). There were statistically significant differences for both T1 and Tp for both distributions and medians using Mann Whitney U test and Kruskall-Walis as follows:

- Chlorhexidine vs teicoplanin   p=0.002
- Chlorhexidine vs co-amoxiclav   p=0.04

- Chlorhexidine vs rocuronium   p=0.004
- Chlorhexidine vs suxamethonium   p=0.002.

None of the muscle relaxants were significantly different from each other although atracurium vs suxamethonium was almost significant at p=0.053.

There was no significant difference between co-amoxiclav and teicoplanin p=0.51, nor chlorhexidine and Patent Blue p=0.31, nor chlorhexidine and atracurium p=0.56.

Figure 4. Peak tryptase in cases where a single culprit was identified

Chlorhexidine

Tp tryptase peak (mcg/L)

Teicoplanin

Tp tryptase peak (mcg/L)

Co-amoxiclav

Tp tryptase peak (mcg/L)

Patent Blue

Tp tryptase peak (mcg/L)
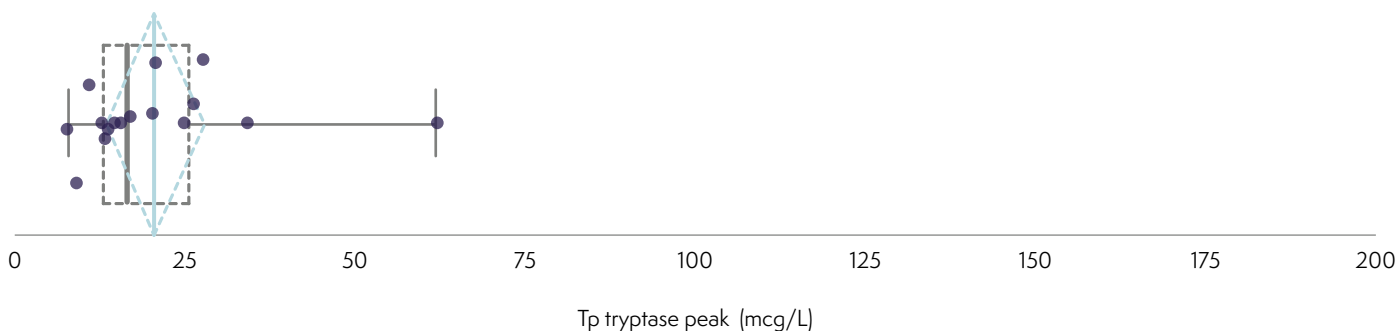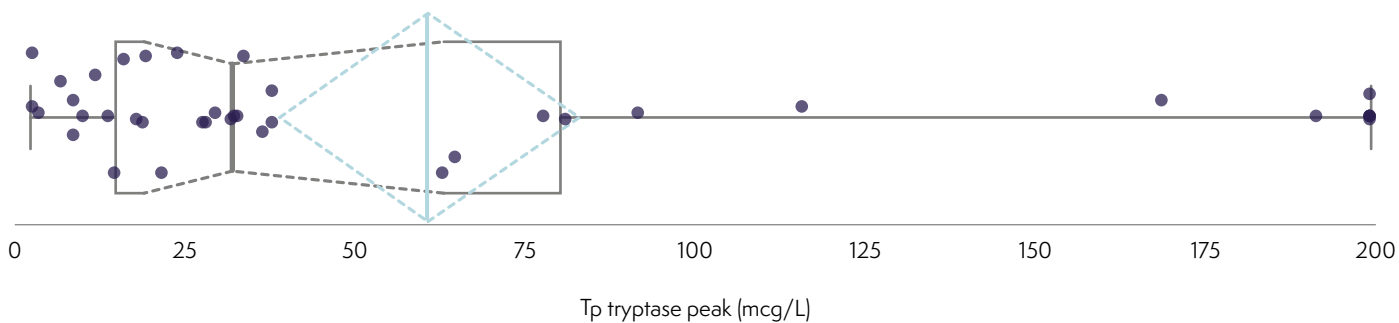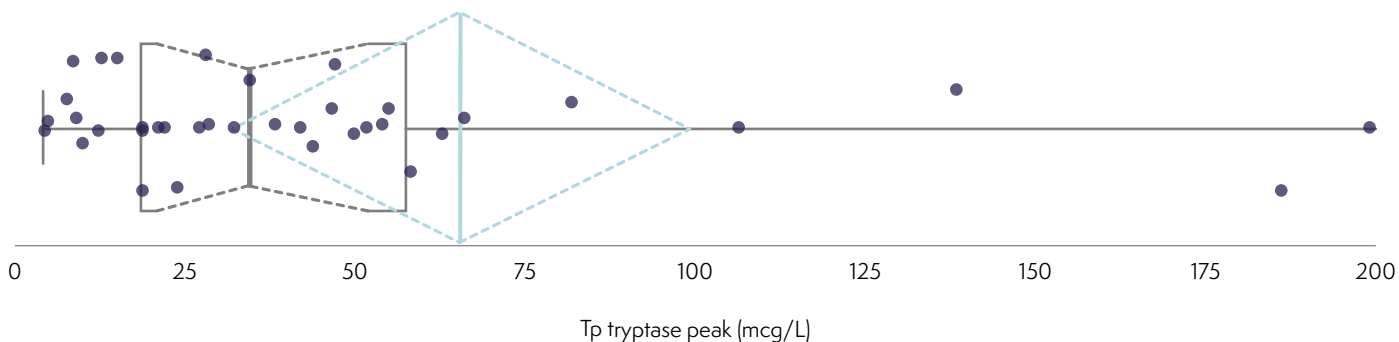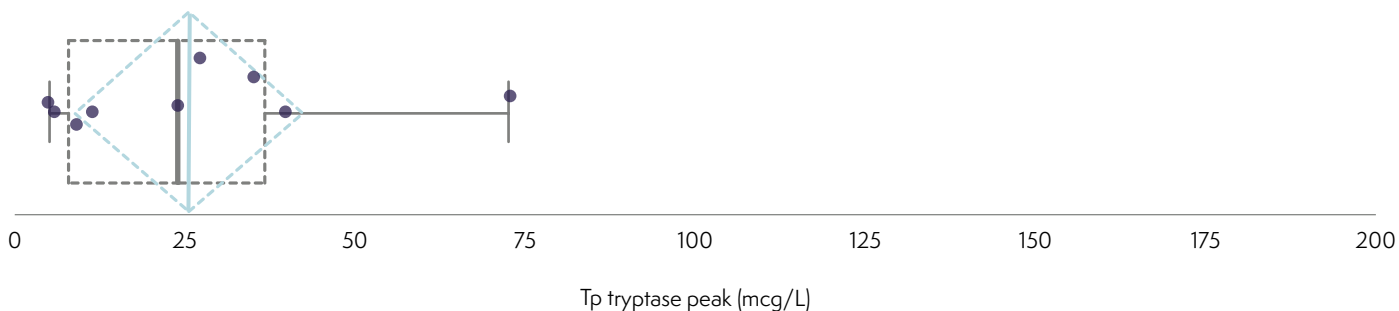
Muscle relaxants
All muscle relaxant reactions

Tryptase peak Tp (mcg/L)

Rocuronium

Tryptase peak Tp (mcg/L)

Atracurium

Tryptase peak Tp (mcg/L)

Suxamethonium

Tryptase peak Tp (mcg/L)
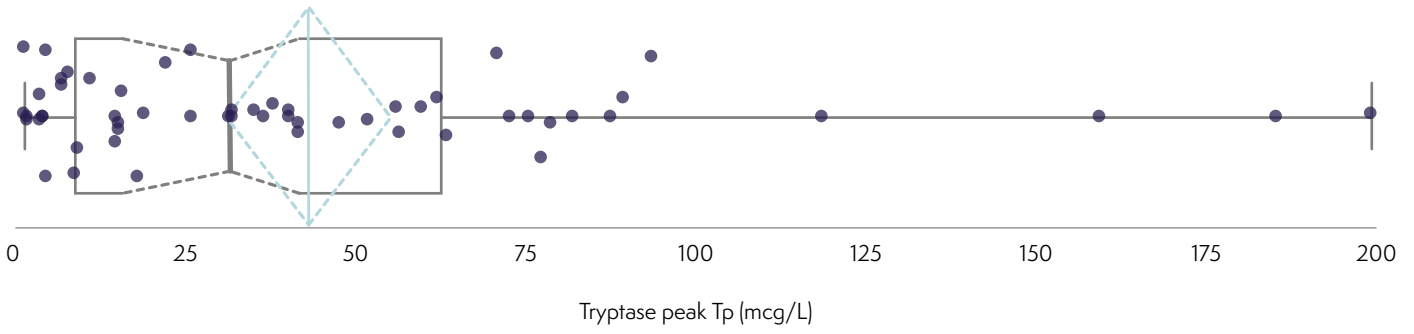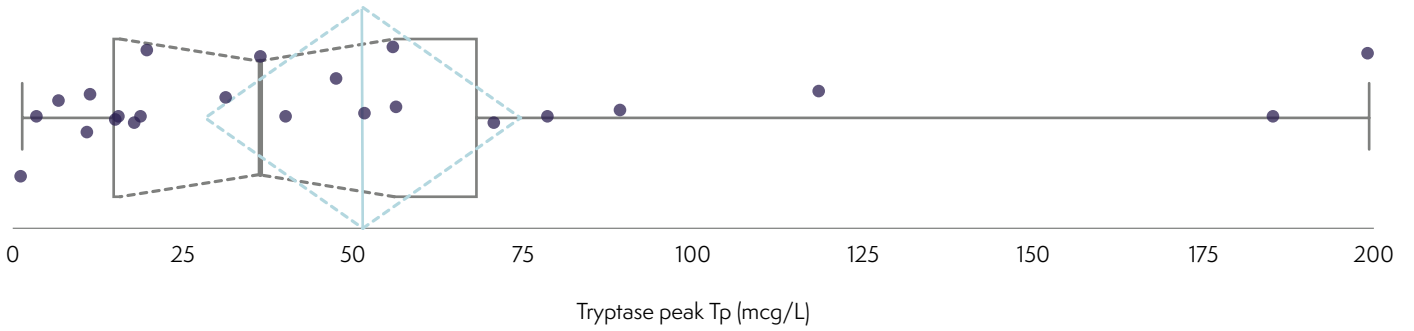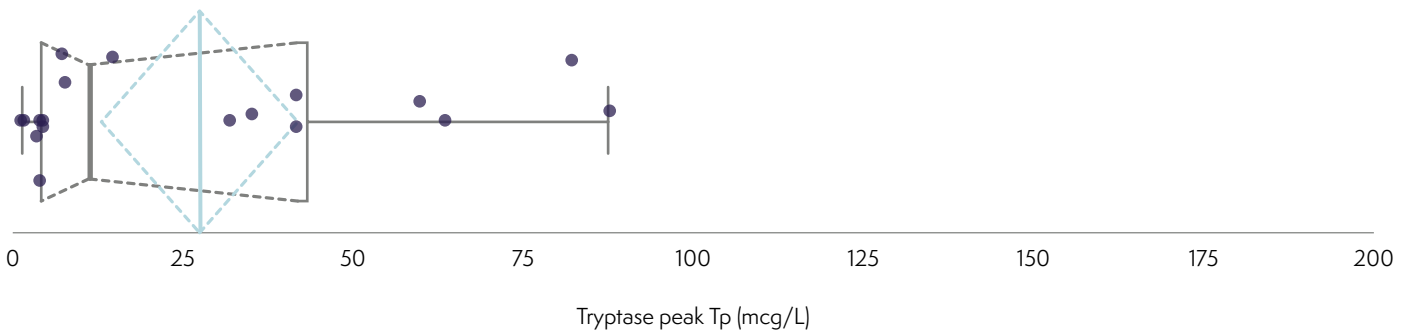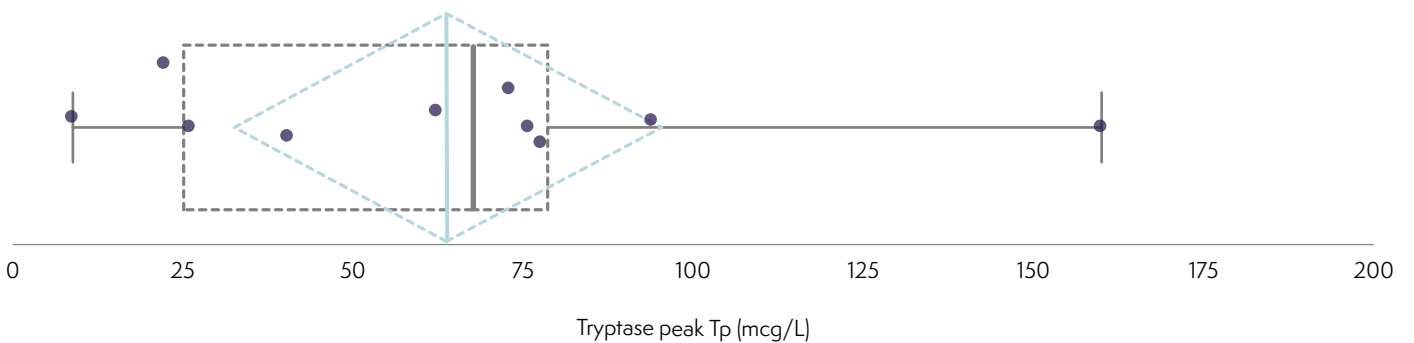
Cases with single tryptases

Twenty-three cases had single tryptases, and most (65%) were positive >=14 mcg/L (median 31, 95%CI 11-63, range 0.1-200). Nine fatalities had tryptase above 19.6 mcg/L (Figure 5).

Tryptase and speed of onset of anaphylaxis

Anaphylaxis onset was fastest (time from drug administration to presenting feature) for muscle relaxants and the antibiotics teicoplanin and co-amoxiclav, and slowest for chlorhexidine (Table 2). For antibiotics and NMBAs, speed of onset was almost universally less than 30 minutes: see also Chapter 10, Clinical features.

Table 1. Correlation between panel-identified trigger and peak tryptase (Tp) levels

Trigger	Number with Tp/ total	Grades 3:4:5	Tp median (mcg/L)	95% CI (mcg/L)
Co-amoxiclav	40/46	21:18:1	34.7	21.2-52.0
Teicoplanin	28/36	15:13:0	32.0	19-63.1
All muscle relaxants (Sux, Roc, Atrac, Miv)	49/65	24:25:0	31.9	15.7-41.9
Suxamethonium	10/13	7:3:0	67.6	22.3-93.8
Rocuronium	23/27	16:4:3	36.4	15.7-56.5
Atracurium	19/23	9:10:0	11.5	4.2-41.9
Patent Blue	8/10*	5:3:0	24.2	5.9-40
Chlorhexidine	14/18	8:6:0	16.5	13-26.2

Figure 5. Tryptase levels in cases with one tryptase measurement only
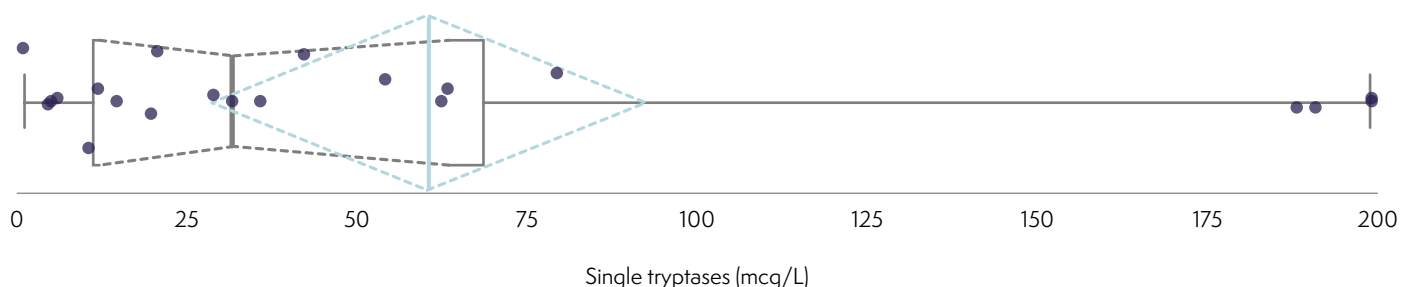
Single tryptases (mcg/L)

Tryptase and speed of onset of anaphylaxis

Anaphylaxis onset was fastest (time from drug administration to presenting feature) for muscle relaxants and the antibiotics teicoplanin and co-amoxiclav, and slowest for chlorhexidine (Table 2). For antibiotics and NMBAs, speed of onset was almost universally less than 30 minutes: see also Chapter 10, Clinical features.

Table 2. Interval between drug administration and first clinical feature

Time (mins) to onset for panel consensus trigger	Median peak tryptase (mcg/L)	0-5	6-10	11-15	16-30	31-60	61-120	>120
Co-amoxiclav	34.7	33	8	3	1	-	-	-
Teicoplanin	32.0	23	7	2	-	-	-	-
Rocuronium	36.4	25	1	-	-	-	-	-
Atracurium	11.5	14	2	3	2	-	-	1
Suxamethonium	67.6	12	1	-	-	-	-	-
Patent Blue	24.2	2	2	1	1	1	2	-
Chlorhexidine	16.5	5	3	-	3	4	-	1

Tryptase levels and severity of anaphylaxis

There was no correlation between T1 and nadir oxygen saturation, lowest recorded blood pressure, or the total dose of adrenaline given (Figure 6).

Figure 6. Tryptase levels do not correlate with severity indices

Lowest SpO$_2$ vs. T1
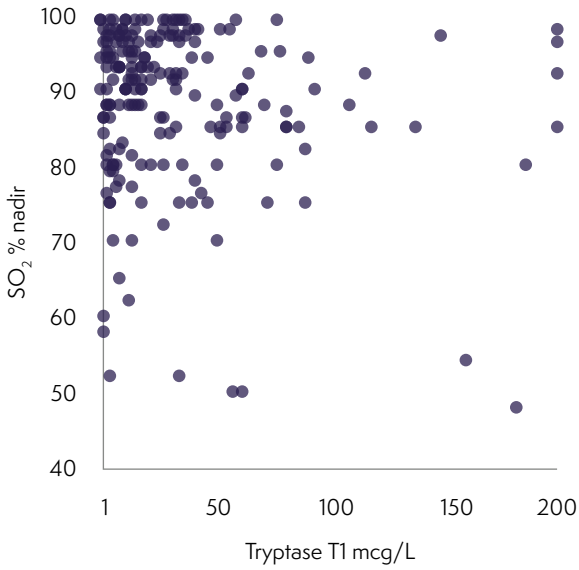
Lowest systolic blood pressure vs. T1
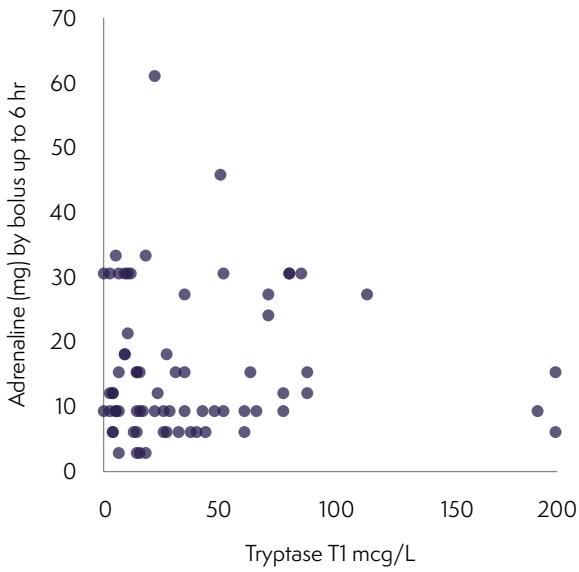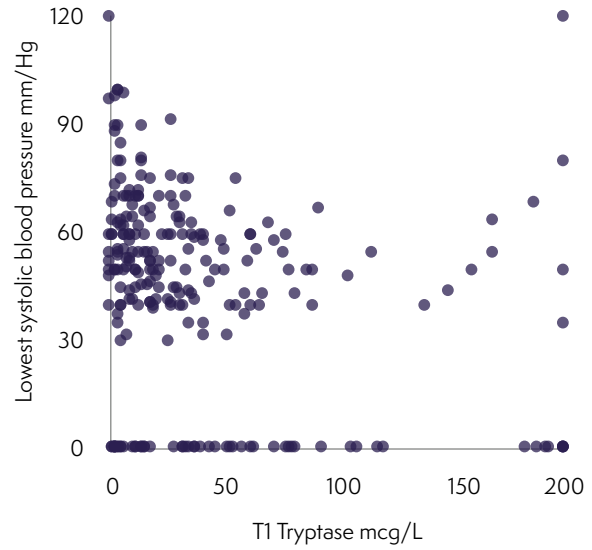
Median T1 tryptase levels rose with reaction grade (Figure 7 and Table 3), though this was less clear for peak levels (Figure 8 and Table 3) – the T1 level may be more relevant for Grade 5 cases, as only one sample is usually feasible.

Figure 7. First tryptase level (T1) and grade of anaphylaxis

All Grade 3 reactions n=125. Median 14.9 (95% CI 11.5-18.9), range 0.1-576)

Tryptase T1 (mcg/L)
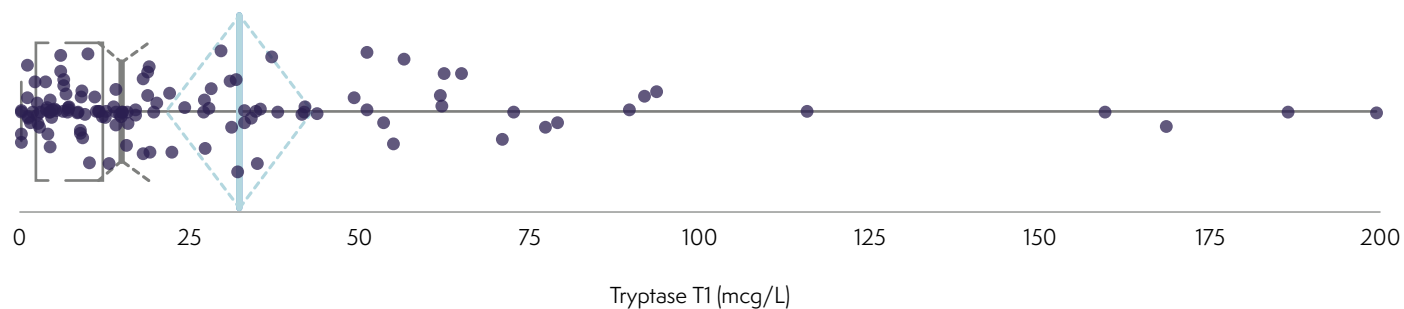
All Grade 4 reactions n=110. Median 32.8 (95% CI 22.9-40.5), range 0.1-200

Tryptase T1 (mcg/L)
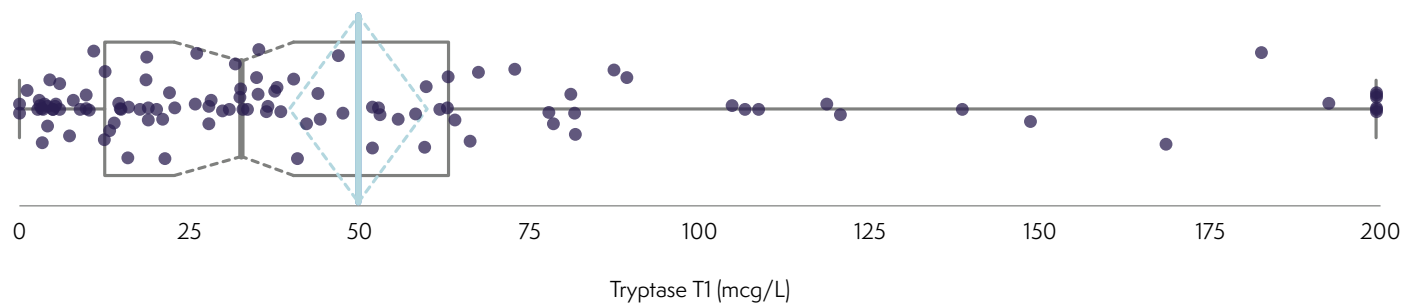
All Grade 5 reactions n=10. Median 134 (95% CI 19.8-200), range 11.6-300

Tryptase T1 (mcg/L)
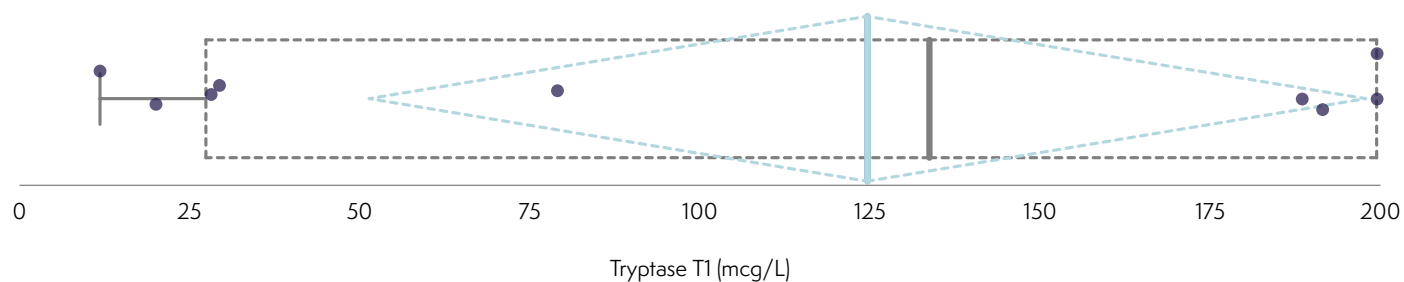
Figure 8. Peak tryptase level (Tp) and grade of anaphylaxis

Grade 3 reactions n=116. Median 17.5 (95% CI 14-25), range 1.1-576

Tryptase Peak Tp (mcg/L)
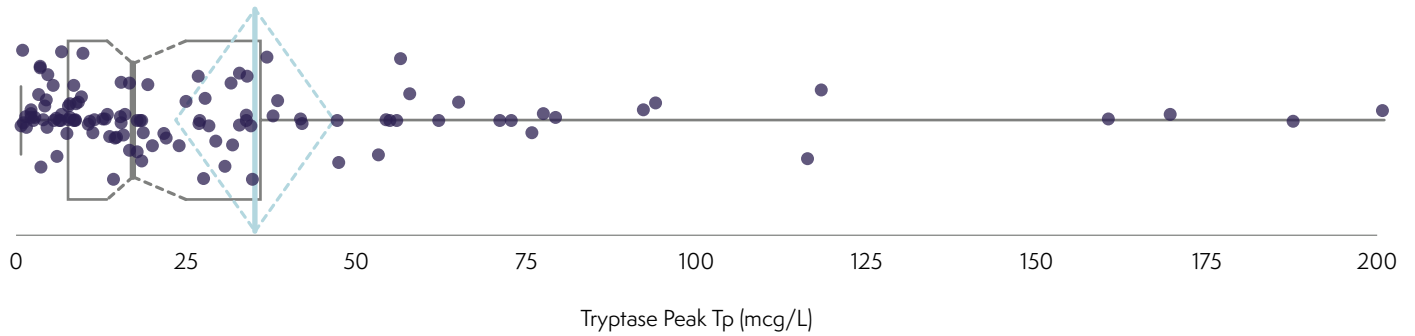
Reaction Grade 4 n=106. Median 35.3 (95% CI 26-48), Range 2.7-200

Tryptase Peak Tp (mcg/L)
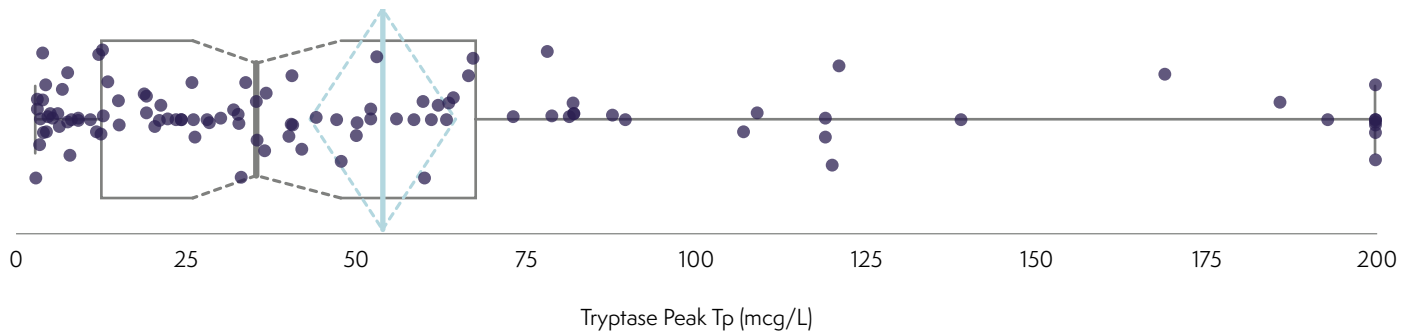
Reaction Grade 5 n=5. Median 11.6 (95% CI n/a), range 11.6-300
*Peak tryptase can only be estimated where 2 or more samples are available

Tryptase Peak Tp (mcg/L)
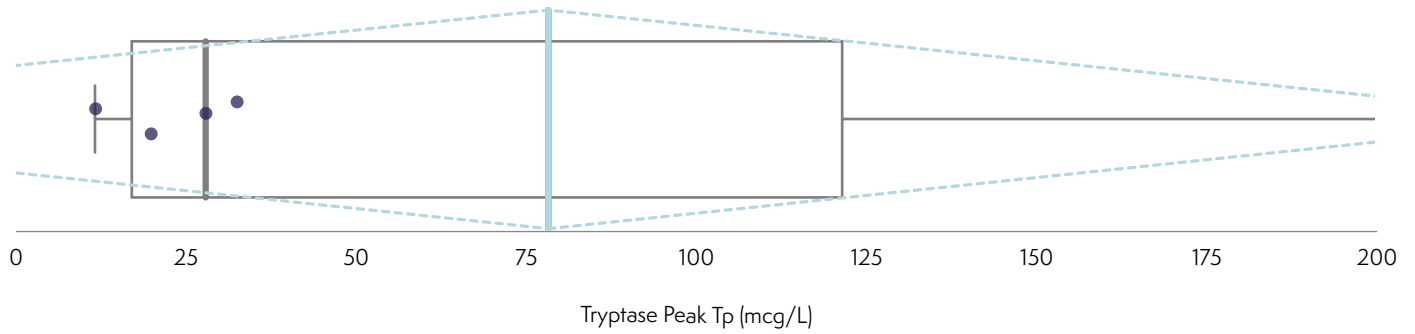
Table 3. Median tryptase values by reaction grade
*Peak tryptase can only be estimated where two or more
samples are available, hence T1 is a more accurate reflection
of levels in Grade 5

Reaction grade	Number (n)	T1 median (mcg/L)	95% CI (mcg/L)	Tp Median (mcg/L)	95% CI (mcg/L)
Grade 3	125	14.9	12-19	17.5	14-25
Grade 4	110	32.8	23-41	35.3	26-48
Grade 5	10	134*	10-200	11.6*	n/a

Speed of sampling and tryptase levels

The first tryptase sample was taken within 5 minutes of drug administration in 161 cases. Earlier samples gave higher T1 results which rapidly fell within 30 minutes and rapid onset events were associated with higher peak tryptase levels (Figure 9).

Figure 9. Timing of sampling and tryptase level

Peak tryptase in samples taken at 0–5 minutes n=46. Median 32.5 (95% CI 18.7-47.7), range 2.5-576
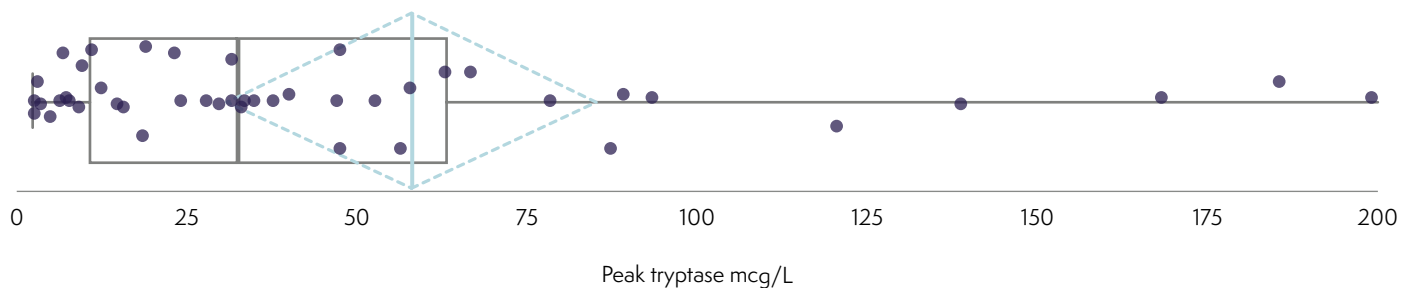
Peak tryptase mcg/L

Peak tryptase in samples taken at 6–10 minutes n=38. Median 27.5 (95% CI 12-35.3), range 1.1-187
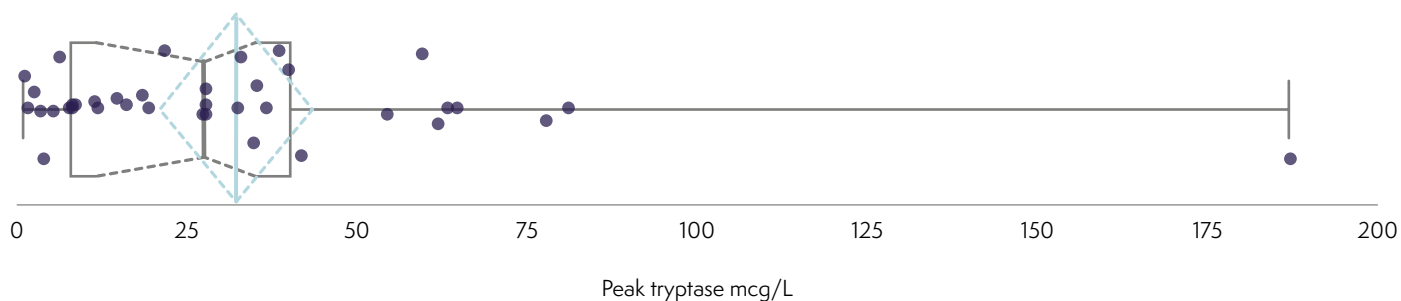
Peak tryptase mcg/L

Peak tryptase in samples taken at 11–15 minutes n=9. Median 19 (95% CI 3-60), range 1.7-41.7
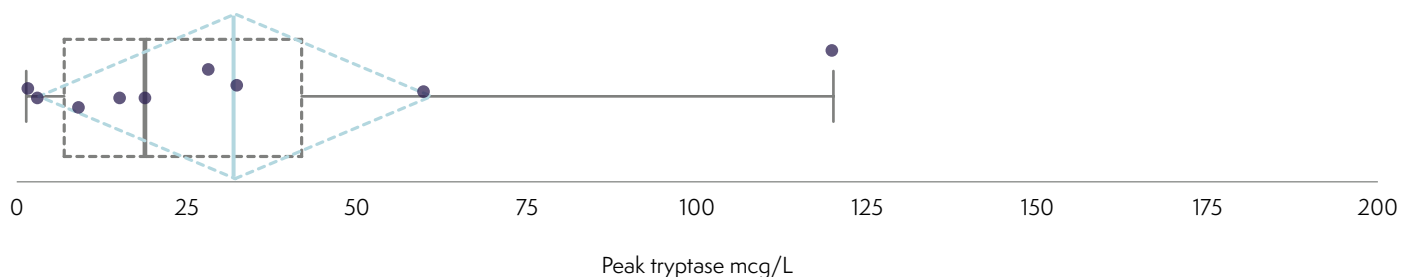
Peak tryptase mcg/L

Peak tryptase in samples taken at 16–30 minutes n=15. Median 34.1 (95% CI 10.1-64.2), range 7-81.8.
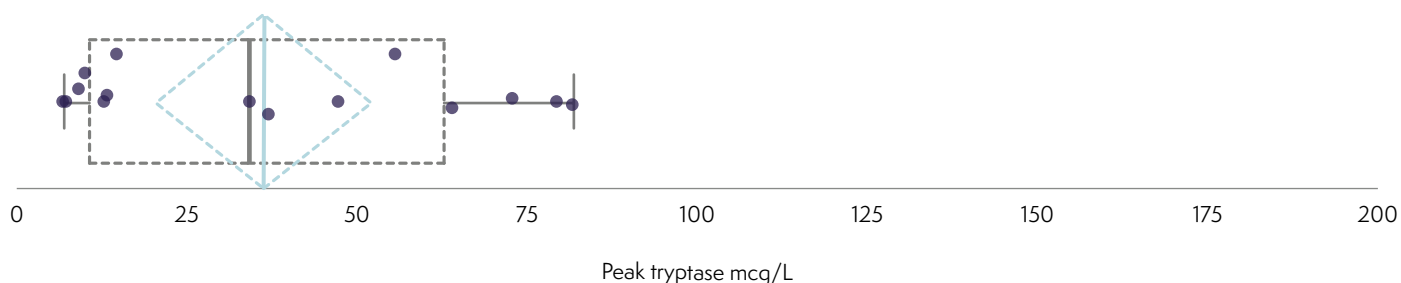
Peak tryptase mcg/L

Tryptase levels in anaphylaxis

Median T1 levels were higher in allergic anaphylaxis (Figure 10).

Eight per cent of allergic anaphylaxis reports showed no tryptase rise. Twenty per cent had a peak tryptase of <14 mcg/L though most of these showed a dynamic tryptase rise.

Figure 10. Tryptase results in panel-defined anaphylaxis with and without evidence of sensitisation to the trigger are not significantly different (p>0.05)

T1 in panel-defined Allergic Anaphylaxis (positive IgE test confirming trigger or very high probability of allergic anaphylaxis where tests not possible/not positive)* n=138 Median 34.3, 95% CI 18.8-60.0

Tryptase sample 1 (T1, mcg/L)
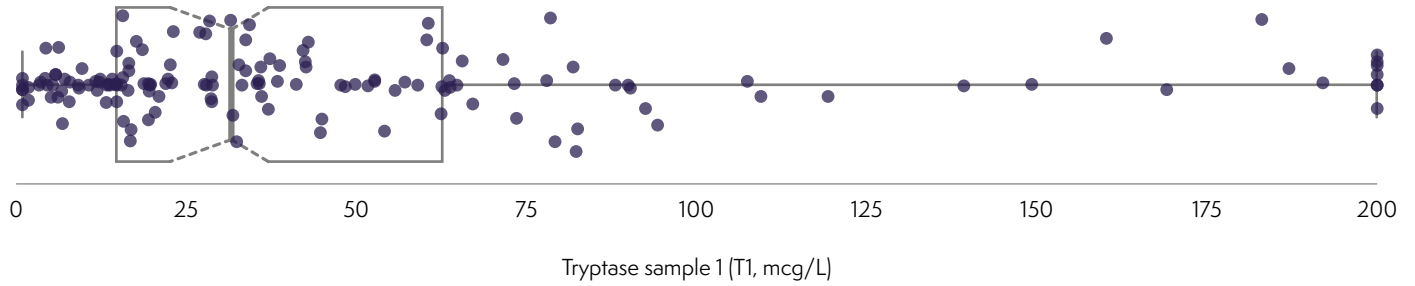
T1 in panel-defined Non-Allergic Anaphylaxis (no confirmatory positive sIgE tests to the trigger)
n=24 Median 29.4, 95% CI 14.7-79.0

Tryptase sample 1 (T1, mcg/L)
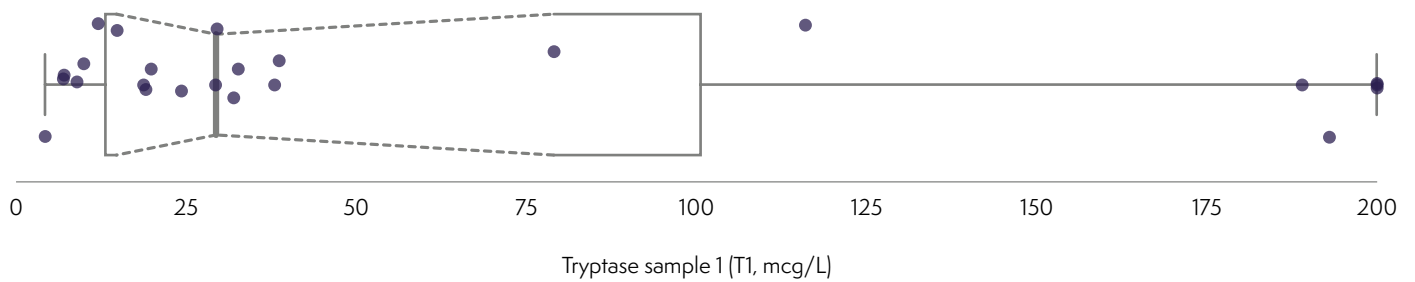
T1 in panel-defined Non-Allergic Anaphylaxis (panel determined anaphylaxis was probably non-IgE mediated)
n=6 cases, Range 1.7-24.9

Tryptase (T1, mcg/L)
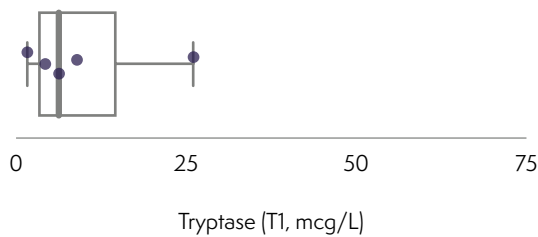
T1 in panel-defined diagnosis uncertain (unable to determine)
n=16 Median 6.6, 95% CI 1.4-30

Tryptase (T1, mcg/L)
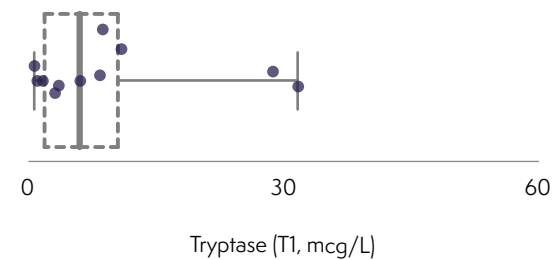
*There was no significant difference between allergic anaphylaxis and non-allergic anaphylaxis (p>0.05).

Dynamic tryptase (DT)

Two hundred and twenty-nine cases with ≥2 tryptase results enabled examination of the dynamic-tryptase algorithm. This postulates definitive acute tryptase release if the peak tryptase exceeds (baseline tryptase x1.2) +2 mcg/L, even when the result lies within the reference ranges.

Dynamic tryptase detected an additional 37 (16%) cases where peak tryptase was <14 mcg/L. (99th centile reference limit) (Table 4). Dynamic tryptase was also useful at an 11.4 mcg/L (95th centile) threshold.

Table 4 illustrates that the best detection strategy is to use dynamic tryptase for any case where tryptase release is not obvious and the peak tryptase is below the upper limit of the reference range.

Table 4. Use of the dynamic tryptase algorithm to enhance diagnosis of mediator release where peak tryptase (Tp) is within the reference range. Results from 229 cases with ≥2 tryptases

Peak tryptase (Tp)	Number of Tp above or below	Cases without dynamic tryptase pattern	Cases detected by dynamic tryptase	Total positive cases (% of 229)
Tp >=11.4 mcg/L	162	9	12	174 (76%)
Tp >=14 mcg/L	150	5	1	151 (66%)
Tp <11.4 mcg/L	67	41	26	26 (11%)
Tp <14 mcg/L	79	42	37	37 (16%)

Dynamic tryptase is most sensitive where Tp is in the reference range, and can produce false-negative when tryptases are high. The total number of cases detected using the 95th centile of the reference range was 200 (87%) and using the 99th centile was 188 (82%).

Figure 11. Information provided at referral
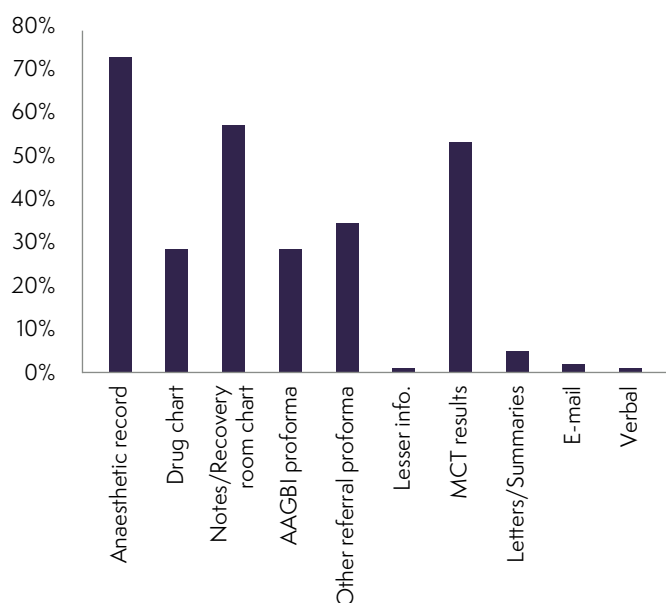
Referrals to allergy clinics

Who referred?

Ninety-eight per cent of survivors were referred for investigation.

One hundred and ninety (71%) of referrals were by the index anaesthetist, 45 by another anaesthetist (total 88% adherent to AAGBI recommendations), 17 by surgeons, two by GPs, six by others, and 14 not specified.

Was referral information appropriate?

The panel graded 60% of referrals 'good', 19% 'good and poor', 9.5% 'poor' and 11.6% unassessable.

Use of referral pro-forma (AAGBI or other) was infrequent, many referrals failing to provide guideline-recommended information (Figure 11).

Further information was needed from the anaesthetist on 22 (8%) occasions before clinic assessment and on 14 (5%) afterwards; this was provided in 21 and 9 cases.

Perioperative specialist allergy clinic assessment

Investigation of paediatric cases is discussed in Chapter 21, Paediatric anaesthesia. The following results describe investigation of the whole dataset except where specified.

Of the 252 patients referred to allergy clinics, the time taken to be seen was available for 233; the average wait time before they were seen was 101 days. The range was large – 0 days and 450 days.

As a result of the anaphylactic episode, 61% of all patients had a procedure delayed, modified or abandoned. Delays were detrimental in 29 (12%) patients requiring urgent and 30 (12%) requiring expedited surgery. This included eight patients requiring urgent cancer surgery and seven requiring non-urgent cancer surgery. Thirty-two per cent had delays to non-urgent treatment. Six per cent of patients had further surgery before clinic assessment.

Timeliness of clinic assessments

NCEPOD non-urgent cases

Only 39 (16%) were seen within the ideal six weeks. Twenty-three per cent breached the UK national 18-week target for first appointments, and 7% waited longer than 6 months (Figure 12a).

Final clinic appointments occurred at a median of 24 weeks, range 3–54.

The median time from allergy clinic referral to receipt of allergy clinic conclusions was 12.5 weeks (range 6–62) (Figure 12b).

NCEPOD urgent cases

Of 29 patients whose assessment was judged urgent, 11 (38%) waited more than 18 weeks.

Median wait from referral to conclusions was 14 weeks (range 3–60 weeks) compared with 12.5 weeks for non-urgent cases.

Overall waiting times varied little between urgent and non-urgent cases (Figure 12c).

Figure 12. Time to first allergy clinic assessment
Blue bar = 6 weeks (ideal wait), grey bar = 18 weeks (max wait before breach)

Figure 12a. Days from referral to first clinic weeks all patients
Median 90 (12.5 weeks), minimum 1 to max 450 days
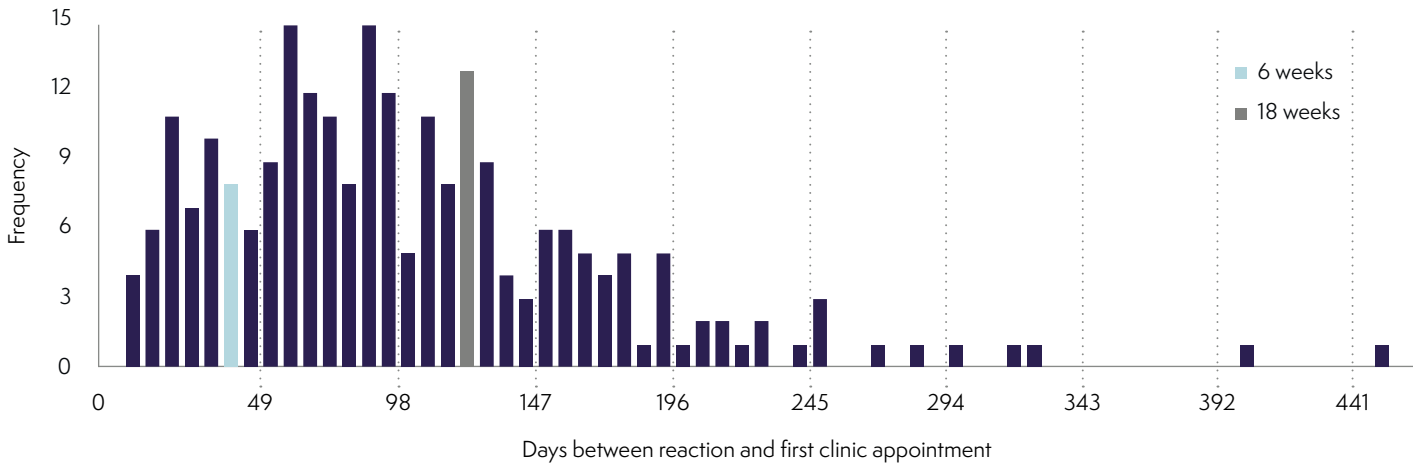
Figure 12b. Weeks from referral to receipt of allergy clinic diagnosis by anaesthetist
Median 12.5 weeks (88 days), 95% CI 10-15, range 0–62 weeks (434 days)
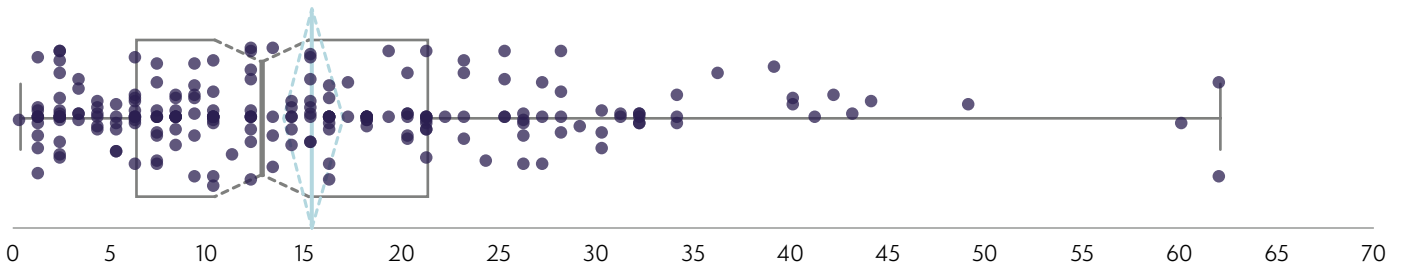
Figure 12c. Weeks from referral to first clinic visit for NCEPOD urgent cases
Median 14 weeks, minimum 42 to max 460 days
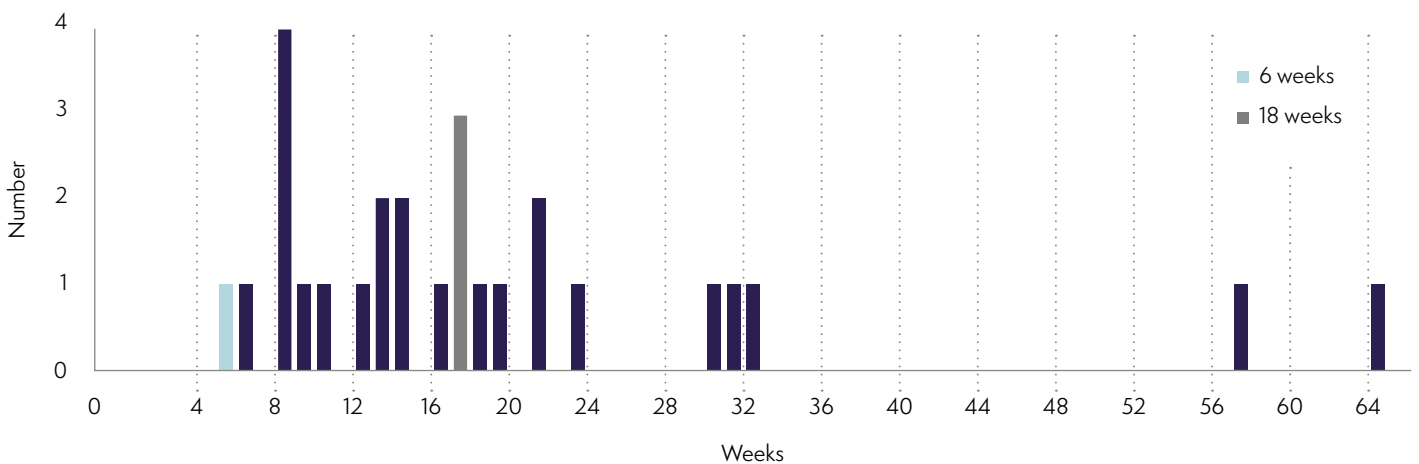
Quality of urgent investigation

Even urgent cases had deficiencies in investigations, with missing culprit agents and incomplete investigation. Of 20 assessments where a judgement was made, two were 'good', twelve 'good and poor', and six 'poor'. The allergy clinic and panel identified culprits in 25 (86%).

NMBA panels were inadequate in 55% of cases, skin prick testing in 69%, and intradermal testing in 76%.

Forty-one per cent had appropriate avoidance advice, and 66–76% had appropriate letters to GP, patient and anaesthetist. Hazard warning advice was issued to 41%.

Ten (34%) patients were still at potential risk after investigation: seven from defective avoidance advice and four due to poor communication. Two anaesthetists received insufficient information to plan safe future anaesthetics.

Few allergy clinics had investigated all potential culprits. Latex, opioids, chlorhexidine, gentamicin, ketamine, propofol, dexamethasone, midazolam, rocuronium and metronidazole were all omitted, and in eight cases challenge testing was appropriate but not undertaken.

Diagnostic concordance between clinic and panel for urgent cases

Of 29 cases, the anaesthetist provided a suspect in 19 cases and the panel agreed with this in 15 (75%). Excluding multiple (>2) triggers the clinic identified a trigger in 18 cases and the panel agreed in 14. The panel identified a definite or probable trigger in 22 (76%) cases. In twelve (41%) cases the anesthetist, the allergy clinic and the panel all agreed the trigger, which was an antibiotic or NMBA in all but two cases.

As a result of extended avoidance advice, the clinic safely advised avoidance of the panel-identified culprit agent in 20/29 (69%) cases.

Overall guidance adherence

Adherence to guidelines was generally poor, in contrast to high self-reported adherence in the NAP6 baseline survey (Figure 13).

There was full compliance with AAGBI guidance in 32% of cases, and with BSACI guidance in 17%. Most non-adherence was through failing to test for potential culprits, deficiencies in communication with patients or healthcare staff. Out of the 184 cases, 26 (14%) had only minor omissions.

Figure 13. Tests used in allergy clinic assessment
SPT = skin prick testing, IDT = intradermal testing
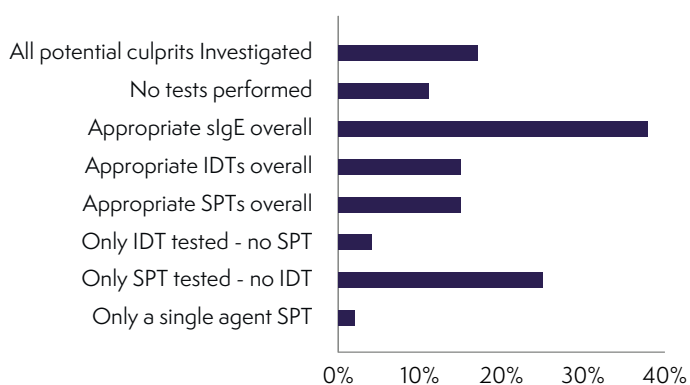
Written communication

Adherence to communication standards was much worse than the NAP6 baseline survey (Figure 14). Provision of written information to patients before clinic was rare, and information on patient support groups was only provided in 25% of cases. Written advice was given on safe alternatives in only 28% of cases and avoidance advice in 63%.

Figure 14. Adherence to guideline communication standards by allergy clinics
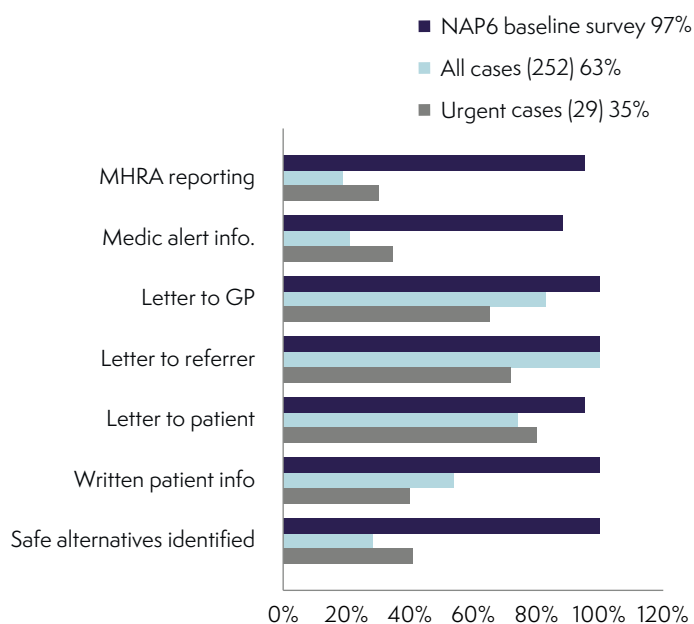
Hazard alert provision

The NAP6 baseline survey suggested that 95% of patients were issued alert information, but only 21% were issued allergy alerts in NAP6, 14% by an anaesthetist and 7% by the clinic (Figure 14).

Testing strategies

Use of skin prick testing (SPT) and intradermal testing (IDT) were similar to that reported in the NAP6 Allergy clinic baseline survey (Chapter 13). Use of the NAP6 minimum NMBA panel and latex testing was less than in the baseline survey (Figure 15).

Figure 15. Adherence to guideline test standards by allergy clinics
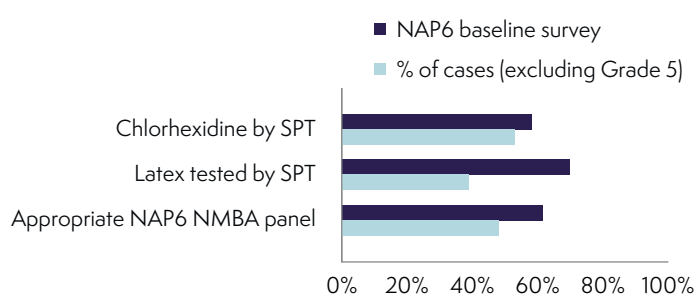
The appropriateness of the tests used was assessed (Figure 13 above). Generally the panels were not comprehensive, and often missed potential culprits.

Use of single tests (or tests to a single set of closely related agents only) was most common for suspected dye reactions and antibiotics.

Forty potential drug culprits were omitted in the 184 reviewed cases (see Supplementary 1). Ondansetron, latex, chlorhexidine and fentanyl were the most frequently omitted.

NMBA

Where the NAP6 minimum NMBA panel was not used, the most common combination was atracurium and rocuronium testing. Suxamethonium was the most common omission.

Chlorhexidine

Routine use of chlorhexidine testing is less common than reported in the NAP6 baseline survey, with only two-thirds of patients having even single-modality testing.

Latex

Only 31% of cases were tested, mostly by sIgE blood tests. Only one weak latex IgE positive was seen, and only one of twelve skin prick tests was positive.

Multiple positivity to other agents

This was especially notable in those with chlorhexidine positive tests, but occurred in all diagnoses (Table 5).

Table 5. Multiple sensitisations observed in the NAP6 cohort

Culprit	SPT positive to other agents/ No. tested to other agents	IDT positive to other agents/ No. tested to other agents	sIgE positive to other agents/ No. tested to other agents
Chlorhexidine	2/14	1/7	1/8
	1 equivocal to latex	1 positive to atracurium, vecuronium, rocuronium, tranexamic acid and fentanyl. Negative to suxamethonium	1 positive to penicillins (V,G, ampicilloyl, amoxicilloyl)
	1 equivocal to povidone iodine	-	-
Teicoplanin	4/26	4/25	0/8
	1 positive to tazocin and amoxicillin	1 equivocal to all agents but teicoplanin, 1 equivocal to chlorhexidine, 1 equivocal to gentamicin	-
	1 positive PPL and MDM penicillin determinants	1 positive to gentamicin	-
	1 positive to atracurium	1 positive to ketamine	-
	1 positive to atracurium	-	-
Rocuronium	9/20	8/14	1/9
	1 positive to vecuronium and pancuronium and suxamethonium	1 positive to atracurium, vecuronium, chlorhexidine, ondansetron but negative to suxamethonium	1 positive to chlorhexidine
	1 positive to pancuronium and suxamethonium	1 positive to atracurium	-
	1 positive to vecuronium	1 positive to suxamethonium, atracurium, vecuronium	-
	1 positive to suxamethonium	1 positive pancuronium, atracurium, mivacurium, and negative to suxamethonium and vecuronium	-
	1 equivocal to chlorhexidine	1 equivocal to alfentanil	-
	1 equivocal to vecuronium	1 equivocal to gentamicin and propofol	-
	1 equivocal to chlorhexidine	1 positive to pancuronium, vecuronium and cisatracurium, and negative to suxamethonium and atracurium	-
	1 equivocal to propofol and fentanyl	1 positive to atracurium, mivacurium and vecuronium, and negative to suxamethonium and pancuronium	-
	1 equivocal to cisatracurium and suxamethonium	-	-
Suxamethonium	5/10	2/6	1/6
	1 positive to rocuronium and suxamethonium (no other NMBA done)	1 positive to rocuronium and atracurium	1 positive to chlorhexidine and suxamethonium
	1 positive to vecuronium and suxamethonium only	1 positive to rocuronium and vecuronium	-
	1 positive to all NMBAs plus chlorhexidine	-	-
	1 positive to cisatracurium, chlorhexidine, atracurium, vecuronium, but not to pancuronium, mivacurium or rocuronium	-	-
	1 positive to atracurium and negative to suxamethonium	-	-

Skin testing and concentrations used

In total, 51% had SPTs reported, 34% IDTs and 71% sIgE. Table 6 shows that the two skin tests to not provide equivalent results.

Few data were returned on use of non-irritant concentrations.

Table 6. Skin prick tests, intradermal tests and sIgE tests are not equivalent. All tests where >25% are positive are in bold

Test results reported	SPT done (% tested)	SPT +ve (%)	IDT done (% tested)	IDT +ve (%)	sIgE done (% tested)	sIgE +ve (%)
Penicillins	26 (15%)	**10 (38%)**	20 (12%)	**5 (25%)**	47 (28%)	**13 (28%)**
Teicoplanin	9 (5%)	2 (22%)	9 (5%)	**5 (55%)**	n/a	n/a
Rocuronium	15 (9%)	**7 (47%)**	18 (11%)	**6 (33%)**	n/a	n/a
Atracurium	31 (18%)	5 (17%)	23 (14%)	**7 (30%)**	n/a	n/a
Suxamethonium	9 (5%)	**6 (67%)**	3 (2%)	**1 (30%)**	27 (16%)	4 (15%)
Chlorhexidine	25 (15%)	**8 (32%)**	11 (7%)	**5 (45%)**	73 (43%)	15 (21%)
Patent Blue	4 (2%)	**4 (100%)**	1 (0.5%)	**1 (100%)**	n/a	n/a
Latex	12 (7%)	1 (8%)	0	0	41 (24%)	1 (2%)
Local anaesthetic	4 (2%)	0	5 (3%)	0	0 (0%)	0

Specific IgE (sIgE) blood tests

A limited range of the available sIgE tests was used, including chlorhexidine, penicillins and latex (Table 7).

Few centres reported use of thiocholine (suxamethonium) or morphine/pholcodine testing. Local anaesthetic and latex sIgE were occasionally performed. Chlorhexidine and penicillin sIgE were frequently positive.

Many potentially relevant sIgE tests were not used at all in NAP6 (see Supplementary 2).

Pholcodine exposure

Pholcodine exposure is rarely queried or recorded in UK practice, in line with the baseline survey. Eighty-seven (33%) reported no exposure. Pholcodine was only tested in four cases.

Challenge testing

Twenty-four (16%) cases reported the results of challenges (Table 8). In ten of these the panel thought the challenges were incomplete or inappropriate.

Table 7. Specific IgE blood test results in the NAP6 cohort

Name	No. Tested	No. Positive
Penicilloyl G (benzyl penicillin)	35	11
Penicilloyl V (phenoxymethylpenicillin)	34	10
Ampicilloyl	15	7
Amoxicilloyl (amoxycillin)	31	1
Clavulanic Acid	2	1
Cefaclor	4	0
Gentamicin	4	0
Suxamethonium	17	3
Pholcodine	4	0
Chlorhexidine	57	16
Latex	28	0
Morphine (quaternary ammonium compounds)	3	2
Diclofenac	1	0
Codeine	1	1
Gelatin Bovine	3	0

Preparation for anaesthesia allergy testing

Table 8. Challenge test results

	Drug – Final Dose	Units	Allergy clinic challenge test results
Amoxicillin	500	mg	Negative
Amoxicillin	-	-	Negative
Amoxicillin	50	mg	Negative
Amoxicillin	500	mg	Negative
Amoxicillin	250	mg	Negative
Amoxicillin oral	250	mg	Negative
Bupivacaine	-	-	Negative
Bupivacaine	5	mg	Negative
Bupivacaine 0.25%	1.25	mg	Negative
Celecoxib oral	100	mg	Negative
Co-Amoxiclav oral	-	-	Negative
Fentanyl	5	mcg	Negative
Lidocaine	5	-	Negative
Lidocaine 1%	-	-	Negative
Lidocaine 1%	-	-	Negative
Methylprednisolone	30	mg	Negative
Metronidazole oral	400	mg	Negative
Ondansetron	-	-	Negative
Teicoplanin	4,40,80,280	mg	Negative
Vancomycin	-	-	Negative
Ibuprofen	300	mg	Positive
Teicoplanin	0.2	mg	Positive
Teicoplanin	-	-	Positive
Teicoplanin	20	mg	Positive

Future risk estimates

Many patients were thought to remain at potential risk after clinic investigation for various reasons, most often because potential culprits had been omitted or not excluded satisfactorily (Table 9).

Some had ambiguous or absent avoidance advice and there was evidence of many defects in patient and clinic correspondence, particularly with regard to details of investigations.

Table 9. Patient risks following allergy clinic investigation

At risk from inadequate allergy referral	At risk from inadequate clinic investigation	At risk from inappropriate clinic advice	At risk from inadequate communication with patient	At risk from inadequate communication with Team
4%	38%	76%	17%	23%

Accuracy of diagnosis and concordance

There was good concordance between the clinic and the panel diagnoses (Table 10). Most lack of concordance between clinic and panel was for ondansetron, teicoplanin and atracurium.

Seven cases had two culprits that were equally probable. Eighty-eight per cent of cases identified the same trigger in the clinic and the panel. 74% were correctly predicted by the anaesthetist.

Table 10. Diagnostic concordance between anaesthetist, clinic and NAP6 panel

Clinic, panel and anaesthetist	Clinic and panel	Anaesthetist and panel but not clinic	Anaesthetist and clinic but not panel
65.5%	22.5%	8.5%	3.5%

Reporting to local incident reporting systems and the Medicines and Healthcare products Regulatory Agency (MHRA)

Less that one quarter of cases were reported to the MHRA, in contrast to approximately three quarters that were reported to the local incident system. In children the frequency of reporting was even lower. This is discussed in Chapter 24, Reporting and learning.

Overall quality of allergy clinic assessment

The panel noted that all potential culprits had been adequately investigated in only 27%.

Of 165 assessable cases 10% of assessments were judged 'good', 49% 'good and poor', and 41% 'poor' (Table 10). The most common deficiencies were failing to test for all potential culprit agents, poor communication with the patient or healthcare staff, and failure to report to the MHRA report (Table 11).

Table 11. NAP6 panel review of quality of investigation

Quality of Clinic Assessment	Number	%
Good	17	10%
Good and Poor	81	49%
Poor	67	41%
Unassessable	15	–

Harm to the patient was rare

Overall, 9% of anaesthetists did not feel that the clinic provided enough information to safely plan future anaesthesia, 4.5% had low confidence in the allergy clinic diagnosis: 4 specifically noted that no trigger was identified, 5 reported a lack of clear alternative drugs to use, 5 noted poor communication of results or avoidance advice, and 4 cited delayed investigation or challenge testing.

Avoidable causal factors

Only three events were judged avoidable. There were few incidences of failed risk-factor identification in preoperative history taking, failed recording or ignoring of relevant information (Table 12). These included administration of diclofenac to a NSAID sensitive individual, penicillin to a penicillin-allergic individual (a recognised cause of litigation) (Cranshaw 2009), and probably the unnecessary co-administration of both co-amoxiclav and teicoplanin.

Table 12. Avoidable causal factors

Incomplete pre-intervention allergy history (n)	Pre-intervention allergy history not heeded (n)	Possibility of cross-sensitivity not heeded (n)	A previous reaction was not appropriately investigated (n)	Was the index event preventable? (n)
3	6	3	3	3 (1.5%)

Discussion

Most referrals were by anaesthetists and were consistent with BSACI (Ewan 2010) and AAGBI (Harper 2009) guidelines, but provision of information to the clinic was suboptimal.

Clinics were unable to make timely assessments for most cases. Patients were rarely seen within six weeks and the excessive waiting times noted in the baseline clinic survey were confirmed. Delay in treatment was common for both urgent and non-urgent cases and underlined the need for better service provision and rapid-referral protocols.

Approximately 400–600 Grade 3–5 cases are expected annually in the UK, which is similar to previously reported estimates (Egner 2016, Low 2016, Mertes 2011) and the NAP6 baseline survey (Egner 2017a). NAP6 received 266 completed and admissible two-part reports from across the UK. This suggests some under-reporting (Egner 2016). Some cases were lost due to lack of Part B forms or insufficient detail to be interpretable.

Tryptase-sample timing was often suboptimal, and was sometimes too late to estimate peak tryptase. NAP6 data shows rapid reduction within 30 minutes and support BSACI and AAGBI Guidelines (first sample immediately post-reaction, second at 1–2 hours, plus a 24-hour baseline) (Harper 2009, Savic 2015). Second samples within 6 hours can still be informative (ANZCA guidelines suggest 1, 4 and 24 hour samples) (Kolawole 2017).

Where resuscitation interferes with timely sampling, prompt liaison with the laboratory to retrieve acute biochemistry or haematology samples may be a practical alternative: serum or plasma is satisfactory. Tests can be performed on very low volumes. Pre-procedure samples also provide effective baseline levels.

Basal tryptase levels did not correlate with severity or grade of reactions – unlike the weak correlation in venom anaphylaxis. (Rueff 2009).

Few cases had elevated baseline tryptase suggesting mastocytosis or raised alpha tryptase due to gene duplication – now sometimes referred to as 'hyper-alpha trypsaemia syndrome' (HATS) (Lyons 2016).

Median peak tryptase and first tryptase results by grade were similar to those previously reported (Egner 2016). Higher values appeared to be more strongly linked to rapidity of onset than to trigger agent.

Anaesthetists predicted the culprit agent correctly in 75% of cases, but were prone to overlook chlorhexidine as a cause (see Chapter 17, Chorhexidine). The closest temporal administration is a good guide to causation, except for chlorhexidine, Patent Blue, latex and orally administered drugs for which later reactions are not uncommon. Late reactions may also occur with atracurium or co-amoxiclav.

Case series have demonstrated that the dynamic-tryptase algorithm can detect possible mediator release more sensitively than thresholds (Egner 2016, Baretto 2017). In NAP6 this algorithm increased detection of acute release, and it should be used when the peak tryptase level is within the reference range.

Compliance with guidelines for investigation was generally poor, and lower than self-reported compliance in the NAP6 baseline survey. Only 32% fully complied with AAGBI guidance, and only 17% with BSACI guidance. Non-compliance was mostly due to failure to test all potential culprits, or to deficiencies in communication with patients and healthcare staff.

Use of skin, blood and challenge testing appears suboptimal even when available. Use of extended NMBA panels is effective in selecting low risk of future reactions (Leysen 2014). Few centres are using an extended panel despite high adherence reported in the baseline survey.

Revised guidelines should specify minimum and clear test sets that all services can use in screening for sensitisation and cross-reactivity, including specific concentrations and modalities. Skin prick tests and intradermal tests do not give the same results for all triggers.

The clinic must identify safe alternatives where multiple NMBAs test positive. It is difficult to know what to do with multiple positive IDTs, particularly as false positives do occur (Leysen 2014, Trautmann 2016, Brockow 2013, Mertes 2007). Cross-sensitisation to NMBAs is discussed in Chapter 16, NMBAs.

Pan-reactivity across related drugs occurs, but is not always clinically relevant; there are reports of patients tolerating drugs which have given positive allergenic tests. Risk assessment is difficult and the presumption to avoid is sensible, but necessitates the provision of a clear alternative plan – either for method of anaesthesia or specific safe drugs. In several cases excessive avoidance advice created problems for patients or anaesthetists after allergy clinic visits. The NAP6 panel recommends that direct involvement of an anaesthetist in all clinics is essential for the provision of reasonable advice on avoidance and on alternative safe drugs/plans.

Few reporters (42%) were able to provide details of the concentrations used, but there was considerable variation in those that did. Specialist centres should use consensus or locally-derived threshold non-irritant doses. Maximum non-irritant concentrations need to be identified for novel drugs with increasing usage.

Importantly, multiple positivity is common in the NAP6 cohort in both skin testing and sIgE tests. This creates at least a possibility that multiple triggers are involved in some cases, including those where a single culprit could not be identified. In this cohort seven of 192 cases with definite or probable triggers were judged to have two equally likely triggers. Further research and guidance is needed.

In the presence of chlorhexidine-positive tests, multiple positivity to other agents was common in intradermal and sIgE testing, but not in skin prick testing. This confirms previous observations in a UK cohort (Egner 2017b). The NAP6 dataset extends this observation of multiple positivity to cases of teicoplanin, rocuronium and suxamethonium allergy. This has implications for order and modality of testing, for the need to test for all potential culprits, and for critical appraisal of the imputability of each potential trigger.

Latex is not a cause of perioperative anaphylaxis in NAP6. Latex allergy has been falling in France since the late 1990s (Vandenplas 2007). Latex-free theatres and hospitals are now common in the UK and new sensitisations unlikely.

The NAP6 panel diagnosis and the clinic diagnosis agreed more frequently than published for the best Bayesian methods in general drug allergy (Agbabiaka 2008, Varallo 2017). This may be helped by the rapid presentation of perioperative reactions.

Excessive avoidance advice may also be harmful. Failure to offer appropriate IDT and challenge testing resulted in inappropriate avoidance in some cases. Inappropriate avoidance advice because of a low probability of penicillin allergy (not confirmed on clinic evaluation) was a problem and caused serious reactions to teicoplanin. Use of teicoplanin as a penicillin substitute is increasing (see Chapter 6, Main findings; Chapter 15, Antibiotics); proper pre-procedure evaluation for true penicillin allergy may reduce this. If penicillin avoidance advice is given, specific advice should also be given on safe alternatives.

Communication to patients and anaesthetists fell short in this cohort. In Appendix A we provide a template of the information dataset that could usefully be included in a report from an allergy clinic to the referring anaesthetist and their GP. In Appendix B we provide a template letter to the patient for use after an allergy clinic visit.

MHRA reporting was poorer than the baseline survey. Reporting through the index anaesthetist (AAGBI guideline) is problematic if identification of the culprit agent may change on clinic investigation. BSACI expects the allergy clinic to report, but this risks duplicate reporting of differing conclusions. Ensuring the MHRA report identifier is provided in clinic letters, or nominating a departmental anaesthetic lead to report after final clinic assessment are potential solutions (see Chapter 11, Immediate management and departmental organisation and Chapter 24, Reporting and learning).

Evidence that future avoidance advice was comprehensive and safe was often lacking, perhaps due to inadequate communication or detail in the correspondence or conclusions issued by the clinic.

Allergen challenge testing is the ultimate arbiter of tolerability but is problematic in perioperative investigations. There were few challenges reported in NAP6, and those were mostly to oral penicillins or intravenous teicoplanin. Three out of four teicoplanin challenges were positive. NMBA challenges are rarely done in the UK, although common in Denmark (where NMBA allergy is rare, and the risks may be different). As an alternative, challenge tolerance to alternative drugs can be established to facilitate other anaesthetic approaches, and this was used by some centres.

In conclusion, NAP6 shows that adherence to existing guidelines is poor and confirms 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
- Patients should not have 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
- Including all potential culprits and all relevant test modalities (SPT, IDT, sIgE and, where appropriate, challenge testing), since different test modalities do not always yield consistent results
- More data on the predictive values of different modes of testing using standardised methods are required for all triggers
- Better standardised clinic reports should be developed to encourage reporting of all the relevant information, which should include, drugs identified, type of reaction, drugs to avoid, safe alternatives, tests used, and recording the communication of results to anaesthetists, GPs and patients
- Improved communication of the results of urgent investigations, clearly and reliably, to the anaesthetist.

Recommendations

National

- 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
- 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

- 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 (Chapter 11, Appendix B)
- 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

- 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

- Outcomes of urgent investigations by allergy clinics should be communicated urgently and directly to the referring anaesthetist, ideally by phone and in writing

- 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

- 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

- 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

- 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

- Where the baseline sample is not collected prior to attending the allergy clinic it should be collected at the clinic

- If the MCT is elevated more than 24 hours after the event, the possibility of a mast cell disorder should be considered

- A dynamic rise and fall in mast cell tryptase should be used to detect mediator release

- 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

- When investigating suspected perioperative anaphylaxis, chlorhexidine and latex should be tested

- More than one test for chlorhexidine is necessary to exclude allergy

- 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

- All potential culprit agents to which the patient has been exposed should be tested. The clinic should make a critical appraisal of the imputabality of each potential trigger in making a diagnosis

- 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

- All skin testing should be at concentrations validated to be below the non-specific histamine-releasing/irritant concentrations (as published and verified locally)

- 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 succinylcholine (suxamethonium) or rocuronium is safe). The NAP6 minimum NMBA panel is suitable for this

- The possibility of reaction to more than one agent should be considered

- Specific IgE bloods tests should be used for agents for which they are available, as no modality is 100% sensitive or specific

- 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

- 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

- 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

- As none of the test modalities is wholly reliable, there needs to be research to establish an appropriate form of challenge testing for chlorhexidine

- More data on the predictive values of different modes of testing using standardised methods are required for all triggers

- 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

- Studies are needed to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.

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Supplementary 1. Forty other drugs were also identified as potential culprits whose investigations were not done or not completed

Atropine, basilixumab, betadine, brufen, ceftriaxone, cefuroxime, chloramphenicol, clonidine, cyclizine, diamorphine, dexamethasone, enoxaparin, ergometrine, fentanyl, flucloxacillin, gabapentin, gentamicin, glycopyrrolate, hydrocortisone, lidocaine, ketamine, latex, levobupivacaine, methylprednisolone, metronidazole, midazolam, mitomycin, neostigmine, NSAID, ondansetron, paracetamol, parecoxib, povidone iodine, prochlorperazine, propofol, ranitidine, rocuronium, remifentanil, teicoplanin, thiopental, tranexamic acid, vecuronium.

Supplementary 2. Potentially relevant sIgE tests not used in NAP6

There was no evidence that potentially relevant sIgE tests that are currently available were used for the following agents: polylysine, iodine, clindamycin, ciprofloxazin cefuroxime, cephalosporin, cephalexin, cloxacillin, diazepam, atropine, metronidazole, lecithin, piroxicam, rifampicin, diclofenac, indomethacin, naproxen, procaine, bupivicaine, ibuprofen, aminoglycosidase mix, streptomycin, chymopapain, doxycycline, acetyl salicyclic acid, macrolide mix, sulfamethoxazole, lidocaine, mepivicaine , prilocaine, trimethoprim, thiopental, prednisolone, pyrazolone, phenacetin, furosemide, tetracycline, erythromycin and methylene blue.

Recommended content of standard allergy clinic letter to the referring clinician following assessment of perioperative anaphylaxis

Type of event	Allergic anaphylaxis/non-allergic anaphylaxis/not an allergic event Description of event detailing exposures	
Cause of event	Culprits identified	List definite culprits
	Culprits identified	List probable culprits
	Culprits identified	List possible culprits
	In non-allergic events	Describe cause, future risk and recommendations
	Drugs administered which are **unlikely** to be culprits	List
	Continued harm from event	eg. new anxiety, a change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of PTSD, myocardial damage, heart failure and new renal impairment
Investigations	Positive tests used – skin prick	List with concentrations
	Negative tests used – skin prick	List with concentrations
	Positive tests used – Intradermal	List with concentrations
	Negative tests used – Intradermal	List with concentrations
	Positive sIg E tests	List with results
	Negative sIg E tests	List
	Total IgE	Result
	Summary of tryptase results	Dated and timed results
	Challenge test results	List, total dose and route of administration
Avoidance	Drugs/Substances to avoid: Definite	List
	Drugs/Substances to avoid: Probable	List
	Cross reactivity with other drugs requiring avoidance	List
Safe alternatives	**Identified safe alternatives for each culprit**	**List**
	If no clear culprits identified	Clear statement on future risk and suitable drugs for future use based on a risk assessment
Communication	Copy letter to patient, referring physician/surgeon and GP	Confirmed in letter
	Hazard warning	Advised/not advised
	Statement on MHRA reporting	Reported/ Not reported by clinic with MHRA reference number
	Additional written information issued	Yes/no and specify content/type/source

Appendix B:

Letter to the patient following allergy clinic visit for investigation of perioperative anaphylaxis

[Hospital HEADER]   Date …………………..

Patient's name ....

Patient's address ....

Medical record number …………………………...

NHS Number …………………………..…….......

Dear ....

**Following your investigation at the ………………..perioperative allergy clinic.
We have concluded the following –**

You have had a reaction classified as:

Allergic anaphylaxis/Non-allergic anaphylaxis/Not an allergic event

The agent(s) identified as the cause of this are:

1) …………………………………………………..

2) …………………………………………………..

3) …………………………………………………..

You should avoid all these drugs and agents in the future as exposure to them may lead to a serious or even fatal reaction.

The diagnosis was made based on the following tests:

1) …………………………………………………..

2) …………………………………………………..

3) …………………………………………………..

We have established safe alternatives to these drugs as:

1) …………………………………………………..

2) …………………………………………………..

3) …………………………………………………..

Your GP has been written a more detailed letter which you may wish to discuss with him/her.

You should consider:

A) Wearing a medic alert bracelet/necklace available from ……………………….……………………

B) Carrying this letter with you to all Medical or Dental appointments and discussing its contents prior to any procedure

C) Carrying an adrenaline auto-injector for emergency treatment yes/no

Yours sincerely,

Consultant Allergist/Clinical Immunologist

Contact phone number………………………………….

Susana Marinho   Shuaib Nasser

Key findings

- 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 all 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.

What we already know

Antibiotics are well-recognised, common causes of perioperative anaphylaxis, noted as being among the main causes in several reports from large international databases, from France, Australia, New Zealand, Norway and the United Kingdom. Nevertheless, there is substantial geographic variability regarding the different drugs or substances causing perioperative anaphylaxis (Mertes 2016), and the true incidence of anaphylactic reactions during the perioperative period and their causes remain poorly defined. These regional differences, likely to be a reflection of local drug preferences and geographical differences in bacterial resistance patterns, are a strong incentive for repeated epidemiological surveys in different countries.

Reactions involving neuromuscular blocking agents (NMBAs) are reported as the leading cause of perioperative anaphylaxis in several countries, including in many European studies (Harboe 2005, Mertes 2011, Dong 2012, Mertes 2012, Tacquard 2017), but are less frequently reported in the United States or Denmark (Garvey 2001, Gurrieri 2011).

Reactions involving antibiotics are reported with a high and sometimes increasing frequency in most series (Volcheck 2014, Mertes 2016). Antibiotics appear to be the most common cause of perioperative anaphylaxis in the United States (Gurrieri 2011) and Spain (Lobera 2008, Gurrieri 2011, Gonzalez-Estrada 2015), accounting for between 40–50% of the reported reactions. Penicillins and cephalosporins are the main antibiotic culprits reported.

A series of multicentre French surveys, which began in the mid-1990s and have continued to the present, reported NMBAs as the main culprit of perioperative anaphylaxis, responsible for as many as 60% of reactions, followed by antibiotics, responsible for ≈20% (of which more than 50% were cephalosporins) (Mertes 2011, Dong 2012, Mertes 2012, Tacquard 2017). These studies report a rapid increase in antibiotics as culprit agents, rising from 2% in the late 1980s to around 20% in recent reports. A German study of 107 cases reported 24 (45%) of the 53 identified culprit drugs to be antibiotics, of which 15 were cephalosporins and five penicillins (Trautmann 2016). In an American series, antibiotics accounted for 50% of IgE-mediated reactions (Gurrieri 2011, Kuhlen 2016).

In the UK, antibiotics have been noted to account for approximately 15% of anaesthesia-related anaphylactic episodes (Harper 2009), but this proportion may have increased in recent years. In a case series of 21 UK patients with identified culprits, antibiotics accounted for 11 (52%) of perioperative reactions (Meng 2017). The antibiotics identified as culprits were penicillins, teicoplanin, metronidazole and rifampicin. In a report of 316 UK cases over a seven-year period, antibiotics accounted for 31% of cases and were the second commonest cause of reactions after NMBAs (Low 2016). Penicillins were prominent causes (74% of antibiotic-induced reactions), but teicoplanin, 5.6%, was not.

The NAP6 Anaesthesia baseline survey of perceptions and experiences of anaesthetists in relation to perioperative anaphylaxis (Kemp 2017, Chapter 7), revealed that antibiotics were suspected by anaesthetists as causative agents in 38% of cases. Penicillins were both perceived to be the most likely causative antibiotics and were avoided most often. Teicoplanin, although prominent among suspected culprit agents, was not frequently avoided.

Penicillin and beta-lactam antibiotics

Penicillin allergy is the most commonly reported drug allergy, with up to 10% of the population and 20% of in patients so labelled (Kerr 1994, Lee 2000, Gomes 2004, Macy 2009, 2014a, 2015, Weiss 2010, Albin 2014). Importantly, 90–99% of patients who report penicillin allergy are mislabelled and could be de-labelled if documentation of the original reaction was adequate or the patient was investigated via skin and drug provocation tests (Borch 2006, Dworzynski 2014, Macy 2015).

Sensitisation to antibiotics requires previous exposure, although in some cases this occurs through exposure to a cross-reacting agent or drug. Individuals may be allergic to only one antibiotic, or have allergy to others containing a cross-reacting allergenic epitope. Allergy to beta-lactam antibiotics occurs through sensitisation to the beta-lactam ring or to a side-chain. Sensitivity to the beta-lactam ring leads to general allergy to penicillins and cephalosporins. Side-chain-specific allergy can lead to unexpected cross-reactivity, for example, between amoxicillin and cefadroxil, or ceftazidime and aztreonam. If allergy to one antibiotic is confirmed, it is important that related antibiotics, eg. other penicillins, are also be tested in order to identify potential cross-reactivity and safe alternatives.

Teicoplanin

Teicoplanin is often used as an alternative to a beta-lactam when there is a history of allergy. There is emerging evidence that teicoplanin is an important trigger of anaphylaxis events (Asero 2006, Savic 2015, Azamgarhi 2018), and in a recent survey it was reported as the suspected cause of 28% of antibiotic-related anaphylaxis (Kemp 2017, Chapter 7, Baseline survey).

A growing body of evidence has shown that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs with increased duration of treatment and hospital stay and leads to higher rates of antibiotic resistance and infections, including methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile (C. diff) and vancomycin-resistant enterococcus (VRE) (Sade 2003, Macy 2014b, Solensky 2014).

Numerical analysis

Ninety-two cases of antibiotic-induced anaphylaxis were identified. In two cases both teccioplanin and gentamicin were judged equally probable as culprits, so there were 94 definite or probable antibiotic culprits in 92 cases – 46% of all cases with identified culprits. The majority were caused by co-amoxiclav or teicoplanin, which between them accounted for 89% of identified antibiotic culprits.

The overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100,000 exposures. The incidences of the three most prevalent antibiotics were:

- *Co-amoxiclav:*
  46/532,580 = 1 in 11,578 (95% CI 1 in 8,680 – 1 in 15,814)
- *Teicoplanin:*
  36/219,62 = 1 in 6,101 (95% CI 1 in 4,407– 1 in 8,710)
- *Cefuroxime:*
  4/424,143 = 1 in 106,035 (95% CI 1 in 41,414 – 1 in >150,000).

The relative anaphylaxis rate using cefuroxime as an index was 17.4 for teicoplanin and 9.2 for co-amoxiclav (Table 1). Eighty-eight per cent occurred during general anaesthesia, 8% during moderate sedation, 1% during minimal sedation and 2% during managed anaesthesia care.

Table 1. Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6
*Annual usage identified from the Allergen Survey (Chapter 9)

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

Patient characteristics

The gender ratio of affected patients (1.4:1) and ethnicity (89% white British) were both similar to the surgical population as shown in the NAP6 Activity Survey (Chapter 8). Obesity was over-represented in the cohort of anaphylaxis patients (37% of the anaphylaxis population and 21% of the surgical population – Chapter 8), but obesity and morbid obesity rates were similar in those with antibiotic-induced anaphylaxis (17% and 12%) and anaphylaxis induced by any trigger (21% and 14%) (Figure 1). There was only one paediatric case (Figure 2) and, while paediatric anaesthesia accounts for 13% of overall activity, antibiotic use is considerably less frequent (see Chapter 21, Paediatric anaesthesia). Overall, there was little evidence that any particular patient characteristics altered rates of antibiotic-induced anaphylaxis.

Figure 1. Body habitus distribution in cases of perioperative anaphylaxis due to antibiotics
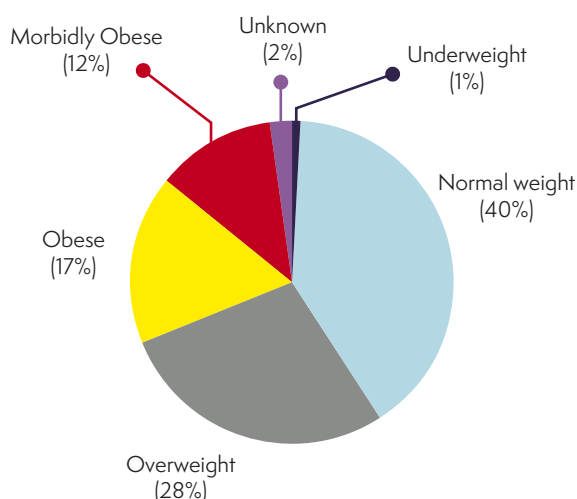
Figure 2. Age distribution (yrs) in cases of perioperative anaphylaxis due to antibiotics
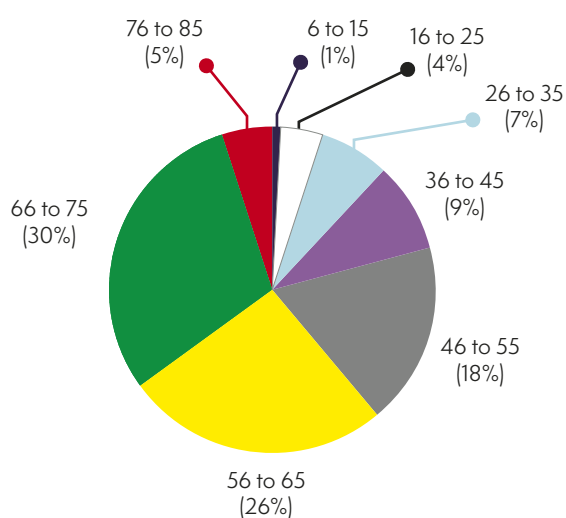
Risk and culprit agents

The NAP6 Allergen Survey (Chapter 9) reported that 1,787,360 (57.2%) patients received 2,469,754 antibiotic administrations annually. The main antibiotics used were gentamicin, co-amoxiclav, cefuroxime, and metronidazole, the first two each accounting for around half a million administrations per year. Distribution of antibiotic use is detailed in Table 1.

Of the 36 patients who reacted to teicoplanin, 20 (56%) stated preoperatively that they were allergic to penicillin. Half of all teicoplanin reactions were either Grade 4 or fatal.

Although the Allergen Survey (Marinho 2018, Chapter 9) demonstrated that teicoplanin was administered to 21% of orthopaedic/trauma patients, it was responsible for 75% of antibiotic anaphylaxis in this specialty (Figure 3). Gentamicin was administered to 33% of these patients, flucloxacillin to 18%, and cefuroxime to 18%, but they were responsible for very few cases of anaphylaxis. Similarly, co-amoxiclav is used in 33% of general surgical procedures, but caused 86% of antibiotic-induced anaphylaxis within that specialty. Metronidazole is used in 23% and gentamicin in 17%, but rarely caused anaphylaxis.

Figure 3. Antibiotic anaphylaxis by surgical specialty
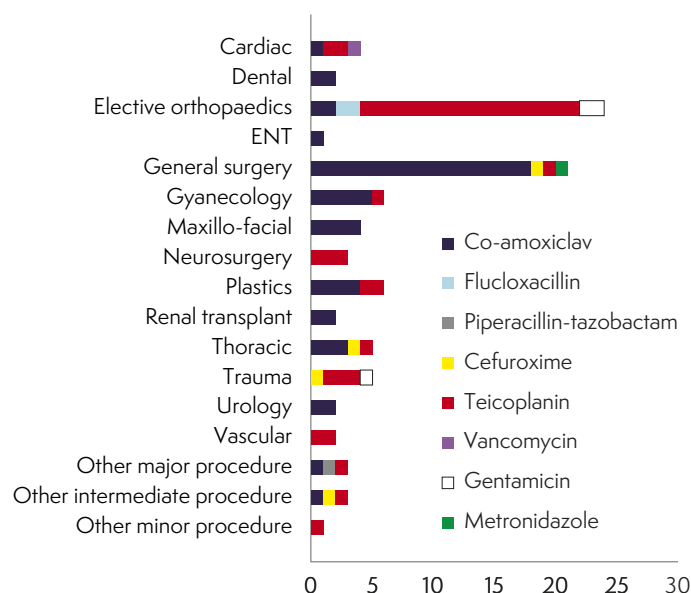
Timing between antibiotic exposure and onset of anaphylaxis

The first clinical feature presented within 5 minutes of exposure in 74% of cases, within 10 minutes in 92.5%. None presented after 30 minutes (Figure 4).

Figure 4. Time interval between exposure to the suspected culprit and appearance of first clinical feature
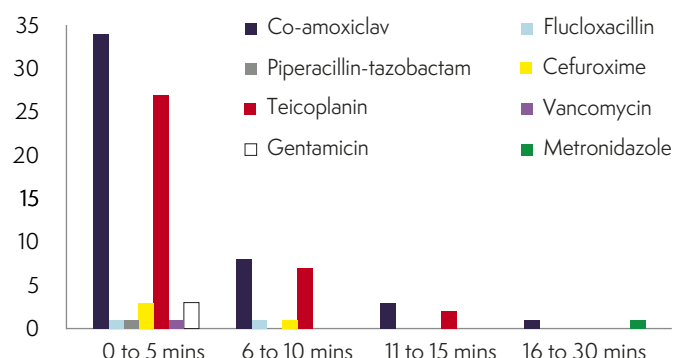
The anaesthetist identified the event as a clinical incident within 5 minutes of antibiotic administration in 65% of cases, and within 10 minutes in 88% of cases. The anaesthetist suspected anaphylaxis within 5 minutes in 53% and within 10 minutes in 85% of cases.

Clinical features

These are discussed in Chapter 10, Clinical features. The most common first-presenting clinical feature (42%) was hypotension followed by bronchospasm/high airway pressure (15%) and tachycardia (13%). During teicoplanin anaphylaxis hypotension was a dominant presenting feature with bronchospasm uncommon (Figure 5).

Considering clinical features present at any time during the episode, hypotension was universal, and blood pressure was unrecordably low in a quarter of cases. Flushing/non-urticarial rash, bronchospasm/high airway pressure and tachycardia were the next most-common features (67%, 53% and 50%, respectively). Bradycardia was present in 11% of cases (Figure 6).

Figure 5. First clinical feature in anaphylaxis due to antibiotics (panel a), and proportionately by antibiotic (panel b)

Figure 6. Clinical features at any time during perioperative anaphylaxis due to antibiotics (panel a) and proportionately by antibiotic (panel b)
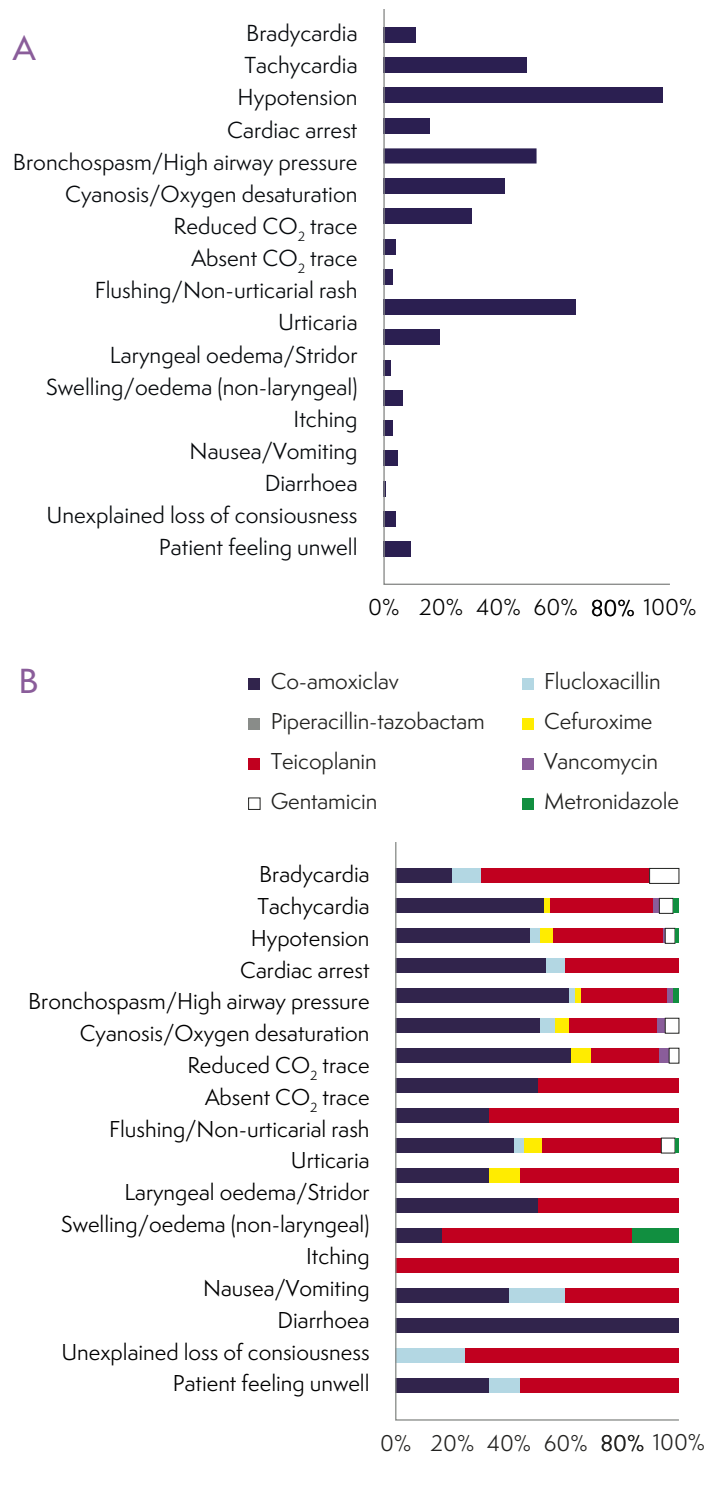
Severity

There were 46 (50%) Grade 3 and 43 (47%) Grade 4 reactions. Three (3%) cases were fatal, of which two were due to teicoplanin and one co-amoxiclav. The severity grade of anaphylaxis resulting from each antibiotic is detailed in Table 2.

Table 2. Grade of anaphylaxis for all antibiotics identified by the review panel

Antibiotic	Grade			
	Grade 3 Total	Grade 4 Total	Grade 5 Total	All Total
Co-amoxiclav	24	21	1	**46**
Teicoplanin	18	16	2	**36**
Cefuroxime	0	4	0	**4**
Gentamicin	3	0	0	**3**
Flucloxacillin	1	1	0	**2**
Piperacillin-tazobactam	0	1	0	**1**
Metronidazole	1	0	0	**1**
Vancomycin	1	0	0	**1**
Total	48*	43	3	**94***

Two cases where teicoplanin and gentamicin were joint probable causes

Antibiotic test doses and timing of antibiotic administration

A test dose was administered to 82 (35%) of 235 patients who received an antibiotic and 18 (20%) of 92 patients in whom an antibiotic was the cause of the reaction. Of these 18, in ten (53%) cases the patient reacted to the test dose itself, which ranged from 5–30% of the therapeutic dose, and the other eight patients reacted to the full dose, which was given within 1 minute of the test dose in all but one case (given within 10 minutes).

Test doses were commonest with meropenem and co-amoxiclav. A test dose preceded 13 (28%) of 46 cases of co-amoxiclav anaphylaxis; seven of these cases reacted to the test dose (5–30% of the full therapeutic dose). Test doses were given in four (11%) of 36 cases of teicoplanin anaphylaxis. Two reacted after the test dose, and two when the full dose was administered almost immediately after the test dose. The only case receiving a test dose of vancomycin also reacted immediately. Thus, there was no evidence that a test dose prevented a reaction.

There was also no evidence that administration of a 'test dose' of antibiotic reduced the severity of an ensuing reaction. On the contrary, in cases of anaphylaxis caused by an antibiotic where a test dose had been given, a slightly greater proportion of severe reactions (Grades 4 and 5) was seen than if no test dose had been given (58% vs 51%).

Several cases of antibiotic-induced anaphylaxis occurred before the patient had been anaesthetised, enabling prompt diagnosis and management of anaphylaxis prior to administration of other possibly confounding drugs. In addition, investigation was facilitated as there were fewer possible culprits to exclude.

A patient scheduled for elective general surgery and general anaesthesia received a test dose of co-amoxiclav 120 mg after induction, and, 10 minutes later, the full dose. Ten minutes after the full dose the patient developed widespread signs of anaphylaxis, including bronchospasm, oxygen desaturation and hypotension. Anaphylaxis was promptly recognised and treated, leading to a good recovery. Anaphylaxis to co-amoxiclav was confirmed by subsequent allergy investigations.

A patient was scheduled for elective surgery and general anaesthesia. Anaesthesia was induced and a test dose of co-amoxiclav 300 mg was given, followed by the full dose one minute later. The patient developed tachycardia, hypotension, swelling, and oxygen desaturation. Hypotension was prolonged and progressed to PEA cardiac arrest, requiring CPR. The patient was treated for anaphylaxis and successfully resuscitated. Subsequent allergy investigations confirmed anaphylaxis to co-amoxiclav..

A patient was scheduled for elective general surgery and general anaesthesia. Following induction of anaesthesia, a test dose of co-amoxiclav 180 mg was given. The patient reacted to the test dose with bradycardia, profound hypotension and rash. The patient was treated for anaphylaxis, making a good recovery. The allergy clinic diagnosed anaphylaxis to co-amoxiclav after appropriate investigations.

Past medical history and history of antibiotic allergy

Seventy-three patients had a preoperative label of antibiotic allergy – 52 to penicillins (49 penicillin, 2 amoxicillin, 1 piperacillin-tazobactam), of whom three also had a label of cephalosporin allergy. Seven patients had a label of cephalosporin allergy and 16 an allergy to a variety of antibiotics, including trimethoprim, co-trimoxazole, erythromycin, metronidazole, doxycycline and tetracycline. Four of these also had a label of penicillin allergy. One patient had a label of multiple antibiotic allergy to penicillin, cephalosporin and other antibiotics.

The NAP6 Allergen Survey (Chapter 9) demonstrated that the choice of antibiotic was influenced by preoperative allergy history in a quarter of patients who received teicoplanin or vancomycin. Among the 36 patients reported to NAP6 with teicoplanin anaphylaxis, more than half stated preoperatively that they were allergic to penicillin. Among the 20 who were likely to have received teicoplanin because of a history of allergy, eight reactions were Grade 4 and one Grade 5, six developed moderate harm, and one died. In at least three cases of teicoplanin anaphylaxis in patients with a reported history of penicillin allergy, this label was subsequently removed as part of the allergy clinic investigations.

A patient scheduled for elective surgery gave a history of penicillin allergy. Teicoplanin and gentamicin were administered shortly before neuraxial block, five minutes after which the patient felt unwell and nauseated. The patient became, clammy and hypotensive, with tachycardia and flushing/non-urticarial rash. Anaphylaxis was diagnosed and treated promptly and successfully. Subsequent allergy investigations ruled out penicillin allergy and confirmed anaphylaxis to teicoplanin.

Drug errors

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

Suspected antibiotics, allergy clinic investigations and diagnosis

Out of the 266 cases of anaphylaxis reported to NAP6, 98 (37%) were suspected by the anaesthetist to be caused by an antibiotic and 92 confirmed by the review panel. The anaesthetist suspected allergy to an antibiotic in 65 (71%) of these 92 cases. Allergy clinics considered 70 cases to have been caused by allergy to an antibiotic. However, in some cases a single culprit was not confirmed and two or more agents were recommended for avoidance.

Diagnostic uncertainty in the allergy clinic was usually caused by incomplete investigations, with either an insufficient panel of skin tests or because drug provocation to exclude possible culprits was not undertaken (Table 3). This is discussed further in Chapter 14, Investigation.

Concordance between the allergy clinic and the review panel

Table 4 compares culprits identified by the review panel with the diagnosis reached by the allergy clinics. Our data suggest that allergy clinics may be underdiagnosing allergy to co-amoxiclav and teicoplanin, potentially placing patients at risk of future reactions.

In one case, the allergy clinic identified co-amoxiclav without skin or challenge testing, but the review panel considered chlorhexidine the most likely culprit. In three cases, the allergy clinic identified gentamicin with intermediate certainty, but the review panel considered teicoplanin the most likely culprit.

Communication with the patient

In two-thirds of cases appropriate advice on future avoidance was not provided by the allergy clinic. This included; no advice given, not all culprits investigated, no culprit identified, no safe alternatives for future surgery stated, and excessive avoidance advice (eg. multiple antibiotics). See also Chapter 14, Investigation.

Table 3. Oral (12) and intravenous (11) challenges NOT undertaken by allergy clinic but considered necessary by the review panel to either exclude or confirm allergy

Antibiotic	Challenges not undertaken when indicated
Co-amoxiclav	7
Teicoplanin	6
Cefuroxime	1
Flucloxacillin	3
Gentamicin	5
Amoxicillin	1
Total	23

A patient scheduled for elective surgery was induced with fentanyl, propofol and atracurium. Levobupivacaine and clonidine were administered in a nerve block. Teicoplanin and gentamicin were given ≈15 minutes afterwards. Widespread signs of anaphylaxis developed within a few minutes. The Grade 3 reaction resolved with treatment. Investigation in the allergy clinic included skin prick tests for atracurium and bupivacaine but no other investigations such as additional skin prick or intradermal tests, drug challenge(s) or measurement of drug-specific IgE. The clinic described no specific tests for teicoplanin or gentamicin and, with negative tests for other drugs, advised the patient to be cautious about teicoplanin and gentamicin.

Discussion

No previous study has undertaken concomitant studies of incidence of anaphylaxis and antibiotic exposure. This is particularly important in the case of some antibiotics, such as teicoplanin, where usage has increased in recent years. This means NAP6 provides a unique opportunity to examine both prevalence of reactions and incidences.

Our findings provide robust evidence that antibiotics are the most common cause of perioperative anaphylaxis in the UK, adding to previously published data (Low 2016, Kemp 2017, Meng 2017). We also unequivocally identify teicoplanin as being associated with the highest per-administration risk, confirming suspicions expressed by the authors of small case series (Asero 2006, Savic 2015, Kemp 2017, Azamgarhi 2018). This is a new and important finding.

Our findings demonstrate that administration of teicoplanin is closely related to patient-reported penicillin allergy, and it is reasonable to assume that in many of the cases of teicoplanin anaphylaxis penicillin would have been the first-line antibiotic choice. Penicillin is the most commonly reported drug allergy in the community, with up to 10% of the population labelled as allergic to it. It is likely that the majority are mislabelled, and that at least 90% could be de-labelled if an adequate description of the original reaction could be obtained or the patient investigated in an allergy clinic (Borch 2006, Dworzynski 2014, Macy 2015). We also identified that in at

Table 4. Culprit antibiotics suspected by anaesthetists, diagnosed by allergy clinics, and identified by the review panel

Antibiotic	Suspected by the anaesthetist	Allergy clinic (high)	Allergy clinic (intermediate)	No clinic culprit	Review panel
Co-amoxiclav	40	24	8	14*	46
Teicoplanin	33	19	8	9*	36
Cefuroxime	6	2	0	2	4
Gentamicin	0	1	2	0	3
Flucloxacillin	6	2	0	0	2
Piperacillin-tazobactam	3	0	1	0	1
Metronidazole	0	1	0	0	1
Vancomycin	2	0	0	1	1
Total	90	50	19	24	94

Three patients died and one did not attend the allergy clinic.

least three cases of teicoplanin allergy in patients with a reported history of penicillin allergy, this label was subsequently removed as part of the allergy clinic investigations. It is currently impractical for all putative penicillin allergy to be investigated in allergy clinics preoperatively, and the process is significantly complex. However, with the ever-increasing importance of antibiotic stewardship, avoidance of a spurious label of 'penicillin- allergic' is an area ripe for research.

Multiple drug allergy may benefit from preoperative investigation. NICE recommends that those with a suspected allergy to beta-lactam antibiotics should be referred if they need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic or are likely to need beta-lactam antibiotics frequently in the future (eg. recurrent bacterial infections or immune deficiency) (NICE 2014). Referral should also be considered where there is suspected allergy to beta-lactam antibiotics and at least one other class of antibiotic. In the elective setting, improved history taking and allergy clinic referral may facilitate de-labelling and the identification of safe alternatives where allergy is confirmed.

We are facing a threat of increasing antibiotic resistance (WHO 2014, WHO 2017), and in addition there is a growing body of evidence showing that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs, with increased duration of treatment and hospital stay, and higher rates of antibiotic resistance and infections including methicillin-resistant Staphylococcus aureus, Clostridium difficile and vancomycin-resistant enterococcus. Our findings provide additional evidence of the use of second-line antibiotics, driven by drug allergy history, and highlight that substitution with an antibiotic carrying a high anaphylaxis risk is not necessarily a safe solution. This further highlights the need, already raised by the international allergy community, for robust programmes to investigate and de-label, where appropriate, patients with reported history of penicillin allergy, thus improving antibiotic stewardship (Sade 2003, Macy 2014b, Solensky 2014, Krishna 2017).

The most common first clinical feature was hypotension, presenting within five minutes of exposure in three quarters of patients. This is in keeping with published data showing that cardiovascular involvement is the predominant feature

(Gonzalez-Estrada 2015, Kuhlen 2016, Low 2016), and confirms the clinical suspicion and available published data that reactions to intravenous drugs, and antibiotics in particular, can be severe and tend to present very quickly after administration (See Chapter 10, Clinical features and Chapter 11, Immediate management and departmental organisation).

The use of antibiotic 'test doses' appears common, and occurs in one fifth of all cases of antibiotic-induced anaphylaxis reported to NAP6. It cannot reasonably be expected that a single test dose will eliminate the risk of anaphylaxis. In the allergy clinic, where challenge testing only takes place after a negative skin test, the starting dose for drug challenge will vary depending on the severity of the index reaction, the dose that is believed to have caused it, the patient's co-morbidities, whether the challenge is oral or intravenous, and the drug itself. With some high-risk drug challenges the test dose can be as low as 10^{-3} of the therapeutic dose, increasing in two-fold to ten-fold increments. A third of UK anaesthetists routinely administer a test dose when administering an intravenous antibiotic (Chapter 7, Baseline survey), despite guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) advising against their use (Harper 2009). We find no evidence to support the practice.

Considerably more than half of all patients received an antibiotic, and almost all were administered after induction of anaesthesia. Avoiding unnecessary antibiotic administration is certainly one way to reduce the incidence of perioperative anaphylaxis, and adhering to hospital protocols is likely to achieve this. In three quarters of cases, signs of antibiotic-induced anaphylaxis were identified in less than five minutes, and almost all in less than ten minutes. Anaphylaxis-induced hypotension is likely to be exacerbated by general or neuraxial anaesthesia. There is a strong argument for antibiotics to be administered several minutes before induction of anaesthesia. There are several potential benefits: first, lack of allergy can be confirmed with the awake patient immediately before administration; second, the severity of physiological derangement due to anaphylaxis may be lessened; and third, investigation of anaphylaxis is considerably simplified if fewer drugs have been administered.

The NAP6 Allergy clinic baseline survey (Egner 2017, Chapter 13), identified that not all were compliant with national guidelines. Our findings reinforce the need for allergy clinics to follow published guidelines on investigation of possible antibiotic anaphylaxis (Ewan 2010, Dworzynski 2014, NICE 2014, Mirakian 2015).

Allergy clinics did not identify the antibiotic culprits in a quarter of all cases, mostly as a result of investigations that were incomplete in such areas as skin tests and drug provocation challenges. Clinics may be underdiagnosing antibiotic allergy, potentially placing patients at risk of future reactions.

Recommendations

Institutional

■ 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)

■ If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed

■ Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

Individual

■ Antibiotic administration should strictly follow national or local guidelines

■ A test dose of antibiotic should not be used, as it will not prevent or reduce the severity of anaphylaxis

■ 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

■ The anaesthetist should consider co-amoxiclav or teicoplanin among the likely culprits when anaphylaxis occurs after their administration

■ 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.

IV drug challenging may be required to exclude penicillin allergy

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Neuromuscular blocking agents and reversal agents

Nigel Harper

Key findings

- In the baseline survey, neuromuscular blocking agents (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.

- In contrast to the majority of previously published studies, NMBAs were the second most common trigger agent, being 1.4-fold 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 that 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.

- 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.

- Allergy Clinic investigation of NMBA-induced anaphylaxis had significant shortcomings. Use of the NAP6 minimum NMBA panel will help identify the culprit and safe alternatives, especially for rapid-sequence induction.

What we already know

Neuromuscular blocking agents (NMBAs) are generally accepted to be responsible for a high proportion of cases of perioperative anaphylaxis. Major centres report that NMBAs are responsible for between 40% and 66% of all cases (Leysen 2013, Mertes 2003, Mertes 2011), but the proportion appears to be historically lower in Denmark (Garvey 2001) and, until recently, higher in Norway (Harboe 2005).

Sensitisation to NMBAs may result from previous exposure, but this is not always the case: it is likely that environmental exposure to the quaternary ammonium (QA) epitope is sufficient in some individuals to stimulate allergy to NMBAs (Didier 1987). In addition to QA compounds found in detergents and many other products, there is evidence that exposure to pholcodine-containing cough medicines may cause sensitisation to NMBAs (Johansson 2010): NMBA anaphylaxis has declined in Norway since withdrawal of cough medicine containing pholcodine (de Pater 2017).

The quaternary ammonium epitope present in all NMBAs is predominantly responsible for their allergenic properties. Currently-used NMBAs are either monoquaternary (vecuronium and rocuronium) or bisquaternary (suxamethonium, atracurium, mivacurium, pancuronium). There is no evidence that the risk of anaphylaxis is related to the number of quaternary ammonium groups. Individuals may be allergic to more than one NMBA. Cross-sensitivity, based on skin testing and specific IgE, is common, with suxamethonium being the most commonly cross-reacting drug (Sadleir 2013). Cross-sensitivity may occur between different classes of NMBA (for example, benzylisoquinoline and aminosteroid) as well as within classes. Therefore if an NMBA is suspected as a cause of anaphylaxis, it is important that a panel of NMBAs is tested in the allergy clinic to detect cross-reactivity and to establish safe alternative NMBAs (Ewan 2010), especially for use during rapid sequence induction (RSI). In Chapter 13, we proposed the NAP6 NMBA minimum panel – the minimum panel of NMBA tests, which is judged sufficient if it includes the suspected agent, together with suxamethonium, rocuronium, and either atracurium or cisatracurium (Egner 2017).

Non-allergic anaphylaxis may occur with atracurium and mivacurium. There is recent evidence implicating specific receptors on the surface of mast cells (McNeil 2014). Variation in receptor expression may explain why these drugs cause non-IgE-mediated mediator release in some individuals but not in others.

No previous study has undertaken concomitant studies of prevalence of NMBA events and NMBA exposure, enabling incidence to be estimated directly; NAP6 collected information on the number of patients receiving NMBAs during the same year

as the case reporting phase. Previous studies have relied on sales of drug ampoules to estimate the number of patients receiving individual drugs. Ampoule sales are unlikely to accurately reflect the number of patients being exposed. This is particularly important in the case of suxamethonium where ampoule sales are likely to exceed actual usage as a result of high rates of waste when the drug is prepared 'just in case'. It is generally accepted that, among NMBAs, suxamethonium carries the highest risk of anaphylaxis. It has also been suggested that rocuronium is associated with a relatively higher risk of anaphylaxis compared with vecuronium (Sadleir 2013).

In relation to reversal agents, very few cases of allergic reactions to neostigmine have been reported in the world-wide literature (Seed 2000, Hermite 2015). Sugammadex is a known cause of perioperative anaphylaxis: a recent systematic review identified 15 cases of hypersensitivity to this reversal agent – 11 patients underwent skin testing and 10 were positive (Tsur 2014).

Numerical analysis

Baseline and allergen data

In the baseline survey, NMBAs were the drugs anaesthetists most commonly suspected as the trigger when they suspected anaphylaxis, and were also the drugs anaesthetists most commonly avoided because of concerns about anaphylaxis. Among these, suxamethonium and rocuronium were particularly prominent, with anaesthetists three to four times more likely to avoid these than atracurium (see Chapter 7, Anaesthesia baseline survey).

NMBAs were used in 47.2% of general anaesthetics (approximately 1.2 million patients per year) with atracurium accounting for 49.1% of NMBA uses, rocuronium 40.6% and suxamethonium 11.2%. A reversal agent was used in approximately two thirds of operations where a non-depolarising NMBA was used (≈700,000 cases per year), of which neostigmine was used in 91% and sugammadex in 9% (details in Chapter 9, Allergen Survey).

Numerator data

There were 81 cases in which the anaesthetist suspected life-threatening anaphylaxis to an NMBA (Table 1).

Sixty-four cases of anaphylaxis were triggered by NMBAs, 25% of all cases, 33% of identified culprits and 32% of cases leading to death or cardiac arrest. Ninety-five per cent of NMBA-induced reactions presented within five minutes. Rocuronium was the most commonly identified NMBA (27 cases, 42%), followed by atracurium (23 cases, 35%) and suxamethonium (14 cases, 22%). In one case, suxamethonium and rocuronium were equally 'highly likely' to have been the cause of anaphylaxis, and both drugs are included in the numerator – ie. 65 potential trigger agents but only 64 cases.

There were no cases of anaphylaxis due to vecuronium, pancuronium or cisatracurium. Non-allergic anaphylaxis to atracurium was identified in three cases, and to mivacurium in a single case.

Table 1 shows the NMBAs identified during the registry phase of NAP6 as causative agents, together with their absolute and relative frequency.

The incidences of the three most prevalent NMBAs were:

- *Rocuronium:*
  27/459,047 = 1 in 17,002 (95% CI 1 in 11,686 – 1 in 25,799)
- *Atracurium:*
  23/554,543 = 1 in 24,111 (95% CI 1 in 16,069 – 1 in 38,034)
- *Suxamethonium:*
  14/126,086 = 1 in 9,006 (95% CI 1 in 5,368 – 1 in 16,473).

Fewer anaphylactic episodes were found to be due to NMBAs than was suspected by the reporting anaesthetists. In 71% of cases where the anaesthetist suspected an NMBA, the culprit was confirmed by the review panel, and in 14.3% an alternative culprit was identified. The ratio of suspected/confirmed cases was 1.4 for atracurium, 1.3 for rocuronium and 1.1 for suxamethonium (Table 1).

Table 1. NMBAs confirmed as causative agents by the panel, absolute and relative risk
*Data from the NAP6 Activity/Allergen Survey (see Chapter 9). In one case, suxamethonium and rocuronium were equally 'highly likely' to have been the cause, ie, 64 cases but 65 likely culprits.

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

Risk of anaphylaxis

The estimated rates of life-threatening anaphylaxis per 100,000 patients are atracurium 4.2, rocuronium 5.9, and suxamethonium 11.1 (Table 1). Suxamethonium is almost twice as likely to cause anaphylaxis as any other NMBA. Among the non-depolarising NMBAs the relative risks are all notably similar, with no agent having a risk more than 50% higher or lower than atracurium.

In paediatric practice, NMBA-induced anaphylaxis was less common, probably reflecting lower rates of administration in this patient group. This is discussed further in Chapter 19, Paediatrics.

Presenting features and clinical features during NMBA-induced anaphylaxis

These features are discussed in detail in Chapter 10, Clinical features. To summarise – anaphylaxis induced by NMBAs presented rapidly (85% in <5 minutes, 92% in <10 minutes); hypotension was the commonest presenting feature and was particularly prominent in atracurium-induced anaphylaxis, while bronchospasm/raised airway pressure was more common in suxamethonium-induced anaphylaxis.

Severity

Suxamethonium anaphylaxis was more likely to be of severity Grade 3 than NMBA-induced anaphylaxis caused by other agents (Figure 1). Of nine deaths with an identified trigger, four were due to NMBA anaphylaxis; rocuronium was the trigger agent in three cases and suxamethonium in one case.

Figure 1. Severity of NMBA-induced anaphylaxis
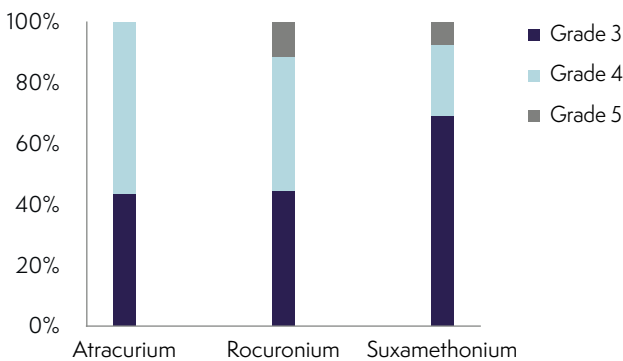
Allergy clinic investigation and diagnosis

Rocuronium was identified by the allergy clinics more frequently than atracurium. There was greater diagnostic uncertainty with atracurium than rocuronium, possibly reflecting the former's propensity for non-allergic anaphylaxis in which skin tests are negative and mast cell tryptase levels may be less elevated. In 10% of cases where atracurium was the culprit agent, the review panel identified non-allergic anaphylaxis as the mechanism, and the mechanism was uncertain in an additional 13%. Pancuronium and cisatracurium were not implicated either by the reporters or the review panel.

We judged adequacy of NMBA investigations based on the NAP6 NMBA minimum panel described above. In 113 cases where the review panel judged clinic investigation for NMBA-induced anaphylaxis was necessary, a sufficient NMBA minimum panel was tested in 67%, with two cases being unclear. The clinic did not identify a safe alternative NMBA in six (5%) cases. Skin testing with the suspected agent was not performed in three (3%) cases and suxamethonium was not tested in four (4%) cases. In sixteen (14%) cases the review panel considered that the patient may be at future risk of anaphylaxis as a result of inadequate advice being given to the patient.

Previous exposure to pholcodine was sought in only 15 patients at the allergy clinic and was recorded in only two patients, both of whom had NMBA-induced anaphylaxis (rocuronium and suxamethonium).

Cross-reactivity

An incomplete picture of cross-reactivity was obtained, as one third of patients were not tested with a full panel of NMBAs. In 27 cases of rocuronium-induced anaphylaxis, cross-sensitivity to other NMBAs was identified on skin prick testing in four, of which suxamethonium was the most common, followed by vecuronium and pancuronium. An additional five patients with rocuronium-induced anaphylaxis were cross-sensitive to atracurium on intradermal testing. Cross-sensitivity to two or three NMBAs was common. Of 23 cases of atracurium anaphylaxis, four showed skin prick cross-sensitivity to cisatracurium and three to mivacurium. Five of 14 patients with suxamethonium anaphylaxis showed cross-sensitivity on skin prick testing and a further two on intradermal testing. In these seven cases, cross-sensitivity was equally likely to occur to aminosteroid and benzylisoquinolinium NMBAs, and one was sensitive to all NMBAs. A total of 17 patients showed cross-reactivity – approximately 40% of those where this was explored.

Reversal agents

No episodes were due to neostigmine. Sugammadex was the suspected trigger agent in two cases but was only confirmed in one case. In this case hypotension, urticaria and hypoxaemia developed in the recovery room approximately 15 minutes after administration. Skin prick and intradermal tests were positive at 1:10 dilution and 1:1000 dilution respectively. The Allergen Survey estimated that sugammadex was administered to 14% of patients receiving rocuronium (Chapter 9, Allergen Survey). We have not estimated the numerical incidence of sugammadex-induced anaphylaxis due to the small number of cases. Neither of the two suspected cases of sugammadex-induced-anaphylaxis was reported to MHRA.

Use of sugammadex for treatment during rocuronium-induced anaphylaxis and anaphylaxis induced by other drugs

This is discussed in Chapter 11, Immediate management and departmental organisation.

Discussion

Anaesthetists appeared to have a high index of suspicion that anaphylaxis is likely to be caused by an NMBA, and they suspected that anaphylaxis was caused by an NMBA approximately 40% more often than was actually the case. The ratio of suspected to confirmed cases was highest for atracurium (1.4:1) and lowest for suxamethonium (1.2:1). This is an unexpected finding as suxamethonium is widely known to be the most allergenic NMBA.

Despite suxamethonium being associated with a higher risk of anaphylaxis, its use should be decided on the overall balance of clinical advantages and disadvantages on a case-by-case basis.

Conclusions concerning the relative incidence of atracurium and rocuronium-induced anaphylaxis should be drawn cautiously. The difficulties inherent in interpreting the reported incidences of uncommon anaphylactic events are described by Laake and colleagues (Laake 2001). In particular, marginal under-reporting has a disproportionately large effect on calculated incidence.

In contrast to the many previously published studies (Mertes 2011, Leysen 2013), NMBAs were the not the most common trigger agent overall: antibiotics were identified as the culprit by the review panel 1.4 times more frequently than NMBAs. It is not known whether changes in the prevalence of antibiotic and NMBA sensitisation in the population, the pattern of perioperative antibiotic use, or the choice of NMBA may have contributed to this trend. NMBAs accounted for approximately one third fewer cases of anaphylaxis than antibiotics, but carry at least as high a risk as antibiotics per administration, with the exception of teicoplanin. The lower prevalence of NMBA-induced anaphylaxis observed is due to ≈2.5 million administrations of antibiotics to surgical patients per year compared with ≈1.2 million administrations of NMBAs. The use of NMBAs in the UK does not appear to have declined significantly – 46% of UK patients undergoing general anaesthesia received an NMBA in 2013 (Sury 2014), and 47.2% in 2016 (Chapter 9, Allergen Survey). However, it is probable that the number of patients receiving suxamethonium, the most allergenic NMBA, is declining. In the 2013 NAP5 Activity Survey, suxamethonium was administered to 13.6% of non-obstetric patients receiving an NMBA, falling to 11.2% in 2016 (Chapter 9, Allergen Survey). In the obstetric setting the fall was even more dramatic – from 92% in 2013 to 72.5% in 2016 (Chapter 20, Obstetric anaesthesia).

Establishing the true incidence, ie. risk, is dependent on an accurate estimation of the number of patients exposed to the trigger agent over the study period. Calculation of the incidence of NMBA-induced anaphylaxis has been hampered in the past by difficulty in obtaining accurate denominator data. Reddy *et al* studied concomitant exposure and anaphylaxis rates over a 6-year period during which the pattern of perioperative anaphylaxis may not have been constant (Reddy 2015). Sadleir, in Western Australia (WA), compared incidence over a 10-year period using 5-year ampoule sales by pharmaceutical companies (Sadleir 2013). The incidence per 100,000 administrations was 8.0, 4.0 and 2.8 for rocuronium, atracurium and vecuronium respectively. In the NAP6

study, the incidence of atracurium anaphylaxis was similar to the WA study, but the incidence of rocuronium-induced anaphylaxis was lower. There are several possible reasons why these estimated incidences do not match exactly with NAP6 data. In the WA study the denominator was reliant on ampoule sales which may not accurately reflect the number of patients receiving the drugs: large patients or those undergoing prolonged procedures may require more than one ampoule and, conversely, drugs may be drawn up and not administered or may simply expire and be disposed of. As suxamethonium is frequently drawn up as an emergency stand-by drug, non-administration of opened ampoules is common. For this reason, previous studies have been unable to provide an accurate estimate of the rate of suxamethonium anaphylaxis. It is also possible that the sensitisation rate in the general population through previous NMBA exposure and environmental exposure to similar molecules differs between the UK and WA. In the UK, the number of patients receiving atracurium exceeds that of rocuronium, whereas in WA, rocuronium has three times the market share of atracurium. Vecuronium is used very infrequently in the UK, representing only 2.2% of all NMBA administrations (Chapter 9, Allergen Survey), but its market share in WA is intermediate between atracurium and rocuronium.

Among survivors of perioperative anaphylaxis, severity, as determined by the review panel, was approximately equally divided between Grade 3 and Grade 4 for atracurium and rocuronium, but a greater proportion of suxamethonium-induced anaphylaxis was Grade 3. Sadleir (Sadleir 2013) reported many fewer Grade 4 NMBA reactions than Grade 3. The greater severity of anaphylaxis in the current study may be partially explained by the inclusion of all patients with profound hypotension (systolic blood pressure <50 mmHg) in the Grade 4 category as a part of the methodology (see Chapter 5, Methods).

Four deaths were attributed directly or indirectly to NMBA-induced anaphylaxis, representing 44% of those fatalities with an identified trigger. The review panel considered that one case of anaphylaxis was definitely caused by rocuronium and one definitely by suxamethonium. Rocuronium was probably the trigger in a further two cases. Statistical analysis of these data would not provide meaningful results. Fatalities due to perioperative anaphylaxis are further considered in Chapter 12, Deaths, cardiac arrest and profound hypotension.

Non-allergic anaphylaxis was positively identified by the review panel in four cases, three of which were due to atracurium and one to mivacurium. Non-allergic anaphylaxis tends to be less severe than its allergic counterpart (Low 2016); Grade 1 and Grade 2 hypersensitivity were excluded from NAP6, probably explaining the small number of non-allergic cases in comparison with many studies in which mild hypersensitivity reactions were included.

It is impossible to draw firm conclusions about the prevalence of cross-sensitivity to NMBAs from NAP6 data, but approximately 40% of those tested adequately showed this. Given the infrequent use of a full NMBA testing panel by allergy clinics, NAP6 data should be considered to be minimum estimates. Only if a full NMBA panel is universally adopted can the true prevalence of cross-sensitivity be established.

Pholcodine exposure in cough medicines has been implicated in sensitisation to the quaternary ammonium epitope, especially in relation to rocuronium-induced anaphylaxis. Consumption of pholcodine per million inhabitants is approximately five times greater in Australia than in the UK (Johansson 2010, Sadleir 2013). A minority of allergy clinics (18%) ask patients about their consumption of pholcodine-containing cough medicines (Egner 2017 and Chapter 13 Allergy clinic baseline survey). In NAP6, of 81 cases where NMBA-induced anaphylaxis was suspected by the anaesthetist, information on pholcodine exposure was entered in only 15. Of these, only two patients were recorded as having taken pholcodine-containing cough medicine. Interpretation of these data is not possible and further UK studies are needed to explore any causal relationship.

Recommendations

Institutional

1. 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

2. 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

3. 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.

4. 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.

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17 Chlorhexidine

Tomaz Garcez

Key findings

- 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.

What we already know

Chlorhexidine is responsible for a significant proportion of cases of perioperative anaphylaxis. Chlorhexidine exposure during the perioperative setting may occur via topical skin disinfection, chlorhexidine-coated central venous catheters, and the use of chlorhexidine-containing lubricating gels (Parkes 2009). It may not be immediately obvious that these products contain chlorhexidine – which has been called the 'hidden allergen' (Ebo 2004).

There are geographical differences in the incidence of chlorhexidine-induced perioperative anaphylaxis. It has been reported to account for 7.7% cases in the United Kingdom (Krishna et al., 2014) and 9.3% in Denmark (Opstrup 2014), but it reported to be a rare culprit in France (Mertes 2016). The cause for the variation is not clear, but may be related to under-recognition and to differences in practice (for example, more use of povidone-iodine and less use of chlorhexidine-coated catheters). As exposure to chlorhexidine is highly likely in any surgical setting, several centres routinely test all patients referred with perioperative anaphylaxis for chlorhexidine allergy. In countries adopting this practice chlorhexidine allergy is frequently identified (Krishna 2014, Opstrup 2014).

Chlorhexidine is a highly effective antiseptic with a broad antimicrobial activity, and it has potential benefits over povidone-iodine. It is therefore widely used in healthcare settings and in the community. Sensitisation to chlorhexidine can occur in either setting as chlorhexidine-containing products are found in both environments. (Garvey 2007, Nakonechna 2014). The true prevalence of chlorhexidine allergy remains unknown, but is likely to be increasing. During a ten-year period up to 2004 only 50 cases of IgE-mediated reactions were reported in the medical literature. More recently, 104 cases were reported in four UK specialist centres during the four-year period from 2009 to 2013 (Egner 2017).

Main exposure routes and possible alternatives

Many lubricating gels containing both chlorhexidine and local anaesthetic are used routinely for urological and gynaecological procedures including urethral catheterisation. Lubricating gels without local anaesthetic or chlorhexidine, or containing local anaesthetics without chlorhexidine are available. These may be acceptable in many settings, and it is logical to choose a chlorhexidine-free product where this is acceptable. In cases of suspected or confirmed chlorhexidine allergy, chlorhexidine-containing gels must be avoided.

Central venous catheters may be chlorhexidine-coated and the operator may not be aware of this. This is particularly important, as chlorhexidine-coated central lines may lead to rapid and severe reactions which will progress if the catheter is not removed. It is of even greater concern that a central line may be placed during the management of perioperative anaphylaxis, bringing the possibility of perpetuating or worsening the reaction. For short-term use in low-risk patients, chlorhexidine-free central venous catheters should be considered; there are alternative antimicrobial coatings available for high-risk cases. It should be noted that a recent Cochrane review questioned the efficacy of chlorhexidine-coated venous catheters in preventing clinically important morbidity (Chong 2017).

In dentistry, chlorhexidine-containing products are widely used because of its wide antimicrobial spectrum and efficacy. Chlorhexidine-containing mouthwashes are regarded as the 'gold standard' against which other antiseptic mouthwashes are usually evaluated. Preparations include mouthwash or spray solutions, gel, and impregnated chips for use in periodontal pockets (Pemberton 2012). Hexetidine mouthwash (chlorhexidine-free) is an alternative, but the evidence base supporting it is much weaker and up to now it has been rarely used. In the situation of suspected or confirmed chlorhexidine allergy, hexetidine should be considered. In a systematic review into the use of hexetidine as a preventer of plaque and gingival inflammation, it was found to 'provide better effects regarding plaque reduction than placebo mouthwashes' but to be 'a poor alternative to chlorhexidine' (Afennich 2011). In known or suspected cases of chlorhexidine allergy, alternatives include:

- As a general antimicrobial mouthwash and for oral hygiene: hexetidine mouthwash

- For endodontic irrigation during root canal therapy: sodium hypochlorite solution

- For periodontic pocket irrigation and oral surgery irrigation of 'dry sockets': normal saline.

Increasingly chlorhexidine is used for skin preparation, including preparation prior to surgery or venepuncture. For both indications, alternatives are readily available, including povidone-iodine for skin preparation and alcohol-based swabs for venepuncture.

In previous studies, up to 80% of patients diagnosed with chlorhexidine allergy had already reported a possible chlorhexidine allergy that could have been confirmed prior to their adverse reaction (Garvey, 2001, Nakonechna 2014). This presents an opportunity to reduce the number of cases of perioperative chlorhexidine anaphylaxis by taking and acting upon a thorough preoperative allergy history.

The warning features of a pre-existing chlorhexidine allergy include:

- Allergic-type symptoms during previous medical or dental procedures

- Allergic-type symptoms when using hygiene products at home or at work

- Itch following preoperative antiseptic body wash

- Itch or rash following cannulation or venesection.

Investigation for chlorhexidine allergy is not currently standardised, and sensitivity and specificity of the available allergy tests is not consistent in reports. Testing includes the use of skin prick tests, intradermal tests, and blood tests for allergen-specific IgE and basophil activation. Testing should ideally be performed within six months of the reaction, as levels of specific IgE have been shown to fall over time (Garvey 2007). The concentration of chlorhexidine used for skin testing varies, and as chlorhexidine may be irritant at intradermal testing it is important to ensure that a non-irritant concentration is used (Brockow 2013, Garvey 2007). Egner recommended performing at least two tests when testing for chlorhexidine allergy, since sensitivity may be improved by using skin prick and specific IgE as initial tests, with intradermal testing reserved for cases where both initial tests are negative and there remains a high clinical probability of chlorhexidine allergy (Egner 2017).

Positive allergy tests to other potential culprit agents have been reported in chlorhexidine-allergic patients, including tests for neuromuscular blocking agents (NMBAs), latex, opioids and beta-lactam antibiotics (Egner 2017, Garvey 2007, Opstrup 2014). The reason for this is unclear, but it means that allergy clinics should investigate all potential culprits regardless of an initial positive result to chlorhexidine.

The MHRA issued a medical devices alert (MDA/2012/075) in 2012, detailing action to be taken to reduce allergic reactions relating to all medical devices and medicinal products containing chlorhexidine (MHRA 2012). Trusts/Boards in the UK were tasked to ensure that the required actions were taken. The development of trust policies was part of that required action.

Numerical analysis

The NAP6 review panel identified 18 cases of chlorhexidine anaphylaxis, accounting for 9% of culprits, making chlorhexidine the third-commonest trigger for perioperative anaphylaxis after antibiotics and NMBAs.

The Allergen Survey identified 2,298,567 annual exposures to chlorhexidine by at least one route, with 73.5% of all patients being exposed (Chapter 9, Allergen Survey). Based on these data, the incidence of anaphylaxis to chlorhexidine is 0.78 per 100,000 exposures – although this may be an overestimate as the denominator data probably underestimates perioperative chlorhexidine exposure.

Among the 18 cases, nine were Grade 3, eight Grade 4 and one was fatal. Sixteen of eighteen cases occurred in males, which is consistent with published data. Age and ASA grade were similar to the main dataset, though there were no ASA 1 patients. Predominant surgical specialties were: urology (six cases), cardiac and orthopaedics (three cases each).

Six cases had only a single reported route of chlorhexidine exposure before the onset of anaphylaxis, while four cases had two and eight had three. Routes of exposure included skin preparation for peripheral cannulation (ten cases), neuraxial block (seven cases) or surgery (four cases), coated central venous catheter (six cases)

and urethral gel (eleven cases). There were no cases where the only recorded chlorhexidine exposure was skin preparation for peripheral venous cannulation.

Time to onset and grade of reaction varied by route of exposure, with quicker onset and higher grade in those with exposure via a coated central venous catheter (mostly onset <5 minutes of exposure and Grade 4) than in those with only topical surgical-site exposure (mostly onset at ≈1 hour and Grade 3).

The presenting clinical features and those occurring at any time during the episode are shown in Figure 1. Approximately two thirds of cases presented with hypotension and none presented with bronchospasm. Bronchospasm was seen in only four (22%) cases compared to 49% of all cases in the main dataset.

Figure 1. Presenting features and those occurring at any time during chlorhexidine-induced anaphylaxis
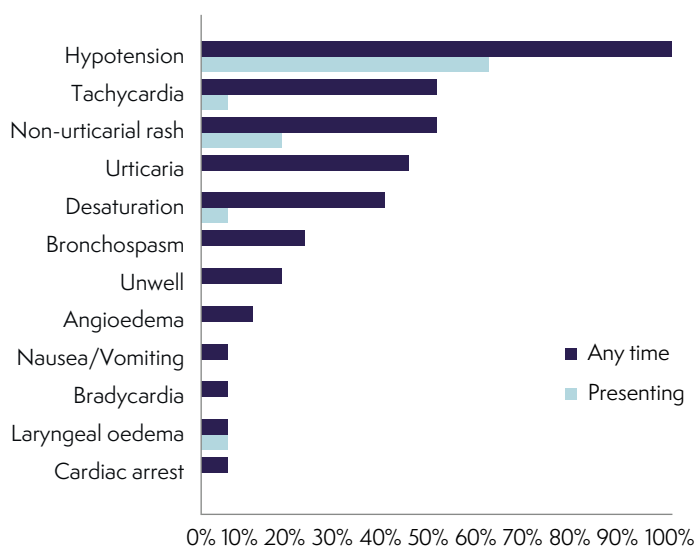
The anaesthetist considered chlorhexidine to be the cause in only five (28%) of the cases.

One patient was exposed to chlorhexidine and developed anaphylaxis despite reporting chlorhexidine allergy preoperatively. In another case a patient reported a prior reaction during anaesthesia that was not investigated, and reacted to chlorhexidine when exposed. In a third case, after the anaphylactic event reported to NAP6, which was investigated and identified and confirmed to be due to chlorhexidine, the patient had a second procedure during which they were again exposed to chlorhexidine and experienced a further reaction.

In two of six cases of chlorhexidine anaphylaxis due to a chlorhexidine-coated central venous line, the line was not removed during resuscitation.

The testing modalities used by allergy clinics, summarised here, are fully described in Chapter 14, Investigation.

Sixteen patients had serial tryptase samples, and all met the NAP6 criteria for a dynamic tryptase rise. One patient did not have a baseline sample taken, but the acute sample level was above the NAP6 cut off, making it compatible with anaphylaxis (discussed

further in Chapter 14, Investigation). One patient had no tryptase samples taken. The mean change from lowest to highest tryptase was relatively modest at 15.8 mcg/L across the 16 cases, and this is discussed further in Chapter 14. The magnitude of the tryptase rise did not relate to the grade of the event.

Seventeen of the cases were investigated in an allergy clinic. Investigation occurred up to 160 days after the event. In the eighteenth case, which was fatal, no blood sample for specific IgE was taken. The investigations carried out are summarised in Table 1.

Table 1. Allergy testing results in cases of chlorhexidine anaphylaxis *there were no equivocal results

Test modalities	Number	Positive*
Skin prick testing only	7	6
Skin prick testing and IgE	3	3 (both tests)
Skin prick testing, intradermal testing and IgE	3	2 (all tests) 1 (IDT & IgE)
IgE only	2	2
Intradermal testing only	1	1
Intradermal testing and IgE	1	1 (both tests)

Only seven (41%) of the cases had more than one test as recommended (Egner 2017). In three (16%) cases, more than one trigger agent was identified.

Discussion

The NAP6 Allergy Survey showed that almost three quarters of patients are exposed to chlorhexidine perioperatively (Chapter 9) – and even this is likely to be an underestimate.

Chlorhexidine is not yet generally considered to be among the 'mainstream' causes of perioperative anaphylaxis, despite evidence to the contrary. This is reflected in failure to investigate appropriately based on perioperative history, in the low suspicion rate we observed when anaphylaxis occurred, in failure to remove chlorhexidine-coated central lines during events, and in patients experiencing second events even after chlorhexidine allergy was identified.

Chlorhexidine anaphylaxis appeared avoidable in three of 18 cases – a considerably higher proportion than in the main dataset. In patients presenting for anaesthesia who had experienced previous perioperative anaphylaxis, chlorhexidine may have been the trigger agent. A thorough preoperative allergy history can reduce the incidence of chlorhexidine anaphylaxis, but only if a positive history is heeded and clinical staff are aware of which medical products and devices contain chlorhexidine.

Any patients with possible warning features should be managed as chlorhexidine allergic and referred to an allergy clinic for further investigation. If the previous reaction occurred during general anaesthesia and it was not investigated, the patient should be referred to an allergy clinic providing perioperative anaphylaxis assessment services. Planned procedures may proceed, but chlorhexidine-free precautions need to be followed. This requires scrupulous attention to the content of all products used on or in the patient.

Despite the 2012 MHRA alert relating to chlorhexidine-containing medical products (MHRA 2012), it appears that many clinical staff are unaware of which products contain this antiseptic, and do not understand the risks of anaphylaxis. Chlorhexidine-coated central venous catheters pose a particular risk, and it is desirable that their chlorhexidine content is clearly and prominently marked.

Products containing chlorhexidine do not currently carry a chlorhexidine allergy warning, and it is very difficult to maintain a complete list of chlorhexidine-containing products. In cases of known or suspected chlorhexidine allergy, any item administered or used for cleaning needs to be scrutinised. An illustrative list from one trust in the UK (Appendix 1) includes many of the pharmaceutical products that contain chlorhexidine. The list of ingredients of all pharmaceutical products and cleaning agents should be checked prior to administration or use on patients with known or suspected chlorhexidine allergy.

It is unsurprising that reactions were more rapid and severe when a central line was the source of the chlorhexidine and the allergen was delivered directly to the circulation. Removing the central line is a key step to treating the reaction under these circumstances, but this requires recognition of the problem and this was not consistently done in NAP6 cases.

National and international guidelines on the investigation of perioperative anaphylaxis do not mandate testing for skin antiseptics but do recommend testing for all relevant exposures. As antiseptics can be 'hidden' on the anaesthetic chart and from the operator, it is pragmatic to include testing for these agents routinely in all cases of perioperative anaphylaxis, as exposure is highly likely (Ewan 2010, Harper 2009, Krøigaard 2007, Mertes 2011). In NAP6, investigation of perioperative anaphylaxis frequently omitted investigation of chlorhexidine (see also Chapter 14, Investigation). When chlorhexidine was tested for, the desirable two tests and testing for other sensitisers was commonly not performed (see also Chapter 14, Investigation).

Although specific IgE testing for chlorhexidine allergy has a sensitivity of around 70% (Egner 2017), this test could help determine the cause of the event in fatal perioperative anaphylaxis. This was not performed in any fatal cases reported to NAP6. A recent preoperative blood sample, for example, one taken for biochemistry, haematology or cross-match purposes, is suitable for use in specific IgE testing.

Recommendations

National

- 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

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

- Investigation of suspected perioperative anaphylaxis should include chlorhexidine

- More than one test for chlorhexidine is necessary to exclude allergy

- 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

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

- 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

- 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.

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Appendix 1:

Products containing chlorhexidine: example from one trust performed in 2012/13

Product	Manufacturer	Ingredients	Indication
Acriflex	Thornton & Ross	Chlorhexidine gluconate	Wounds; burns; scalds
Bactigras	Smith & Nephew	Chlorhexidine acetate	Wounds
Cathejell with Lidocaine	Mediplus	Chlorhexidine hydrochloride lidocaine hydrochloride	Urethral catheterisation
Cepton	LPC	Chlorhexidine gluconate	Acne
ChloraPrep	CareFusion	Chlorhexidine gluconate isopropyl alcohol	Skin disinfection
Chlorohex	Colgate-Palmolive	Chlorhexidine gluconate	Mouth infections and hygiene
Clearasil Pore Cleansing Lotion	Crookes Healthcare	Chlorhexidine gluconate alcohol	Acne
Corsodyl	GSK Consumer	Chlorhexidine gluconate	Mouth infections and hygiene
Covonia Throat Spray	Thornton & Ross	Chlorhexidine gluconate lidocaine hydrochloride	Sore throat
Curasept	Curaprox	Chlorhexidine	Oral hygiene
Cyteal	Pierre Fabre	Chlorhexidine gluconate chlorocresol hexamidine isetionate	Disinfection of skin and mucous membranes
CX Powder	Adams	Chlorhexidine acetate	Skin disinfection
Dermol	Dermal Laboratories	Chlorhexidine hydrochloride Benzalkonium chloride liquid paraffin isopropyl myristate	Dry and pruritic skin disorders
Eczmol	Genus	Chlorhexidine gluconate	Soap substitute
Elgydium	Ceuta	Chlorhexidine gluconate	-
Eludril	Pierre Fabre	Chlorhexidine gluconate chlorobutanol Mouthwash	Mouth and throat disorders

Chlorhexidine

Product	Manufacturer	Ingredients	Indication
Eludril	Pierre Fabre	Chlorhexidine gluconate tetracaine hydrochloride (Throat spray)	Mouth and throat disorders
Germolene (06-Dec-2002)	Bayer Consumer	Chlorhexidine gluconate Phenol	Burns; skin irritation; wounds (Cream)
Germolene	Bayer Consumer	Chlorhexidine gluconate Phenol	Burns; wounds; skin irritation
Hibi	Molnlycke	Chlorhexidine gluconate isopropyl alcohol	Hand and skin disinfection (Topical spray)
Hibiscrub	Regent Medical	Chlorhexidine gluconate	Skin disinfection
Hibitane	Centrapharm	Chlorhexidine gluconate	Obstetric disinfection
Hydrex	Adams	Chlorhexidine gluconate	Skin disinfection
Instillagel	CliniMed	Chlorhexidine gluconate lidocaine hydrochloride	Catheterisation; endoscopy
Medi-Swab H	SSL	Chlorhexidine acetate isopropyl alcohol	Pre-injection swab
Medi-Wipe	SSL	Chlorhexidine gluconate alcohol	Hard surface disinfection
Mycil	Crookes Healthcare	Chlorhexidine hydrochloride Tolnaftate	Fungal skin infections (topical powder)
Naseptin	Alliance	Chlorhexidine hydrochloride neomycin sulfate	Nasal carriage of staphylococci
Nystaform-HC	Typharm	Chlorhexidine acetate or hydrochloride Nystatin, hydrocortisone	Infected skin disorders
Nystaform	Typharm	Chlorhexidine hydrochloride Nystatin	Fungal and bacterial skin infections (Cream)
Periogard	Colgate-Palmolive	Chlorhexidine gluconate	Mouth disorders
Quinoderm Antibacterial Face Wash	Ferndale	Chlorhexidine gluconate Cetrimide, detergents	Skin cleanser; soap substitute
Savlon Antiseptic Cream	Novartis Consumer	Chlorhexidine gluconate Cetrimide	Skin disinfection
Savlon Antiseptic Liquid	Novartis Consumer	Chlorhexidine gluconate Cetrimide	Skin disinfection
Savlon Antiseptic Wound Wash	Novartis Consumer	Chlorhexidine gluconate	Skin disinfection
Serotulle	SSL	Chlorhexidine acetate	Wounds
Spotoway	Health & Diet Food Co.	Chlorhexidine	Skin irritation and spots
Sterets H	SSL	Chlorhexidine acetate Isopropyl alcohol	Skin disinfection
Steripod Chlorhexidine Gluconate	SSL	Chlorhexidine gluconate	Skin disinfection
Tisept	Medlock Medical	Chlorhexidine gluconate Cetrimide	Skin disinfection
Torbetol	Torbet Laboratories	Chlorhexidine gluconate Cetrimide	Acne
Unisept	Medlock Medical	Chlorhexidine gluconate	Skin disinfection
Uriflex C	SSL	Chlorhexidine gluconate	Urinary catheter care
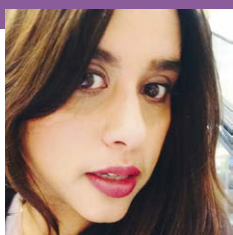
Key findings

■ Anaphylaxis to Patent Blue dye was the fourth most common cause of perioperative anaphylaxis reported to NAP6.

■ Nine cases of Patent Blue dye anaphylaxis were identified. This equates to an incidence of 14.6 per 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 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 anaesthetists' suspicion of Patent Blue anaphylaxis and confirmation by the allergy clinics and the NAP6 review panel.

■ In several cases assumptions that an anaphylactic event after administration of Patent Blue dye had been caused by the dye led to failure to refer for investigation, or poor quality investigation in the allergy clinic.

What we know already

Since the 1960s, blue dyes have been recognised as a rare cause of anaphylaxis. The most widely used blue dye in Europe is Patent Blue (E131). Isosulfan blue is the disulfonated isomer of Patent Blue dye and is used in the USA (Pichler 2007). These two dyes have a high cross-reactivity, although Patent Blue is reported to be the less allergenic of the two (Barthelmes 2010). Methylene blue dye has no structural similarity, but cross-reactivity in those individuals allergic to Patent Blue dye has been described (Keller 2007).

The use of methylene blue in the UK has largely been superseded by Patent Blue because of concerns about the adequacy of lymphatic uptake and fat necrosis at the injection site. The mechanism of sensitisation to Patent Blue is uncertain, but it is highly water-soluble, is found in numerous everyday foods, and is used to colour medication and to dye clothing. It is thought likely that sensitisation occurs through contact with or consumption of everyday products containing E131, but this is uncertain. It is banned as a food dye in Australia, but many cases of suspected allergy are described in Australian breast cancer patients (Wong 2014).

One of the largest case series of patients with formally diagnosed anaphylaxis to Patent Blue dye was published in 2008 (Mertes 2008) and included 14 cases. Hypotension or cardiovascular collapse was the presenting feature in eleven cases, and skin signs were seen in eleven. There were no deaths, but the reactions were severe, with nine patients requiring prolonged intravenous adrenaline and transfer to critical care.

In Mertes' series, skin prick testing alone was found insufficient to confirm the diagnosis, and five patients also required intradermal testing. Conversely, a Norwegian series identified nine patients with hypersensitivity to Patent Blue dye over seven years and all were diagnosed on skin prick testing alone (Hunting 2010). In a UK series of six patients, skin prick testing was sufficient. This group also underwent intradermal testing, and all six patients had positive tests at 1:100 dilution (Haque 2010).

The diagnosis of anaphylaxis during anaesthesia can be difficult, with numerous differentials. When a drug is suspected of having triggered a reaction, the suspicion is usually based on a close temporal relationship between administration and the onset of symptoms. However allergic reactions caused by dyes can be delayed, possibly due to the kinetics of absorption from the subcutaneous tissue at the site of injection. In the Mertes series, the mean time from the injection of the dye to onset of symptoms was 30 minutes. In a French series of six patients with confirmed Patent Blue dye anaphylaxis, mean time to onset of anaphylaxis was 55 minutes (Brenet 2013).

A further potential difficulty in the clinical diagnosis of anaphylaxis to Patent Blue dye is the interaction between the dye and pulse oximetry. This can lead to an artificial lowering in pulse oximetry values. Studies have identified relatively limited changes (mean 1.5%; standard deviation 1.8%) which may be slow in onset (mean time to the maximum change 30 minutes) (Mertes 2008). In another study, Patent Blue was confirmed not to decrease arterial blood oxyhaemoglobin saturation, but to impact on both digital and cerebral oximetry readings by 1.1% and 6.8%, (p<0.0001 for both), with falsely reduced oximeter readings persisting for at least two hours (Ishiyama 2015). Importantly, however, the impact

on oximetry readings is variable between individuals, with some patients unaffected and others falling to saturations of 80%, and for prolonged periods (Murakami 2003, Takahashi 2013). Methylene Blue has been reported to do the same (Gorman 1988).

The reported incidence of allergy to Patent Blue dye varies considerably. In the larger case series, patients had not undergone formal allergy investigation and there was a reliance on the surgeon to make the diagnosis or to report reactions. Some series include all allergic reactions to Patent Blue dye and others anaphylaxis alone. Based on several retrospective and prospective studies, the estimated incidence of reactions of all grades of severity is 0.15–1.1%. A retrospective review of all suspected (unconfirmed) adverse reactions to Patent Blue dye in 7,917 patients after sentinel lymph node biopsy reported an incidence of Grade 1–4 hypersensitivity reactions of 0.85%, with no fatalities and a rate of 0.03% for severe reactions (Barthelmes 2010). A survey of 180 Australasian breast surgeons (with a 42% response rate) estimated an anaphylaxis rate of 0.15%, but only 24% of respondents had confirmed the diagnosis of anaphylaxis with allergy clinic investigation (Wong 2014). The largest case series in which hypersensitivity was confirmed by allergy clinic investigation reported an incidence of 0.34% (6 of 1,742 patients) (Brenet 2013). Other smaller equivalent case series reported incidences of 0.2–1.1% of cases (Mertes 2008, Hunting 2010).

Numerical analysis

Based on data from the Allergen Survey (Chapter 9), the incidence of anaphylaxis to Patent Blue is one case of anaphylaxis to Patent Blue in every 6,863 annual doses, that is 14.6 per 100,000 administrations.
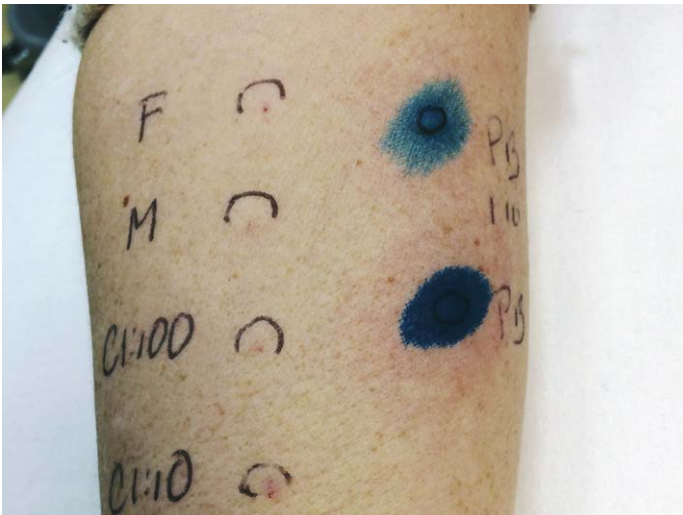
Demographics and Clinical features

All patients were female.

Eight patients received Patent Blue dye to identify sentinel lymph node involvement in surgery for breast cancer, and one to assess fallopian tube patency. Five reactions were Grade 3 and four Grade 4. Six patients required critical care admission and three spent a prolonged period in recovery. In seven cases surgery was completed once the patient had stabilised, and in two it was abandoned.

Time between exposure to Patent Blue and onset of symptoms was variable and sometimes delayed – in seven cases less than 30 minutes and in two more than 60 minutes (Table 1). Interestingly, the patients with the greatest delay in onset were the two heaviest patents.

> A patient was scheduled for elective breast surgery. Intraoperatively she developed a rash and received chlorphenamine and modest boluses of vasopressor. On arrival in recovery approximately two hours after induction, a rash and flushing was noted to be covering her whole body. She became bradycardic, profoundly hypotensive and hypoxic. A diagnosis of anaphylaxis was made and effective resuscitation was provided.

Hypotension was the most common presenting feature (four patients) and during the event all patients were hypotensive, with four having a systolic blood pressure below 50 mmHg. Six patients desaturated to less than 95%, four of these to less than 90%. Skin features (urticaria, angioedema, flushing) were seen in six patients, but three patients developed no cutaneous signs at all and urticaria was the presenting feature in only one patient. (Table 1). A fall in end-tidal carbon dioxide was reported in two cases.

Resuscitation

All cases were resuscitated successfully, and no long-term cardiovascular or cerebrovascular sequelae were reported. The review panel judged that the clinical management by the anaesthetist was 'good' in two cases, 'good and poor' in five, and 'poor' in two where adrenaline administration was delayed or absent (Table 2).

Resuscitation began within 5 minutes of the first sign of anaphylaxis in six cases. In one there was there a delay beyond 10 minutes.

Table 1. Clinical features at any time during Patent Blue anaphylaxis

Patient age (*years* - no. cases)	Time to onset (*mins* - no. cases)	Presenting feature (no. cases)	Lowest blood pressure (*mmHg* - no. cases)	Lowest oxygen saturation (% - no. cases)	Skin signs (no. cases)	Unplanned change in airway (no. cases)
26-45: 5 46-65: 4	0-5: 2 6-10: 2 10-15: 1 16-30: 2 61-120: 2	Hypotension: 4 Desaturation: 2 Urticaria: 1 Tachycardia: 1 Laryngeal oedema: 1	>90: 0 71-90: 2 50-70: 3 <50: 4	>95: 3 90-94: 2 81-90: 2 75-80: 2	Urticaria: 3 Angioedema: 4 Flushing: 4 Non-urticarial rash: 2 None: 3	Intubated: 4 No change: 5

A woman undergoing elective sentinel lymph node biopsy received a Patent Blue dye injection shortly after induction of anaesthesia. She became hypotensive and required multiple bolus doses of ephedrine and then metaraminol throughout surgery. In recovery she was still hypotensive. She developed skin flushing, itching, oxygen desaturation and complained of feeling unwell. She was resuscitated with metaraminol boluses and large volumes of crystalloids. No adrenaline was administered.

In four cases the patient's systolic blood pressure fell below 50 mmHg but chest compressions were not started. In three patients, tracheal intubation was performed as part of resuscitation.

Within five minutes of Patent Blue dye being injected, a patient developed laryngeal oedema, stridor, hypotension and mild desaturation. She was resuscitated with intramuscular adrenaline, chlorphenamine and hydrocortisone. A decision was made not to intubate. No airway complication occurred.

Adrenaline was administered to seven of nine patients. In the cases where it was omitted, multiple doses of ephedrine, metaraminol, and in one case phenylephrine were used. All patients received intravenous crystalloid and eight patients received chlorphenamine and hydrocortisone.

Table 2. Initial management of Patent Blue dye anaphylaxis

Time to Initiate treatment (*minutes - no. cases*)	Administration of adrenaline when Indicated	Adrenaline given IV	Adrenaline given IM	Anaesthetist management (panel rating)
0-5: 6 6-10: 2 11-16: 1	Yes: 7 No: 2	Yes: 5 No: 4	Yes: 2 No: 7	Good: 2 Good and poor: 5 Poor: 2

Tryptase

Mast cell tryptase levels were available for eight cases. In six of these a dynamic MCT was seen (highest level - 72.7 mcg/L), in one case there was no rise, and in one case levels were elevated both at baseline and during anaphylaxis suggesting that the patient had an underlying mast cell disorder.

Referral

Referrals to the allergy clinic were mostly made by the index anaesthetist and were 'good', with the exception of one case which was not referred at all for further investigation. This decision appeared to be made on the basis of the urgency of cancer treatment, and in a subsequent anaesthetic the patient received identical drugs with the exception of omission of Patent Blue dye.

In one case the patient was referred for evaluation of suspected anaphylaxis to methylene blue dye when they had in fact received Patent Blue dye.

A patient who received an antibiotic, skin preparation with chlorhexidine, and a Patent Blue dye injection developed skin flushing, hypotension, tachycardia, and oxygen desaturation. She was resuscitated uneventfully and her surgery was completed. She was not referred to an allergy clinic, but the anaesthetist diagnosed anaphylaxis to Patent Blue dye based on the timeline alone. She went on to have further surgery, receiving identical drugs with the exception of Patent Blue dye.

Investigation

All eight patients referred to an allergy clinic had a positive skin prick test to Patent Blue dye which confirmed the diagnosis. An intradermal test to Patent Blue dye was also performed in one case, and this was also positive. In one case skin prick testing to Patent Blue dye was the only investigation performed and no other drugs were investigated.

There was good correlation between the anaesthetists' opinions that Patent Blue dye had caused anaphylaxis and the findings of allergy clinics and the NAP6 review panel. Of the nine cases evaluated by the panel, eight patients were judged to have definitely reacted to Patent Blue dye and one to have probably reacted.

The review panel judged that investigation by the allergy clinic had been 'good' in four cases, 'good and poor' in two cases, 'poor' in one and was not assessed in one. The most common deviation from BSACI (British Society for Allergy and Clinical Immunology) guidelines was failure to investigate as culprits all drugs that the patient received in the hour prior to their anaphylaxis.

Time to clinic appointment and delays in surgery

The time before being seen at an allergy clinic appointment varied from 15 to 162 days. Reasons for prolonged waits were unknown, but it is noted elsewhere that urgent investigations were often delayed (see Chapter 14, Investigation). Despite some long waiting times, there was no evidence that urgent treatment had been delayed.

Discussion

Anaphylaxis to Patent Blue is a relatively common cause of perioperative anaphylaxis. Difficulty in recognising it may occur because:

- There may be delay in onset
- Falsely low peripheral oximetry readings may lead to distraction or mask true hypoxia associated with severe anaphylaxis
- Skin features may be absent.

Although no patient died, it should not be assumed that such reactions will be mild: many of the events were Grade 4 and required postoperative critical care. There was omission of cardiac compressions in the face of profound hypotension, and

not all patients received timely adrenaline. These findings are not restricted to the management of Patent Blue anaphylaxis and are discussed in Chapter 12, Deaths, cardiac arrest, and profound hypotension, and Chapter 11, Immediate management and departmental organisation, respectively.

Peripheral oxygen concentrations can be low after administration of Patent Blue dye without hypoxia or anaphylaxis, but the impact of Patent Blue on oxygen saturations is variable. This might lead anaesthetists to assume that apparent hypoxia is artefactual, or may delay diagnosis of anaphylaxis or other acute conditions. Great caution is required when there is apparent hypoxia, and management should proceed with the presumption that the measurement is correct. A change in airway device (intubation during resuscitation) was more common during Patent Blue dye anaphylaxis than in other cases. This may be a consequence of concerns about difficulty in interpreting oximetry readings, and it is a welcome finding that there were no airway complications. The low rate of airway difficulty or complications in NAP6 is discussed in Chapter 11, Immediate management and departmental organisation.

Most cases occurred during surgery for breast cancer, and all occurred after surgery had started. Many reactions were severe, but no patient developed cardiac arrest or died. In this situation, it may be difficult to decide whether to complete the surgery (which is often less major than other cancer operations) or to abandon it. In general, judgement seemed to have been good. Where surgery is abandoned an individual decision will need to be made regarding future options. Allergy clinic appointments at less than six weeks may lead to incomplete investigation, or false negative results. Options therefore include urgent allergy clinic assessment, proceeding with surgery before allergy clinic investigation (see Chapter 11, Appendix C), or non-operative treatments. Where urgent clinic assessment is desirable or surgery is to take place without full assessment, urgent discussion with the allergy clinic is likely to be useful, and improved routes of communication between departments of anaesthesia and specialist allergy clinics are likely to facilitate this (see Chapter 11, Immediate management and departmental organisation).

Anaesthetists were generally correct when they suspected Patent Blue dye as a cause of perioperative anaphylaxis. However, there is a danger of confirmation bias. It was of concern that one patient was simply assumed to have reacted to Patent Blue dye when other potential culprits had also been administered, and the panel judged that allergy clinic referral should take place after all such events. In another case, the allergy clinic only tested for allergy to Patent Blue dye and ignored all other drugs, and in other cases after exposure to Patent Blue dye there was an incomplete search for other culprits. All drugs that the patient received should be investigated during the patient's allergy clinic investigations. Skin testing for the key suspect drugs is not sufficient. In all these there was the potential that another cause of anaphylaxis might have been missed with the potential for harm to the patient.

Recommendations

Individual

- 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
- 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
- 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.

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Colloids and infrequent trigger agents

Nigel Harper

Key findings

- 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.

- There were single cases in which one of the following triggers were identified:
  - Propofol
  - Aprotinin
  - Protamine
  - Heparin.

- 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.

Table 1. Trigger agents identified in NAP6 with low prevalence

	Definite	Probable	Total
Succinylated gelatin-containing IV fluids	3	-	3
Ondansetron	1	1	2
Propofol	1	-	1
Ibuprofen	1	-	1
Protamine	1	-	1
Aprotinin	-	1	1
Heparin	-	1	1
Blood product	2	-	2

What we already know

A number of drugs are rare causes of perioperative anaphylaxis either because they have a very low incidence of per-use anaphylaxis or because they are used only in a fraction of anaesthetics. These drugs are discussed individually in this chapter.

Methods of analysis are the same as in other sections of the report (Chapter 5, Methods).

Intravenous gelatin solutions

There were three cases of anaphylaxis caused by succinylated gelatin solutions – one each due to Gelofusine, Geloplasma and Isoplex. The patients were scheduled for general surgery or urological surgery, which was abandoned in one case after the surgical procedure had started. The first feature of anaphylaxis was hypotension in two patients and bronchospasm in the third. Onset occurred within five minutes in two patients, and between 5-10 minutes in the third. Two patients received general anaesthesia with propofol, fentanyl and rocuronium. One patient received epidural anaesthesia, and initial hypotension was treated with vasopressors and an intravenous (IV) gelatin infusion, following which the patient's condition rapidly deteriorated. Cardiac arrest (pulseless electrical activity – PEA) occurred in one patient.

All cases received IV adrenaline boluses and one required a continuous infusion. One patient received vasopressin. Two patients required continuing vasopressor therapy in the ICU. One patient died.

In each of the cases the anaesthetist correctly suspected that the IV gelatin solution was responsible for anaphylaxis, although recognition of anaphylaxis was not prompt in all the cases due to confounding differential diagnoses.

Comment

The Allergen Survey (Chapter 9) estimated that each year 48,203 UK patients are exposed to gelatin or gelatin-containing IV fluids during anaesthesia. The calculated incidence was 6.2 per 100,000 administrations, a rate similar to that of rocuronium (Chapter 16, NMBAs).

In a single specialist UK allergy clinic, Low *et al* described three cases (≈1.7% of all cases) over a seven-year period (Low 2016). In an eight-year multi-clinic report, Mertes *et al* recorded 56 cases of IgE-mediated anaphylaxis due to IV gelatin solutions, but Grade 1 and 2 reactions were included and the total number of patient exposures during that period was not stated (Mertes 2011).

Ondansetron

The review panel identified two cases of ondansetron-induced anaphylaxis. In the first case the patient developed cough and felt unwell and anxious after the administration of ondansetron prior to induction of anaesthesia. Following induction, there was rapid-onset urticaria and hypotension, progressing to PEA cardiac arrest. Adrenaline and noradrenaline were required during resuscitation. Skin prick and intradermal tests were positive to ondansetron. The second patient underwent spinal anaesthesia and became unwell, with respiratory distress, itching and flushing almost immediately

after receiving ondansetron. There was severe hypotension which was unresponsive to phenylephrine but resolved after administering intramuscular (IM) adrenaline. The review panel considered that ondansetron was the probable cause as skin testing was not conclusive.

Comment

Ondansetron is administered very commonly during anaesthesia as a prophylactic anti-emetic. The Allergen Survey estimated that this drug was administered in 78% of general anaesthetics and 66% of all cases (Chapter 9). The occurrence of only a single definite case of ondansetron-induced anaphylaxis during NAP6 indicates the extreme rarity of this reaction. However, these reactions may be severe: two fatal reactions and one case of PEA cardiac arrest attributed to ondansetron-anaphylaxis have been reported (Ouni 2017, Goyal 2016). In relation to drugs that are only rarely allergenic, there may be uncertainty about the optimum concentration to use for skin testing in order to avoid false positives due to non-specific irritation and false negatives due to over-dilution. It has been suggested that ondansetron 0.02 mg/ml is optimum for intradermal testing (Fernando 2009).

Propofol

A single case of propofol-induced anaphylaxis was confirmed by the review panel. The event occurred within five minutes of induction of anaesthesia with propofol, rocuronium and fentanyl, and the anaesthetist suspected that rocuronium was the culprit drug. The first clinical feature of anaphylaxis was flushing, which proceeded to hypotension, wheeze, and oxygen desaturation. This was a severe reaction and the patient required several doses of IV adrenaline. The mast cell tryptase measurements demonstrated a dynamic increase, and skin prick and intradermal tests were positive to propofol with other potential trigger agents excluded by negative testing.

Comment

Propofol is an extremely uncommon cause of anaphylaxis. The NAP6 Allergen Survey estimated that more than two million patients in the UK are exposed to this induction agent each year (Chapter 9). Twenty-four IgE-mediated cases were reported in an eight-year French study (Mertes 2011), and two cases were recorded in a seven-year single-clinic UK study (Low 2016). Asserhøj and colleagues in Denmark recently suggested that propofol-induced anaphylaxis may occur in some patients through a non-IgE-mediated mechanism (Asserhøj 2016). Skin testing would be negative in this situation, and controlled provocation testing with IV propofol is necessary to confirm the diagnosis. This procedure is probably restricted to the Danish clinic, although other clinics may offer this test in the future. In the same publication, the authors dispelled the notion that propofol is contraindicated in adults who are allergic to egg, soya or peanut, but some uncertainty still exists in the case of children who have experienced anaphylaxis to egg (Harper 2016). A diagnosis of hypersensitivity to propofol has serious implications for the patient, given the ubiquity of this induction agent and thelikelihood of re-exposure unless a hazard warning is carried at all times.

Protamine

The review panel attributed anaphylaxis to protamine in one case, with high probability. The patient received protamine after cardiac surgery, and immediately developed severe hypotension and bronchospasm necessitating cardiopulmonary bypass and IV adrenaline. Skin testing was positive and the mast cell tryptase level was greatly elevated.

Comment

Several case reports of anaphylaxis due to protamine have been published, mainly relating to cardiac interventions. Mertes reported four cases in an 8-year multicentre study in France, but the severity of the individual cases was not described (Mertes 2011). It has been suggested that patients who have been exposed to Neutral Protamine Hagedorn insulin, which contains protamine, are more likely to experience protamine-induced anaphylaxis (Stewart 1984). Fish allergy has been implicated as a risk factor for protamine-anaphylaxis, as protamine is traditionally extracted from the sperm of fish. It is possible that the drug will be increasingly synthesised by recombinant biotechnology, and sensitisation to the fish-derived product may be unlikely to result in anaphylaxis when a patient is exposed to the recombinant formulation.

Ibuprofen

A single case of anaphylaxis to ibuprofen was reported, in which the review panel considered that there was high diagnostic certainty. This was a delayed reaction to oral premedication in a child (further described in Chapter 21, Paediatric anaesthesia). An oral provocation test was positive, but skin testing was negative, indicating a non-IgE-mediated (non-allergic) mechanism.

Comment

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

Aprotinin

A single case of aprotinin-induced anaphylaxis occurred within 5 minutes of administration. The clinical presentation was bronchospasm, followed by hypotension and cutaneous features. The review panel designated this case 'probable'.

Comment

Hypersensitivity to aprotinin is well-recognised. A series of over 12,000 exposures to aprotinin during cardiac surgery identified 23 cases of anaphylaxis, with a greater incidence in patients who had been previously exposed (Dietrich 2007).

Heparin

A single case of anaphylaxis to unfractionated heparin was reported, given IV during surgery. The reaction was delayed and presented with hypotension, flushing and urticaria. Mast cell tryptase results were not available. Skin prick tests were positive to unfractionated heparin and enoxaparin and all others were negative. The review panel judged the likelihood was 'probable'.

Blood products

There were only two incidents related to blood products: one to cryoprecipitate and one to fresh frozen plasma. The very small number of cases of reactions to blood products (with none to red blood cells) is notable. The Activity Survey estimated approximately 84,000 perioperative administrations of blood products. The relative infrequency of these reactions is perhaps attributable to the success of the Serious Hazards of Transfusion (SHOT) haemovigilance scheme https://www.shotuk.org/.

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Nuala Lucas

Key findings

- 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.

- Hospital Episode Statistics data for 2015-16 showed that 259,243 women were delivered by caesarean section. This gives an incidence of perioperative anaphylaxis in obstetric patients as 3.1 per 100,000 caesarean sections.

- There were no obstetric cases of anaphylaxis caused by 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 the starting of anaphylaxis-specific treatment was slower than in non-obstetric cases. This probably illustrates the wide differential diagnosis of hypotension in the obstetric patient and 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 are 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.

What we know already

Anaphylaxis and perioperative anaphylaxis in pregnancy

Until recently, anaphylaxis specifically in obstetric patients had received only limited prospective examination, and available knowledge was limited to case reports, case series and reviews. Anaphylaxis in obstetric patients is rare. The Scottish Confidential Audit of Severe Maternal Morbidity identified 18 cases of anaphylactic shock (defined as an allergic reaction resulting in collapse with severe hypotension, difficulty breathing and swelling/rash, and broadly equivalent to severity Grade 3 as used in NAP6), over the period 2003-2012, giving an incidence of 3 per 100,000 births (Lennox 2014). Mulla reviewed the hospital discharge records of parturients in Texas over a two-year period; women who had delivered a neonate and simultaneously had a diagnosis of anaphylaxis were selected for study, and Mulla reported an incidence of maternal anaphylaxis of 2.7 per 100,000 deliveries (Mulla 2010). More recently the UK Obstetric Surveillance System (UKOSS) conducted a population-based prospective study of anaphylaxis in pregnancy from all obstetrician-led maternity units in the UK over a three-year period (McCall 2017). There were 37 confirmed cases of anaphylaxis in pregnancy: an estimated incidence of 1.6 per 100,000 maternities. Of the 37 cases, 19 occurred in association with perioperative care, caesarean section or surgical management of post-partum haemorrhage after vaginal delivery.

Immunological impact of pregnancy on anaphylaxis

Previous epidemiological studies of perioperative anaphylaxis have identified a predominance of cases in females (Mertes 2011) – though this is not seen in NAP6 (see Chapter 10, Clinical features). The immune status is altered in pregnancy, and it has been suggested that increased progesterone levels during pregnancy may predispose pregnant patients to anaphylaxis. Meggs and colleagues described a patient with recurrent anaphylaxis which worsened dramatically during pregnancy. The episodes resolved after delivery when the woman started breastfeeding (Meggs 1984), but recommenced when breastfeeding ceased. The recurrent anaphylaxis finally responded to suppression of gonadotropin by luteinising hormone-releasing hormone, and then to oophorectomy. However, given the paucity of similar reports,

and also the behaviour of other conditions in pregnancy with an immune basis, such as asthma where a significant proportion of patients report an improvement in symptoms (Vatti 2012), it seems unlikely that a generalisation of increased susceptibility to anaphylaxis can be applied to all pregnant women.

Anaphylaxis during caesarean delivery

The predominant use of neuraxial techniques in obstetric anaesthesia limits the exposure to many of the widely recognised trigger agents for anaphylaxis. In a literature review of anaphylaxis in obstetric patients over an eleven-year period, 14 cases of anaphylaxis in association with caesarean section were identified, (27 obstetric cases reported in total) (Hepner 2013). The most common trigger agent was latex, occurring in ten of the 14 cases. In that series there were also three cases of anaphylaxis with suxamethonium. In the UKOSS study twelve women had a reaction to prophylactic antibiotics given at the time of caesarean delivery, with five reactions occurring when the antibiotics were given after the baby was born – which is not currently recommended practice (National Collaborating Centre for Women's and Children's Health, 2011). This raises the question of the potential impact on neonatal morbidity of anaphylaxis occurring in association with prophylactic antibiotics. The overall incidence of prophylactic-antibiotic-related anaphylaxis during caesarean delivery in the UKOSS study was 2.1 per 100,000 caesarean deliveries (McCall 2017). The agents responsible for reactions to anaesthetic drugs were suxamethonium, thiopental, and a component of spinal anaesthesia.

Maternal outcomes

Reported maternal and neonatal outcomes vary significantly, depending on the timing of onset of the anaphylactic reaction. In the UKOSS study there were two maternal deaths (giving a case fatality ratio 5%, (95%CI 0.7-18.2%), both of these deaths occurring in women who had already delivered), and 19% of women suffered one or more additional severe maternal morbidity (including haemorrhagic events, cardiac arrest and pulmonary embolism) (McCall 2017). In the Confidential Enquiries into Maternal Deaths in the UK, four deaths have been reported from anaphylaxis since 2000. In Hepner's case series no maternal morbidity or mortality was observed when maternal anaphylaxis occurred during labour (Hepner 2013). The picture appears to vary for anaphylaxis arising during caesarean section. In Hepner's series, severe maternal morbidity, pulmonary oedema, acute respiratory distress syndrome, and disseminated intravascular coagulation were reported in 20% of women who developed anaphylaxis in this setting.

Impact on the neonate

Neonatal outcomes show a different pattern, in that they appear to be worse when maternal anaphylaxis develops during labour, something which is likely to be related to poor or inadequate maternal resuscitation. The effect of maternal anaphylaxis on the foetus is largely as a result of the impact on the uteroplacental circulation arising from maternal hypotension. The placenta is metabolically active and produces diamine oxidase, a histaminase that metabolises histamine and other endogenous mediators.

(Baraka 1980, Maintz 2008). In the UKOSS study no babies died, but in those babies whose mother had anaphylaxis before delivery 41% suffered morbidity (Neonatal Intensive Care Unit admissions, preterm delivery, or whole body cooling for neonatal encephalopathy (McCall 2017)). In Hepner's case series, no neonatal neurological abnormalities were reported when maternal anaphylaxis developed during caesarean delivery (Hepner 2013).
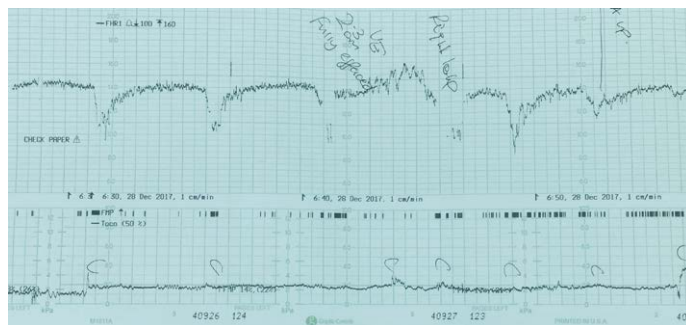
Cardiotocograph showing unprovoked fetal heart rate decelerations

Numerical analysis

We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey estimated 233,886 obstetric anaesthetics are administered per annum in the UK, giving an incidence of severe obstetric perioperative anaphylaxis of 3.4 per 100,000 (95% Confidence interval 1.48-6.74 per 100,000). The incidence in obstetric patients is therefore lower than in non-obstetric adult patients (247 cases in 2,489,428 patients: 9.92 per 100,000 95% CI 8.72 - 11.24 per 100,000, Fisher P=0.002).

Six cases occurred in association with anaesthesia for caesarean section (Category 1–2 three cases; Category 3–4: three cases). One case was related to anaesthesia for a post-partum procedure and in one case the nature of surgery was unknown.

Six patients had received neuraxial anaesthesia and two patients had received general anaesthesia.

Details of the event

All eight cases presented in the operating theatre. In five out of the six caesarean section cases anaphylaxis developed after the baby had been delivered. Three cases occurred during daytime hours Monday–Friday, with the remaining five cases occurring out of hours in evenings or at weekends. In three cases the primary anaesthetist was a consultant, in three cases an anaesthetist in training, and in two cases a non-consultant career grade anaesthetist. In all except one case a consultant was present for resuscitation. The theatre team were judged to have contributed effectively to management of the case in all except one case.

Presentation

In four out of the six patients who developed severe anaphylaxis during neuraxial anaesthesia, a common feature of presentation was that the patient complained of feeling unwell prior to the onset of hypotension or other clinical signs. All patients developed hypotension, in some cases profound.

In four of the cases (both general anaesthesia cases and two of the neuraxial cases) there was prompt recognition of the clinical event. In only one case (neuraxial anaesthesia) was the event promptly recognised as anaphylaxis.

> A woman received spinal anaesthesia for caesarean section performed out of hours. She received diamorphine and bupivacaine in the spinal anaesthetic after skin preparation with chlorhexidine. She received prophylactic phenylephrine boluses for the pre-emptive management of spinal hypotension and a cephalosporin for surgical prophylaxis. Following delivery of the baby she received syntocinon and ondansetron. One hour after the spinal was sited she complained of feeling unwell and developed profound hypotension that was managed with multiple phenylephrine boluses and intramuscular adrenaline.

> An obese woman underwent caesarean section. She received propofol and suxamethonium as part of a rapid sequence induction followed by atracurium, morphine and syntocinon given after delivery of the baby. Soon after delivery she developed sudden profound hypotension, and this was initially managed with phenylephrine and ephedrine boluses. However, she required a noradrenaline infusion to effectively treat the hypotension. Subsequent allergy clinic testing revealed sensitivity to atracurium.

Management

Specific treatment for anaphylaxis was initiated promptly in five cases once the clinical event was recognised as anaphylaxis. It was judged as slow in the remaining three. The vasopressors used to manage hypotension are shown in Table 1. Phenylephrine was the predominant agent used. Four patients received adrenaline as part of the management of anaphylaxis.

Table 1. Vasopressor drugs used in the management of perioperative anaphylaxis in obstetrics

	Adrenaline bolus		Ephedrine	Metaraminol	Phenylephrine
	IV	IM			
All cases (n=8)	1	3	3	2	6
GA cases (n=2)	0	1	2	0	1
Neuraxial cases (n=6)	1	2	1	2	5

Five of eight patients received chlorphenamine and six received hydrocortisone. Fluid management was deemed to be appropriate in all patients where that information was supplied (five out of eight).

A specific anaphylaxis pack was used to assist management in only two cases.

Mast cell tryptase levels to support diagnosis were measured in all cases.

The review panel were able to assess the anaesthetist's clinical management in five out of eight cases; in four cases this was judged as good' and in one 'good and poor'.

Maternal and neonatal outcomes

Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during neuraxial anaesthesia required tracheal intubation. No woman progressed to cardiac arrest. After the anaphylaxis event two women were transferred to the critical care, two were cared for in an observation bay on the delivery suite, two were transferred to the recovery unit and two were cared for in the operating theatre. Hospital discharge was delayed for three women, but the remaining five were discharged at the time anticipated prior to the anaphylactic reaction. One woman subsequently reported anxiety about future anaesthetics. There were no reports of any woman developing post-traumatic stress disorder or any other sequelae.

In five of the six women who developed anaphylaxis in association with caesarean section, the onset of the reaction was after delivery of the baby. In one case the onset was immediately before delivery; there is no further information about neonatal outcome in this case.

Referral for investigation

Seven women were referred to an allergy clinic for investigation. At the time of referral four women were provided with written or oral information about which drugs or substances to avoid before they were seen in an allergy clinic, and three women received no information. The quality of referral to the allergy clinic was 'good' in three cases, 'good and poor' in one, 'poor' in one and 'unassessable' in two.

No cases were reported to the Medicines and Healthcare products Regulatory Agency (MHRA).

Of the eight cases, the review panel identified the agent responsible for the anaphylactic reaction in four (Table 2).

Table 2. Identified causative agents in obstetric perioperative anaphylaxis in NAP6

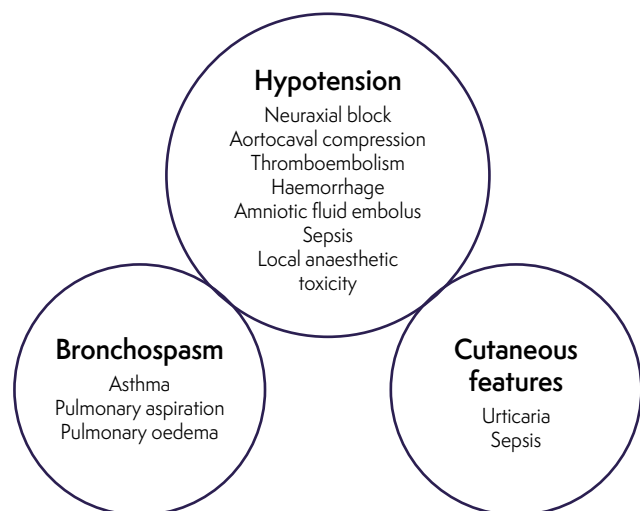|	Certainty of agent as cause of anaphylaxis
Suxamethonium	Definite
Atracurium	Definite
Chlorhexidine	Definite
Ondansetron	Probable

The anaesthetist made a correct judgement about the responsible agent at the time of the reaction in only one case.

Discussion

Severe perioperative anaphylaxis in obstetric patients is extremely rare. In the NAP6 dataset the outcomes for women and their babies were good. Anaesthetists however should not be complacent: anaphylaxis can still be fatal in the obstetric setting, and indeed this was reported in the most recent MBRRACE report (Knight 2017). In NAP6, delays in diagnosing anaphylaxis (as opposed to recognising an acute event) and in starting anaphylaxis-specific treatment were greater in obstetric cases than in others.

There is a broad differential diagnosis for anaphylaxis in pregnancy, including pulmonary thromboembolism, amniotic fluid embolus, cardiac disease, complications of anaesthesia (including high/total neuraxial block and local anaesthetic toxicity), sepsis, and post-partum haemorrhage (Figure 1). Disseminated intravascular coagulation (DIC) is a very common finding in amniotic fluid embolus and can develop with other obstetric complications but can also be present in anaphylaxis (Borahay 2011, Truong 2015).

Figure 1. Differential diagnosis of anaphylaxis in obstetrics

Hypotension
Neuraxial block
Aortocaval compression
Thromboembolism
Haemorrhage
Amniotic fluid embolus
Sepsis
Local anaesthetic toxicity

Bronchospasm
Asthma
Pulmonary aspiration
Pulmonary oedema

Cutaneous features
Urticaria
Sepsis

The overlapping clinical features of anaphylaxis with other acute obstetric morbidities can hinder the diagnosis of anaphylaxis, particularly during the onset or in the presence of neuraxial block. It has been suggested that, because of the altered immune response in pregnancy, the classical clinical features of anaphylaxis may be modified, such that hypotension may be the predominant or only sign (Rosen 1992), although in published case series cutaneous and respiratory manifestations were also common (Adriaensens 2013, Hepner 2013). In the absence of prophylaxis, hypotension can occur in two thirds of patients with spinal anaesthesia, though this can be effectively prevented with vasopressors. However, other conditions, such as aortocaval compression, haemorrhage, and, much more rarely, amniotic fluid or thromboembolic embolus, can lead to hypotension.

As many perioperative obstetric patients are awake, it is unsurprising that presenting features differ from anaesthetised patients. A subjective feeling of being 'unwell' is generally preceded by physiological disturbance, and this should be a key indicator for obstetric anaesthetists of the possibility of anaphylaxis.

Hypotension was the commonest objective physiological disturbance in obstetric anaphylaxis in NAP6. In four of the women who developed anaphylaxis during neuraxial blockade in NAP6, 'new' hypotension developed – that is, hypotension developing after the period of time during which spinal hypotension would have reasonably been expected. Nevertheless, whenever hypotension develops, obstetric causes are likely to be uppermost in the anaesthetist's mind when working on the labour ward, and this in itself could be a source of delay.

Adrenaline was administered to half the obstetric cases compared with 83% of all NAP6 cases. It was administered intravenously to only one of eight obstetric patients, compared to three quarters of all patients, and intramuscular adrenaline was administered in three obstetric cases and to 14% of non-obstetric cases. In contrast, phenylephrine was the vasopressor most commonly used to treat hypotension associated with obstetric anaphylaxis. Phenylephrine infusions are recommended to prevent and treat hypotension associated with spinal anaesthesia (Kinsella 2018). Phenylephrine is therefore immediately available and familiar to the anaesthetist working on the labour ward. In the presence of spinal anaesthesia, and thus effective sympathectomy, hypotension from other causes can be exacerbated and require large doses of vasopressor to treat effectively. Adrenaline is the agent recommended for the management of anaphylaxis, but in obstetric patients there might be concerns about the potential effect on the uteroplacental circulation when used to treat anaphylaxis before delivery. The effect of adrenaline administered intravenously on uterine blood flow has largely been studied in animal models (Chestnut 1986, Hood 1986). Adrenaline causes uterine vasoconstriction and can cause uterine blood flow to decrease by as much as 40%, but this effect is short-lived and Hood has suggested that the effect is similar to the decrease that occurs during a normal uterine contraction. The uteroplacental circulation is low resistance and not subject to autoregulation. The most important determinant of uterine blood flow is maternal blood pressure. Although there are isolated case reports of poor neonatal outcome, which the authors have attributed to the detrimental effects of adrenaline on the

uteroplacental circulation (Entman 1984), in Hepner's case series fetal outcomes were good when adequate doses of adrenaline were used. Gei reported a case of anaphylaxis occurring in a woman in labour where an adrenaline infusion was used to manage hypotension for several hours (Gei 2003). The maternal and neonatal outcome was excellent. Therefore, available evidence would appear to suggest that maintenance of maternal blood pressure is the over-riding factor in ensuring fetal wellbeing, and that adrenaline should be used.

There were no particular themes in the agents identified as causative agents. The absence of antibiotics is of interest, but the numbers are so small that this is likely to be a statistical quirk. The range of agents identified does, however, highlight the fact that even low-risk agents can, on occasion, cause severe perioperative anaphylaxis.

There were no cases of anaphylaxis caused by latex. Hypersensitivity to latex increased dramatically from 0.5% in the 1980s to almost 20% of all perioperative allergic reactions in the early part of the 21st century (Mertes 2011). The obstetric population has previously been identified as being at high risk for latex sensitivity in a number of studies (Draisci 2007, Draisci 2011). There were no cases of latex anaphylaxis identified in the UKOSS investigation (McCall 2017) and, with the findings of NAP6, this suggests that strategies to screen pregnant women and also the reduction of latex-containing equipment in the theatre environment have been effective.

There were no cases of anaphylaxis attributable to an anaesthetic induction agent. A UK survey published in 2013 reported that thiopental was the preferred induction agent for caesarean section for 94% of UK obstetric anaesthetists (Murdoch 2013). In the same year the NAP5 Activity Survey (Sury 2014) found that thiopental was administered during induction in 97% of caesarean section cases. However, the NAP5 Report on Accidental Awareness during General Anaesthesia highlighted thiopental, rapid sequence induction and obstetrics as all being risk factors for accidental awareness during general anaesthesia (Pandit 2014). A change to propofol was recommended and this has subsequently been reinforced in the 2015 MBRRACE Report (Knight 2014) and by others (Lucas 2015). In the NAP6 Allergen Survey (Chapter 9) thiopental was the induction agent in 62.7% of caesarean sections and propofol in 29.7% (<3% in NAP5), demonstrating a significant change in practice.

Recommendations

Institutional

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

Individual

- An allergy history should be taken even when there is extreme urgency to deliver the baby
- Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients
- 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
- Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase levels should be measured
- Anaesthetists should be aware that hypotension due to anaphylaxis can be exacerbated by neuraxial blockade and or aortocaval compression.

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Key findings

- 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: approximately a quarter of the rate in adults.

- The commonest presentation was bronchospasm or 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.

- After physical recovery sequelae included withdrawal, anger and anxiety about future treatments.

- Antibiotics and neuromuscular blocking agents (NMBAs) are used about half as frequently in paediatric anaesthesia as in adult practice and this may partially explain 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 and families being inadequate. Some patients were left at risk of future anaphylaxis as a result.

What we already know

Perioperative anaphylaxis is uncommon in children, and reported incidences vary considerably.

In 1993, a prospective paediatric study estimated the incidence to be 1 in 7,741 anaesthetics (Murat 1993). Latex was the main cause in that series, and the incidence of anaphylaxis caused by NMBAs was very low at 1 in 81,275 cases.

A French series in 2011 reported 122 cases of IgE-mediated hypersensitivity of any severity in patients younger than 18 years over an eight-year period (Mertes 2011). Latex accounted for the largest proportion of cases (42%), followed by NMBAs (32%) and antibiotics (9%). In patients of all ages NMBAs were the most common trigger agents (58%), followed by latex (20%) and antibiotics (13%).

More recently, the APRICOT study in 2017 reported three cases of anaphylaxis in 30,874 paediatric anaesthetic cases, giving an incidence of approximately 1 in 10,000 (Habre 2017).

Clusters of cases of latex allergy and anaphylaxis have been reported (Gold 1991, Kelly 1994). Children with spina bifida having multiple operations throughout childhood were identified as being particularly at risk. The insidious onset from between 40–290 minutes from induction makes this a particularly challenging diagnosis to make. Increased awareness of latex allergy and the avoidance of powdered latex gloves (Newsom 1997, Vandenplas 2009) has reduced latex exposure in the hospital setting.

Latex and NMBAs have historically been prominent triggers, with antibiotics less commonly cited. This is likely to have been influenced both by differences in procedures commonly undergone by children and by anaesthetic technique.

Numerical analysis

A child was defined as a person aged less than 16 years. For the purposes of analysis, patients were age-banded as age 0–5 or 6–15 years. Methods are described in detail in Chapter 5.

The Activity Survey (Chapter 8) included 2,053 paediatric cases, all involving general anaesthesia, with an estimated annual caseload of 402,753 cases.

Eleven cases of perioperative anaphylaxis in patients <16 years were reported, three of which were emergency procedures. With an estimated 403,000 paediatric cases performed per annum, the incidence of Grade 3-4 anaphylaxis is 2.73 per 100,000 paediatric anaesthetics (95% Confidence interval 1.36-4.89 per 100,000). The incidence in paediatric patients is therefore lower than in adult patients (255 cases in 2,723,314 patients: 9.36 per 100,000, 95% CI 8.42-10.59 per 100,000, Fisher p<0.001).

Patients

Of the eleven reported cases, one was younger than 5 years and ten were 6–15 years.

All cases had general anaesthesia: anaesthesia was induced with propofol in eight cases, with thiopental in one, and with an inhalational induction in two. Anaesthesia was maintained with a total intravenous technique in one case. There was an equal number of male and female patients where this information was recorded. Four cases were ASA 1, three ASA 2 three ASA 3, and one ASA 4 (ASA 3–4 36% vs 9.2% in the Activity Survey, (Chapter 8)). Four of ten in whom body habitus was recorded were reported to be overweight. Two patients had well-controlled asthma. All events occurred during normal working hours, with the exception of one night-time case and one weekend case.
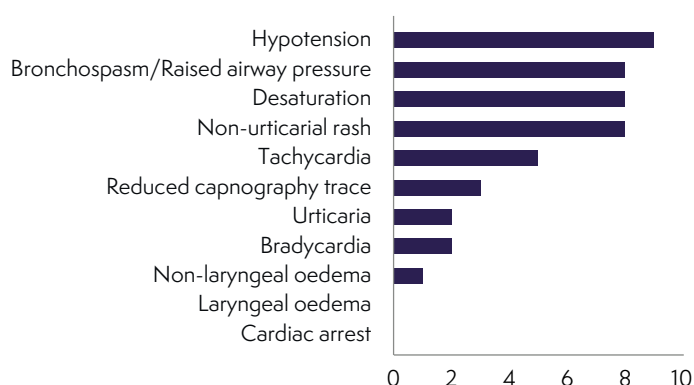
Features

Six cases presented in the operating theatre, three in the anaesthetic room, one during transfer from the recovery room to the ward, and one in the radiology department. Seven cases presented after induction and before surgery.

A consultant anaesthetist was present from the start in eight cases, two were started by a career grade anaesthetist and one by an ST7 anaesthetist in training. A consultant anaesthetist was present during resuscitation in all cases.

The first clinical feature was bronchospasm and/or high airway pressures in seven (64%) cases, hypotension in two, tachycardia in one, and non-urticarial rash in the remaining case. Bronchospasm presented within five minutes, whereas hypotension was generally slower in onset. A decrease in end tidal carbon dioxide levels was noted in three cases, with an absent capnography trace in two of these at some point. Two cases exhibited non-laryngeal oedema, which was delayed in one case. There were no cardiac arrests and no fatalities in children.

Considering clinical features that appeared at any time during the anaphylactic episode, hypotension featured in nine cases, bronchospasm in eight, oxygen desaturation in eight, non-urticarial rash in eight, tachycardia in five, reduced capnograph trace in three, urticaria in two, bradycardia in two and non-laryngeal swelling in one (Figure 1). The lowest recorded systolic blood pressure was lower than 50 mmHg in four cases and the lowest recorded oxygen saturation was less than 85% in five cases. All cases were judged Grade 3 by the index anaesthetist, but on panel review, six were judged as Grade 4.

Figure 1. Number of children exhibiting clinical features at any time during the anaphylactic episode

Resuscitation

Specific treatment for anaphylaxis was started within five minutes in six of the seven cases where bronchospasm and/or high airway pressures were the presenting features. When hypotension or tachycardia were the presenting features, specific treatment tended to be started later. This finding was also seen in adults (Chapter 10, Clinical features). Anaphylaxis-specific treatment was delayed for more than 15 minutes in one case where flushing/non-urticarial rash was the presenting feature, and 11–15 minutes in one case where hypotension was the first feature.

All patients received intravenous (IV) adrenaline, with one exception where ephedrine and metaraminol alone were administered. Three patients received IV and intramuscular adrenaline and four patients received an infusion of adrenaline. The median number of doses of IV adrenaline was 2.5 (range 0–9). One patient received IV atropine and one required an infusion of noradrenaline to treat refractory hypotension. Two patients received inhaled salbutamol and one received magnesium sulphate for bronchospasm. No patients received phenylephrine, vasopressin, glucagon, glycopyrronium, aminophylline, or sugammadex for treating the reaction.

A child with hay fever presented for elective minor surgery. They received general anaesthesia which included atracurium and almost immediately became profoundly hypotensive, with bronchospasm and desaturation. Resuscitation required multiple boluses of adrenaline as well as chlorphenamine, salbutamol, magnesium, hydrocortisone and a substantial volume of fluid. The child was transferred to critical care for Level 3 care. Allergy clinic investigation confirmed atracurium-induced allergic anaphylaxis.

Eight patients received hydrocortisone, one patient received dexamethasone and one methylprednisolone. Two children did not receive a corticosteroid. Eight patients received chlorphenamine.

Ten patients received IV crystalloid, one IV gelatin, and one no IV fluid. The volume of IV crystalloid administered during the first five hours is shown in Figure 2.

Figure 2. Volume of IV crystalloid (ml/kg) administered after the event (bar - median, line - range)
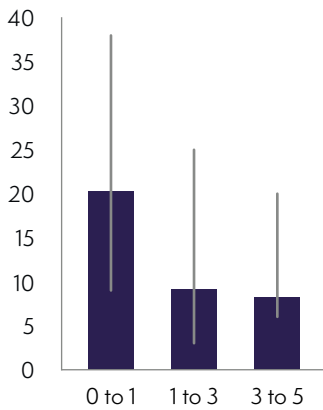
AAGBI guidelines (Harper 2009) were used in 5 (45%) cases and Resuscitation Council UK guidelines (RCUK 2016) in one (9%) case. There was immediate access to a guideline in seven (63%) cases (all as a laminate) with none opting to access guidelines on a smartphone.

Surgery was abandoned in six cases and continued in five. Four of the abandoned cases were rescheduled. Three patients were admitted to critical care as a result of perioperative anaphylaxis, one of whom was transferred to a different hospital for Level 3 care. Hospital stay was extended as a result of anaphylaxis in seven cases (median 2 days, range 1–4). There were no further episodes of anaphylaxis during their stay.

The review panel judged the quality of clinical management in seven cases: good in four cases, good and poor in two cases and poor in a single case (where adrenaline was not administered). All cases were abandoned or proceeded with appropriately except for one case which, although there was a good outcome, the panel judged that it had been imprudent to proceed.

Following resuscitation and clinical recovery, psychological sequelae were reported including withdrawal, anger and anxiety about potential future anaesthesia.

Referrals

Eight cases of eleven had at least one mast cell tryptase sample taken. All cases were referred to an allergy clinic. Eight patients were referred to the allergy clinic by the index anaesthetist, two by another anaesthetist and the final patient by someone other than an anaesthetist or surgeon.

Seven cases were reported through the trust's local critical incident reporting system, but only one case was recorded as being reported to the Medicines and Healthcare products Regulatory Agency (MHRA); two patients were issued with a hazard alert by the anaesthetist.

Investigation

Four of eight mast cell tryptase series showed elevation or dynamic changes. The reaction was allergic anaphylaxis in three cases, non-allergic anaphylaxis in one case, anaphylaxis not-specified in two cases and uncertain in five. Culprit agents

were: atracurium in three cases and one each of; succinylcholine, aprotinin, cefuroxime, ibuprofen and cryoprecipitate. The trigger was not confidently-identified in the three remaining cases. The mechanism of the reaction to ibuprofen was judged to be non-allergic anaphylaxis.

Identified allergens

The Allergen Survey (Chapter 9) identified that an NMBA was administered in 24.7% of paediatric cases and atracurium was chosen in 14% of cases (57% of paediatric NMBA uses). The next most frequently used NMBAs in children were rocuronium in 5.2% of children (21% of NMBA uses) and suxamethonium in 2.5% of cases (10% of NMBA uses).

In terms of exposure to the suspected trigger agents identified above, Table 2 shows the proportion of children receiving each across the Allergen Survey (Chapter 9).

Table 2. Percentage of children in Allergen Survey cohort (n=2,053) exposed to agents identified as triggers in NAP6

Agent	Exposures	Proportion of cases receiving (%)	No. of cases NAP6
Atracurium	282	14	3
Ibuprofen	358	17.4	1
Cefuroxime	70	3.4	1
Suxamethonium	52	2.5	1
Aprotinin	4	0.2	1
Cryoprecipitate	Unknown	–	1

A child received a non-steroidal analgesic orally as part of a premedication. The surgery was uneventful but the patient developed signs of anaphylaxis more than an hour later on the ward, most likely from the non-steroidal analgesic. The insidious onset, with no clear immediate culprit amongst many possibilities, makes this type of case difficult to recognise and thus promptly treat. The team did well to consider and correctly identify anaphylaxis in this case. Cases of latex allergy or chlorhexidine allergy may present similar challenges of slow and delayed onset.

Allergy clinic investigation

The allergy clinic identified seven triggers and the panel eight. In one case the panel judged that the clinic had identified the wrong trigger agent. In seven of eight cases where this was assessed the clinic investigation had deviated from British Society for Allergy and Clinical Immunology (BSACI) guidelines. Problems included: failure to test for all possible triggers, failure to test for chlorhexidine or latex, failure to identify or provide advice on safe alternative drugs, excessively broad avoidance advice, and failure to establish a baseline mast cell tryptase level. In total, five of eight patients who were fully reviewed were judged by the panel to remain at risk of future anaphylaxis due to incomplete investigation or poor advice given to the patient or family.

Overall allergy clinic investigation, in eight cases fully reviewed as good in one, good and poor in three and poor in four.

An overweight child undergoing general anaesthesia received general anaesthesia including atracurium and developed profound bronchospasm, hypotension, desaturation and a rash two minutes after atracurium administration. A single dose of intravenous adrenaline and 1.5 L of crystalloid were sufficient for resuscitation. At allergy clinic investigation there was no mast cell tryptase rise. The drug suspected by the anaesthetist (atracurium) was not tested for but vecuronium intradermal skin testing was positive. Atracurium was not listed by the allergy clinic among the drugs to avoid despite it being judged the most likely agent by the anaesthetist. It was not clear whether testing for vecuronium (instead of atracurium) arose because of poor communication from the anaesthetist or misunderstanding at the allergy clinic.

Discussion

The low incidence of paediatric perioperative anaphylaxis (about a quarter of that in adults) may have several causes. Latex exposure – previously a common trigger in children – has reduced significantly in recent years. It is also likely that children are both less sensitised prior to anaesthesia and less exposed to allergens during the perioperative period than adults. NAP6 indicates that NMBAs and antibiotics were used in 24.7% and 26.4% respectively of paediatric general anaesthetics, compared to 47% and 57% in adults (Allergen Survey, Chapter 9). When tracheal intubation is required in children, there is an increasing trend to achieve this without the use of NMBAs, which avoids exposure to a potent trigger for anaphylaxis (Simon 2002, Morton 2009, Sneyd 2010)

The Allergen Survey also showed that 14% of children received only sevoflurane, a low anaphylaxis-risk anaesthetic, for induction and maintenance of anaesthesia. Children are more likely than adults to receive general anaesthesia for non-surgical procedures and for diagnostic purposes. The APRICOT study, for example, found that 22% of their 30,874 cases had a general anaesthetic for an MRI procedure (Habre 2017).

Given the small number of cases reported in children, it is not possible to make confident conclusions concerning risk rates with different drugs. However, the number of cases of atracurium and suxamethonium appear to be proportionate to the number of exposures. Atracurium was the most-used NMBA in children (57%) by a large margin, followed by rocuronium and suxamethonium.

There was only one case of antibiotic-induced anaphylaxis in children (antibiotics are used less frequently in paediatric anaesthesia than in adults). Teicoplanin was a prominent trigger agent in the adult population (14% of all adult reactions and 19% of identified culprits in adults) but was not confirmed as a trigger in any paediatric case. Teicoplanin was administered in the perioperative period to 0.9% of children and 7.1% of adults – probably reflecting both lower rates of antibiotic use and lower rates of penicillin allergy in the younger age groups.

Allergic reaction to cryoprecipitate is rare and does not feature in recent Serious Hazards of Transfusion reports (SHOT 2016), although it is reported in the literature elsewhere (McVerry 1979).

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

Presenting features

Unlike in adult patients, bronchospasm and/or high airway pressures were the most common presenting features in children. Children are known to have more reactive airways with an incidence of laryngospasm 2–3 times that of adults (Gavel 2014). Anaphylaxis presenting in this manner was generally promptly recognised and treated.

Bradycardia was also more common in children compared with adults (18% vs 12.6%), although the degree of bradycardia was not reported. Strictly speaking, according to RCUK guidelines (Maconochie 2015), if there are no signs of life, and unless a pulse of greater than 60 beats per minute can be confidently palpated, cardiopulmonary resuscitation (CPR) should commence. Again, one must assume that each case was judged to have sufficient perfusion not to warrant CPR.

Cardiopulmonary resuscitation was not performed in any paediatric case. Four children had a recorded systolic blood pressure of less than 50 mmHg – the panel's threshold for designating a Grade 4 reaction in adults. However, unlike in adult patients, expert opinion did not favour setting a blood pressure below which CPR should be initiated.

Resuscitation

All cases were resuscitated by an appropriate senior anaesthetist, and RCUK and/or AAGBI guidelines were generally well followed. All except one received adrenaline. Three received it intramuscularly, and in each of these cases they also received it intravenously. The AAGBI guideline (Harper 2009) advises intravenous administration, whereas the RCUK guideline (RCUK 2016) advises intramuscular except for 'experienced specialists'. The RCUK guidance is directed at a wider 'rescuer' population, many of whom will not have intravenous access, and it is clear that anaesthetists are relatively comfortable with the intravenous route here. However even paediatric anaesthetists encounter paediatric anaphylaxis only rarely : it is worthy of note that rehearsal of paediatric anaphylaxis drills in the simulator (Johnston 2017) or in a low-tech in-theatre setting (Kerton 2018) can improve adherence with guidelines and aid prompt management.

A single patient received ephedrine which is likely to be more readily available during routine anaesthesia. Ephedrine does have some beta-adrenoceptor agonist activity (Ma 2007) but is not included in any current guidelines. In general, there were omissions in case management in the administration of steroid and/or chlorphenamine as well as in the tryptase requests. Guidelines were not universally available or used in the paediatric cases, and no one opted to access them on a smartphone.

In one case gelofusine was used as the resuscitation fluid. Gelatin-containing fluids can themselves cause anaphylaxis – indeed, in one adult case in NAP6 the use of a gelatin-containing fluid to resuscitate from low blood pressure caused an anaphylactic reaction. There was also one adult death from a gelatin-containing fluid. There is no evidence to recommend gelatin-containing fluids over crsytalloids, and the AAGBI guidelines specify use of crystalloids (Harper 2009), which NAP6 endorses.

Clinic investigation

Investigation of paediatric allergy can be very difficult. In particular skin prick and intradermal testing may be difficult or impractical to perform. This was taken into account in assessing performance of allergy clinics. There were significant limitations to allergy-clinic investigation, which was frequently incomplete, and which frequently provided inadequate advice to patients/families. Some patients were left at risk of future anaphylaxis as a result. No clinic investigation was judged to have adequately explored all potential culprits. The majority were assessed as poor and only one of eight as good. This, together with the data presented in the Allergy clinic baseline survey (Chapter 13), provides evidence to support the contention that specialist paediatric investigation of perioperative anaphylaxis would be likely to benefit from improved network provision and the standardisation of approach.

Recommendations

National

- Consideration should be given at a national level to reconfiguring paediatric services for investigation of perioperative anaphylaxis in order to 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

- Protocols and anaesthetic anaphylaxis treatment and investigation packs appropriate for children should be immediately available wherever paediatric anaesthesia is administered

- All anaesthetists administering anaesthesia to children should be trained in the management of paediatric anaphylaxis

- 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.

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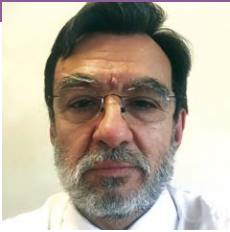
Mark Bellamy

Key findings

- 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.

What we already know

Intensive Care is defined by the Faculty of Intensive Care Medicine as follows:

"An Intensive Care Unit (ICU) is a specially staffed and equipped, separate and self-contained area of a hospital dedicated to the management and monitoring of patients with life-threatening conditions. It provides special expertise and the facilities for the support of vital functions and uses the skills of medical, nursing and other personnel experienced in the management of these problems. It encompasses all areas that provide Level 2 (high-dependency) and/or Level 3 (intensive care) care as defined by the Intensive Care Society document 'Levels of Critical Care for Adult Patients' (2009) (FICM 2015)".

Level 2 and Level 3 care are commonly provided in critical care units, and the requirement for this level of care is the leading indication for critical care admission (ICS 2009). In essence, Level 2 care includes single-organ support, and Level 3 care either advanced respiratory support or multi-organ support.

Management in critical care (ie. in an ICU or a high-dependency unit – HDU) of the patient experiencing an allergic reaction remains a relatively uncommon event, and therefore not well quantified. This is perhaps surprising, given the nature of critically ill patients, and the plethora of pharmacological agents (including blood and blood products) to which they are exposed. It is likely that the prevalence of allergic reactions treated in critical care is often underestimated, possibly due to failure to recognise such episodes. Nevertheless, the principles of managing severe anaphylactic reactions are similar to those of managing other catastrophic shock states and this management is therefore probably best delivered in the critical care environment (Kanji 2010).

In addition to anaphylactic reactions, involving multiple organ systems and potentially causing death (Sampson 2005), critical care may be of value in treating skin reactions, particularly the Stevens–Johnson syndrome, respiratory reactions, hypersensitivity vasculitis and angio-oedema. A number of guidelines and algorithms are used, but all share a common 'ABC' approach and rely on adrenaline as the treatment mainstay.

Consequently, we have attempted to extract from the NAP6 dataset estimates both of the prevalence of perioperative anaphylactic reactions requiring critical care admission, and factors which identify which patients are most likely to require this level of support.

Numerical analysis

It was our intention to capture any cases of anaphylaxis that occurred in critical care during general anaesthesia. The NAP6 case report form included the question "If the event occurred in HDU/ICU/ED, was the patient undergoing an interventional procedure (not resuscitation) under general anaesthesia, administered by an anaesthetist?" Twelve responses to this question were 'yes'. However, in these cases the location of the event was subsequently recorded as:

- 10 in theatre/anaesthetic room
- 1 during transfer
- 1 unknown.

None of the accompanying narratives indicated that the case originated in critical care or the emergency department. While it is possible that up to twelve patients may have sustained their primary anaphylactic reaction in a critical care or emergency department unit, this appeared unlikely. It is possible that such cases were under-reported. Consequently, no further analysis of this subgroup of patients has been attempted, and they have been grouped with other patients transferred to critical care following a reaction.

In the following analyses, where odds ratios (OR) are presented, these are followed by 95% confidence limits.

In total, 144 (54%) of patients with Grade 3 and Grade 4 anaphylaxis were subsequently transferred/admitted to critical care. One patient, requiring vasopressor support (noradrenaline), was not admitted due to bed unavailability. A further patient was transferred to a coronary care unit, and ten (7%) patients were transferred to critical care units in another hospital or facility. Of those admitted to a critical care unit, 117 (81%) were admitted solely because of anaphylaxis (ie. no other reason for admission coexisted).

The highest level of support received was:

- Level 3   93 (65%)
- Level 2   37 (26%)
- Other/unknown   14 (10%).

Among the 261 patients who survived the initial anaphylactic event:

- 78 patients (30%) received an adrenaline infusion
- 12 (5%) patients received an adrenaline infusion without admission to critical care
- 47 (18%) patients received a noradrenaline infusion
- 6 (3%) patients received noradrenaline outside critical care.

Once admitted, no patients required an increase in their level of care. No cases consistent with recrudescence of anaphylaxis were reported.

This resulted in an additional (unplanned) burden of critical care days of:

- Level 3
  - Mode 1   Median 1   Mean 1.1 (SD1.9)
- Level 2
  - Mode 1   Median 1   Mean 1.3 (SD 2.38).

The mode is a useful indication of the typical duration of critical care stay and is useful as a description of patient experience. The median gives a non-parametric average of length of stay, whereas the mean is useful for estimating total resource use/costs.

For the entire study population this equates to a total of 115 extra Level 3 bed-days (ie. over and above what could otherwise have been expected for routine care). Similarly, the excess of high-dependency days, or total extra Level 2 days, was 151. While the study was not designed to collect health economic data, it is perhaps useful to give very rough estimates of the associated additional critical care-related healthcare costs. Using the standard cost of a bed-day for Level 2 or Level 3 care (based on estimates of critical care costs in 'Guidelines for the Provision of Intensive Care Medicine') (FICM 2016), the estimated cost for the entire cohort is £438,102.

Of those who died, where the place of death is known, five patients died in or following critical care. Five patients died without reaching critical care (see Chapter 12, Deaths, cardiac arrest and profound hypotension).

Resultant harm

NAP6 classified harm as 'none', 'mild', 'moderate' or 'severe' (see Chapter 5, Methods). Comparing those admitted to critical care with those not requiring admission, the rate of harm (described here as moderate/severe harm) was similar:

Comparing the groups there is no significant difference, P=0.62, Fisher exact test

	Moderate/ severe harm	Mild/ no harm
Critical care admission	25	119
No critical care admission	18	104

Risk factors for critical care admission

Risk factors for critical care admission and harm (moderate/severe) were further explored using backward stepwise logistic regression. Patient factors examined as covariates included age band, gender, and ASA status. The resulting model was predictive for critical care admission (P=0.0034):

- Age 65–75   OR 2.0   (1.1–3.7)
- Age 75–85   OR 2.4   (0.9–6.6)
- ASA 2   OR 0.54   (0.32–0.89).

However, when the model was explored for harm as an outcome, none of the above was identified as an independent risk factor.

Initial resuscitation may have had an impact on the requirement for subsequent critical care admission (P=0.0006). Patients requiring an adrenaline infusion had an odds ratio for critical care admission of 2.7 (1.0 – 7.4). However, the risk for critical care admission was reduced by administration of crystalloid in the first hour, OR 0.49 (0.25 – 0.93) for each litre administered. The confidence intervals for the odds ratios are wide, so the apparent 'effect' may be a statistical artefact. Similarly, subsequent fluids, and other pharmacological agents, failed to reach statistical significance as risk factors. These results suggest that there is scope for studying optimal fluid management prior to critical care admission, as this appears to be a potential modifying factor for the requirement for critical care. However, this could only be done using very large registry data to garner sufficient numbers for statistical power.

Discussion

Duration of admission to intensive care was generally short, although the immediate severity of illness necessitating admission was high. It therefore follows that critical care admission should be prioritised for patients who have suffered significant anaphylactic events in theatre or elsewhere. Some patients were successfully managed in recovery rooms and other areas, but there are insufficient data to point to whether this leads to better or worse outcomes.

There is considerable benefit to be gained even from short critical care admissions, as despite high levels of acuity at admission, in general the outcomes were good, and therefore the use of critical care resource represents 'good value' and is easily justified. Although not investigated in this report, it is likely that transfer to the critical care unit, in addition to providing a higher level of resource, also introduces additional clinical input which may be more objective and emotionally detached, with implied patient benefit.

Secondary or relapsing reactions did not seem to be a feature in the current dataset, although this remains a theoretical possibility and therefore intensive care admission is justified for a short period of monitoring even in those patients whose reactions are already resolving.

Before NAP6, relatively few data had been published on the critical care implications of perioperative anaphylactic reactions. The most recent major study covers a 4-year period 2005–2009 (Gibbison 2012). This study extracted data from three key UK national critical care databases, the Intensive Care National Audit and Research Centre's Case Mix Programme, the Scottish Intensive Care Society Audit Group, and PICANet (a national clinical audit of paediatric critical care). The study collected data on 1,269 adult and 81 paediatric anaphylaxis-related admissions. Inclusion was by clinician diagnosis as recorded in the databases and accounted for 0.3% of adult and 0.1% of paediatric critical care admissions. Gibbison's study therefore differs from NAP6 in that all grades of severity were included, whereas only Grade 3 and 4 reactions were included in NAP6. Moreover, in NAP6, inclusion was based

on more stringent diagnostic criteria. When cases admitted from wards and the emergency department in Gibbison's paper are stripped out, the numbers are similar to ours, suggesting that cases 'missed' in either study were similar and few.

Gibbison reported a 91.9% survival rate to hospital discharge in adults, again, very similar to our data (137/142, 96.5%). The mean length of stay in Gibbison's paper was 1.2 days for survivors and 2.1 days for non-survivors, compared with NAP6 data of an overall (combined) mean length of stay of 1.1 days (Level 3 care) or 1.3 days (Level 2 care). It is likely that any small differences can be explained by organisational factors such as ward-round timings and discharge pathways.

Overall, our data support the previous critical care data. This is important, as the methodologies differ, approaching the problem from opposite directions, yet the outcomes are remarkably similar. Further work could focus on combining the methodologies with the existing data sets. The similarities between our data and Gibbison's could be further explored by cross-tabulating the critical care databases, using their methodology with our data for the same time-period. This would allow validation of outcomes, and might allow research into pre-admission resuscitation factors as outcome modifiers.

Recommendations

Institutional

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

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Key findings

- 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 either on the frequency of perioperative anaphylaxis in independent hospitals, or 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.

Introduction

Independent sector hospitals provide a parallel healthcare service to NHS hospitals in the UK. Traditionally, these hospitals provided care for fee-paying and insured patients. More recently, increasing numbers of NHS-funded patients have had surgery in independent sector hospitals, based initially on the 'any willing provider' scheme introduced in 2009, which became 'any qualified provider' in 2011.

Since 2015, NHS patients undergoing surgery have a choice of providers through NHS Choices (https://www.nhs.uk/pages/home.aspx) and the NHS e-Referral Service. This system replaced 'Choose and Book', which was established in 2005. In 2016, the UK government committed to extending choice for patients (Department of Health 2017).

In 2017, it was reported that 45% of in patients in independent sector hospitals are NHS-funded, and that in a quarter of private hospitals this number exceeds 50% (CHPI 2017). NHS-funded patients receiving care in independent sector hospitals should receive the same quality of routine and emergency care as NHS patients in NHS hospitals and, of course, these standards should also apply to privately-funded patients. It is also logical that the care provided in independent sector hospitals, particularly when NHS-funded, should be subject to the same degree of audit and quality assurance as NHS hospital care. Engagement by independent sector hospitals with national clinical audits has previously been recommended (Leys 2014).

Most independent sector hospitals are relatively small, and few have High Dependency or Intensive Care facilities (Leys 2014). For this reason, the nature and extent of surgery conducted there and the patients who undergo surgery tends to be of lower risk than in many NHS hospitals (CHPI 2017). With a lower-risk surgical population in these hospitals, it can be anticipated that major complications will arise less frequently. When complications do arise during or after surgery, there may be a need to transfer patients to other hospitals for specialist care. Unlike many such complications, perioperative anaphylaxis is an unpredictable, and therefore largely unavoidable, complication.

Anaesthetists and surgeons may work as individuals in independent sector hospitals, or they may be formed into groups, partnerships or 'chambers'.

For logistical reasons, independent sector hospitals have not been included in previous National Audit Projects. At the inception of NAP6, it was decided that there should be an intention to include independent sector hospitals.

Engaging with the independent sector

In 2015, we began attempts to include all independent sector hospitals in NAP6 in the same manner as NHS hospitals. In May 2015, the President of the Royal College of Anaesthetists wrote to all independent hospital chief executives highlighting the recommendations made in the 4th National Audit Project (Cook 2011) and seeking their engagement in NAP6. This correspondence was followed by further letters to all hospitals in June 2015. In September 2015 a letter was sent describing the process of NAP6 to those hospitals who had registered an interest.

Also in September 2015, a further letter was sent by the President of the Royal College of Anaesthetists to independent sector hospital chief executives to remind them that 30 October 2015 was the deadline for registering interest in NAP6. As few positive responses were received by this deadline, an email was sent in December 2015 to all independent hospital leads with information about the project and a list of those hospitals participating. Hospitals were contacted using a list provided by the Association of Independent Healthcare Organisations based on Lang & Buisson data.

Many hospitals did not reply to our correspondence. Of those that did, some gave reasons why the hospital could not take part in the project, including:

- The absence of an anaesthetic department to coordinate the project

- The absence of an anaesthetist who could act as Local Coordinator

- The large number of anaesthetists with practicing priviledges to the hospital (in one case more than 200) and the variability of their presence at the hospital, meaning that dissemination of relevant information and tracing responses was impractical

- The rarity of anaphylaxis at that hospital

- That the data would be 'confidential' or of a 'competitive nature'.

In view of the practical difficulties, we allowed non-anaesthetist hospital employees to be Local Coordinators, provided they were willing to accept the responsibilities that the role required. By January 2016 41 hospitals had agreed to take part. The NAP6 steering panel met to consider whether the independent sector should be included at all in the project in view of the low rate of engagement. Some of those hospitals and individuals that had engaged had clearly made considerable efforts to do so, and were keen to be part of the project. Conversely, the panel took the view that, with approximately 10% of the sector engaged, the data would not be representative of the sector as a whole and that there was a danger of its inclusion leading to biased results. After much discussion, it was agreed that those hospitals that had volunteered to take part in NAP6 would be included. However, in view of the small number of independent sector hospitals that had agreed to participate, it was agreed that this sample would not be representative of practices or events in this healthcare sector, and a decision was made to include their data only for examination of isolated events, ie. a thematic analysis, and not for numerical analysis.

Local Coordinators in the independent sector were sent an information pack designed specifically for the independent sector. We did not perform the anaesthetic baseline survey (see Chapter 7) in the independent sector, as most anaesthetists working in those hospitals would also be employed in NHS hospitals and would have completed the survey at their NHS post. We did not perform an Activity/Allergen Survey (see Chapter 8 and 9) in the independent sector because too few independent sector hospitals were engaged in NAP6 to make any results meaningful. Local Coordinators were asked to complete the Brief Organisational Survey describing local services at their hospitals and to send monthly returns of cases reported including 'nil returns'.

The main registry phase of NAP6 started on 5 November 2015, but because of limited responses it was decided to delay the independent sector part of this until early 2016. Reports from the independent sector were accepted from 5 February 2016 for a period of nine months.

Numerical analysis

Brief Organisational Survey

Twenty-six responses were received covering 33 hospitals (range of hospitals covered by each response 1–4), a response rate of 80% of those who agreed to participate and 11% of all independent sector hospitals. These included both traditional 'private hospitals' and Independent Sector Treatment Centres. Anaesthetic services provided at the location included general anaesthesia in 33 (100%), regional anaesthesia in 32 (97%), sedation in 33 (100%) and managed anaesthesia care in 26 (82%). Thirteen (39%) hospitals had a High Dependency or Intensive Care Unit and two (6%) an emergency department.

The number of consultant anaesthetists on the hospital staff varied widely from 10 to more than 200 (mean 50, median 30).

Eleven (33%) hospitals had an anaphylaxis lead anaesthetist. Guidelines for the management of anaphylaxis were immediately available in the majority of theatres in 28 (85%) hospitals: predominantly the AAGBI guidelines (54% of those with guidelines) or the guidelines of the Resuscitation Council UK (RCUK) (39%), though it was not certain the latter were anaphylaxis-specific rather than Advanced Life Support (ALS) guidelines. Sixteen (49%) hospitals reported having a guideline for immediate investigation of anaphylaxis, and three (9%) a guideline for referral for investigation. Twenty-six (79%) hospitals reported immediate availability of an anaphylaxis pack. Fifteen (45%) hospitals were able to provide details of locations where patients would be referred for specialist investigation; 15 of these were NHS hospitals and one a clinician in the independent sector. Four (12%) commented that referral would be to the patient's general practitioner, and four (12%) described management as 'consultant dependent'. The largest hospital (in terms of consultants with practising privileges) provided a full range of anaesthetic services. It had no anaphylaxis lead, no access to guidelines in theatres, no anaphylaxis pack, and no guidelines or pathways for investigation or referral of cases of perioperative anaphylaxis.

Table 1 compares the responses to the Brief Organisational Survey from NHS and independent sector hospitals.

Table 1. Brief Organisational Survey: NHS and independent sector hospitals

	NHS	Independent sector
Responses		
Number	323	33
% of relevant UK hospitals in that sector	91%	11%
Response rate of hospitals that agreed to take part in NAP6	91%	80%
Staffing		
Consultants (median, range)	32 (1-150)	10-220
Overall size of department	77 (1-228)	-
Services provided		
General anaesthesia	98.1%	100%
Regional anaesthesia	99.4%	97%
Sedation	96%	100%
Managed anaesthesia care	84.8%	82%
ICU or HDU	72.1%	39%
Emergency department	63.5%	6%
Local preparedness		
Anaphylaxis lead	47.1%	33%
Guidelines immediately available	95%	85%
AAGBI guidelines	88%	54%
RCUK guidelines	13%	39%
Anaphylaxis pack	50%	79%
Guidelines for investigation	42.1%	49%
Referral for investigation		
Pathway for referral	13.3%	9%
Known referral location	94.8%	45%
Refer to GP or undefined	0.3%	24%

Main NAP6 case reporting phase

Reporting involved completion of two parts of a case report form: Part A describing the patient details and clinical event, Part B describing allergy clinic investigation (see Chapter 5, Methods). Eligibility required both parts to be submitted.

There were seven requests from independent hospitals to report cases, and each was issued with log-in details. In two cases Part A and Part B of the report form were received and in five only Part A was received.

We do not have data to enable us to calculate incidences of perioperative anaphylaxis in independent sector hospitals. We also have insufficient data to make judgements or comments about the quality of care delivered to patients.

A full analysis of these seven cases is not appropriate, but a few pertinent findings are:

- Four of the patients were aged 66–75 years

- Five patients were undergoing orthopaedic surgery

- All were undergoing elective surgery

- All patients were ASA 2 or 3

- Five patients received antibiotics (nine in total) and four patients received neuromuscular blocking agents (NMBAs)

- Anaphylaxis was reported as Grade 3 in four cases, Grade 4 in two, and the grade was not recorded in one. However, as several cases had a lowest systolic blood pressure below 50 mmHg, the panel would classify three cases as Grade 3 and four as Grade 4

- An anaphylaxis pack was used in three cases, and an algorithm to guide management in six cases

- In five cases the anaesthetist managed the event without assistance; in one case assistance was called for from nursing staff and in one case from another anaesthetist

- CPR was not performed in any of the four cases where systolic blood pressure fell below 50 mmHg

- In four cases the surgery was abandoned, in one it was modified and in two it was completed

- Transfer to critical care was required in three cases

- In two cases the patient was transferred to another hospital for further care

- All seven patients were referred to an allergy clinic for further investigation by the index anaesthetist

- Six of the events were reported to hospital incident reporting systems and none was reported to the Medicines and Healthcare products Regulatory Agency (MHRA).

Discussion

Organisation

This is the first time there has been an attempt to engage the independent sector in a National Audit Project by the RCoA.

We were unable to recruit the vast majority of independent sector hospitals to the NAP6 project. This was despite considerable effort. We are particularly grateful to those individuals and hospitals that did engage with the NAP6 project, and this has provided some exploratory data.

The organisation of consultant services within independent sector hospitals was judged by some hospitals to be a barrier to engagement in and delivery of such a project. The Care Quality Commission (CQC) has previously highlighted the large number of consultants with practising privileges in private hospitals as a risk to patient safety due to infrequent attendance and unfamiliarity with hospital equipment, procedures and policies (CQC 2016). The fact that hospitals considered their large consultant base a barrier to engagement with NAP6 suggests that this may also impact on information dissemination and engagement in safety-related audit, quality assurance and governance.

It is possible that independent sector hospitals that have anaesthetic groups might be better able to manage projects such as NAP6, but we were not able to explore this directly.

Several independent sector respondents noted that they had concerns about reporting data that might be considered 'competitive'. It is difficult to understand why the sharing of information about adverse incidents in a national audit such

as NAP6 can be deemed to be commercially or competitively sensitive, and it is possible that better prior communication might have allayed these concerns.

The Private Healthcare Information Network (PHIN https://www.phin.org.uk/) is an independent, not-for-profit organisation mandated by the government to improve data quality and transparency in the independent hospital sector. PHIN and regulators and inspectors, such as the CQC and the Healthcare Inspectorate Wales, should cooperate, to support or mandate improved engagement in safety-related national audits in the independent hospital sector.

Clinical issues

There is no reason to think that unpredictable severe complications such as perioperative anaphylaxis might not occur in independent sector hospitals. The cases reported to NAP6 confirm this to be the case. Each of these events was unpredictable, potentially life-threatening, and time-critical.

The mainstay of independent sector surgical work is elective orthopaedics, which accounts for a quarter of surgical workload in that sector (Competition and Markets Authority 2014). In 2012, almost 1 in 5 NHS-funded knee and hip arthroplasties were performed in a private hospital (Arora 2014). It is therefore likely that many patients will be relatively elderly, and that many will receive antibiotics (the commonest cause of perioperative anaphylaxis). Our exploratory data support this supposition and also showed that patients may well receive an NMBA. As antibiotics and NMBAs are together the cause of 80% of life-threatening perioperative anaphylaxis events, it is predictable that these events will occur from time to time in independent sector hospitals. It therefore behoves organisations and individuals working in independent sector hospitals to be prepared for the management of these cases.

The Brief Organisational Survey shows that among those hospitals responding from the independent sector there was a degree of preparedness for perioperative anaphylaxis. In some matters preparation appeared less than in NHS hospitals and in others greater. The AAGBI anaphylaxis guidelines were less likely to be available in the independent sector, and it is possible that some respondents were referring to the Resuscitation Council UK ALS guidelines when indicating that the RCUK anaphylaxis guidelines were immediately available. The provision of anaphylaxis packs appears higher in responding independent sector hospitals than in NHS hospitals, but policies and plans for referral for investigation of anaphylaxis appeared unsatisfactory in a substantial number of cases. The data should be interpreted with caution as, although the NHS data is from 91% of hospitals, the 33 responding hospitals from the independent sector represent only 11% of hospitals in this sector. Consequently, there may be inaccuracy or bias in the results. The organisational survey which we used has the potential to identify both good and poor preparedness and this, or a similar set of questions, might be of value to regulators and inspectors in assessing safety of independent hospitals.

In contrast to NHS hospitals, where an anaesthetist in training may join a consultant and where many theatres are generally active simultaneously, this is less likely to be the case in independent sector hospitals, particularly in small units. In most cases anaesthetists will work individually and there may or may not be other anaesthetists present. If they are present, they may or may not be known to each other. When life-threatening anaphylaxis occurs, resuscitation may require more than one person, and sometimes more than one anaesthetist may be necessary. This is particularly so if there are airway complications or cardiac arrest during perioperative anaphylaxis. Ensuring the rapid availability of additional anaesthetists who can assist in these circumstances may be a practical challenge in the independent healthcare sector. This issue has been highlighted before (Leys 2014). Where anaesthestists work together collaboratively, this may be easier to achieve.

Resuscitation from life-threatening perioperative anaphylaxis may require establishment of intensive (Level 3) care. This may be outwith some anaesthetists' normal practice. Where this is the case it can present a significant challenge, and prompt involvement of a specialist intensivist or anaesthetist with the requisite skills may not be easy in an independent sector setting. Again, where anaesthestists work together collaboratively in the independent sector this may be easier to achieve.

After, or sometimes during, resuscitation from life-threatening perioperative anaphylaxis, patients may need transfer to critical care. As most independent sector hospitals do not have critical care facilities, this again poses both organisational, logistical and patent-safety challenges. Not all anaesthetists are skilled in managing transport of critically ill patients. Independent hospitals should consider agreed arrangements for the transfer of patients to nearby hospitals with appropriate facilities.

In NHS hospitals, clinical governance meetings, including Morbidity and Mortality meetings, are a routine part of all anaesthetic departments' practice. These arrangements rarely exist in independent sector hospitals, and the potential to present, discuss, reflect and learn from relevant cases is therefore absent.

Finally, as most independent sector hospitals do not have an in-house specialist allergy clinic, the management of the referral process, ensuring that this is completed, the patient is fully informed and that important drug reactions are reported to regulatory authorities is yet another challenge that should be met by agreed and documented referral and reporting procedures.

In summary, all hospitals, whether NHS or independent sector, must be prepared to treat patients with life-threatening anaphylaxis and manage their onward care. When this occurs in an independent sector hospital, and particularly in small units, there are unique challenges over and above those found when managing patients in large NHS hospitals.

Recommendations

National

- 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

- 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

- Independent sector organisations should work to improve engagement with national audits and registries that focus on quality and safety of patient care

- 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

- 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

- Anaesthetists working in independent sector organisations should be trained and prepared to manage life-threatening anaphylaxis

- Anaesthetists working in independent sector organisations should participate in national audits and registries

- 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.

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Key findings

- 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. Reporting is usually by the index anaesthetist.

- Reporting to the UK regulatory system, the Medicines and Healthcare products Regulatory Agency (MHRA), is poor, occurring in fewer than one quarter of cases.

- From a general public health perspective, the potential value of reporting to the MHRA is much greater than that of local reporting.

- Current reporting levels and processes mean that data held by the MHRA are 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.

- A lack of feedback from the NRLS and MHRA may negatively impact on reporting rates.

- Combining relevant data from the NRLS and MHRA (taking care to avoid double-reporting of cases) may have considerable benefit.

Reporting systems

"Without principles, practice is a mere routine; the good or ill results of which the cause is not discerned, are equally lost to the progress of Art. The success which cannot explain often leads us into error, and serves only to perpetuate, under the names of experience, a blind conduct, of which we know neither the good nor the evil."
— Benjamin Travers, Surgeon to the Honourable East India Company, 1812.

In many healthcare settings, data on side effects of medicines and complications of procedures may be limited, and this increases the need for accurate and timely reporting of complications and hazards. Such reporting helps build a safety profile so that complications and hazards can be identified in a manner which is not possible in the practice of individual clinicians or teams.

Reporting, particularly of rare events, provides an opportunity for a better overview and understanding of known complications and hazards associated with a process, and has the potential to detect and enumerate new and unforeseen complications and hazards. Reporting can also identify emerging trends of known complications and hazards, and may also provide clues to aid in further risk reduction where innovative and novel treatments emerge.

Without reporting, as doctors, we are confined to our own limited sphere of knowledge and experience supplemented by reliance on intermittent study of research, which may or may not be focused and which may not provide answers to important patient-safety questions.

Although in the ideal situation there would be no hazards, side effects or complications, the reality with all healthcare is that there will always be risk to some degree. With this in mind, there can be reassurance when reporting can confirm a steady state of complications and hazards that is consistent with known, accepted or benchmarked data. The value of reporting is perhaps best illustrated by the vacuum within which we would operate if no reporting of complications were to take place.

The usefulness of reporting is increased greatly when there is accurate denominator data and known risks have been properly quantified. For example, using registry data it was possible to identify the premature wear and failure of certain types of hip replacement prostheses which had metal-on-metal bearing surfaces. This wear in vivo had not been detected in pre-implantation engineering testing (Fary 2011, Haddad 2013). This led to a series of alerts being issued by the MHRA, the first being in 2010 to alert surgeons to the possibility of emerging problems (MHRA 2010), and subsequent actions to further determine the extent of the problem and, where necessary, to address it – both in terms of identifying patients at risk of problems and in preventing further operations with this technology.

Data generated by reporting can be used for numerous purposes, including:

- Identifying critical incidents which need investigating
- Identifying trends
- Identifying emerging issues
- Audit, for monitoring performance of:
  - The individual
  - The team
  - The healthcare institution
- Monitoring the introduction of new processes or procedures
- Reducing the likelihood of litigation by preventing safety issues going unnoticed
- Fulfilling a doctor's obligation to the GMC (GMC 2014).
- Enabling healthcare institutions to fulfil their obligations to patient safety as determined in the Health and Social Care Act 2008 and other regulatory updates (CQC 2015).

All these activities contribute to the general culture around enhancing patient safety.

However, barriers to reporting are numerous (Vincent 1999, Mahajan 2010, Whitaker 2016) and include:

- A lack of perceived or actual value in the eyes of the potential reporter
- Poor education regarding the value and methods of reporting
- Difficult or time-consuming data entry
- A requirement to enter excessive or unnecessary data
- Absence of feedback from reporting systems
- Failure to provide feedback on what action is to be taken
- Requirements to report to more than one system
- Lack of resources for reporting.

Only a fraction of critical incidents may be reported in many systems (Evans 2006, Kaldjian 2008).

For reporting systems to be effective a number of principles need to be followed (Vincent 2014):

- All incidents which could have led to harm should be reported, (to ensure today's near-miss does not turn out to be tomorrow's disaster)
- Information reported must be:
  - Accurate
  - Timely
  - Succinct/manageable
  - Include everything being requested by the reporting system to ensure consistency
- Data should be reviewed promptly
- Data should be only what is required, and should only need to be entered once
- Data should be analysed regularly to identify trends and emerging hazards

- Action should be undertaken in a timely way where this is deemed necessary
- There should be feedback to the reporters/teams involved. This will vary in detail, but must include some element of what action is to be taken, even if this is just to be mapping of trending and continuing surveillance
- Reporters should have a voice in what is being collected, and be given confidence of its value
- Sufficient resources should be given to reporters to undertake reporting activities.

Reporting improves in a no-blame culture. In the NHS there are plans to improve future reporting, for example, by bar-coding using systems such as 'Scan4Safety', and unique device identifiers (NHS Improvement 2017a).

Numerical analysis

We have made the assumption that responses from Local Coordinators stating that reporting status was 'unknown' indicate that reporting did not occur. The data therefore represent minimum reporting levels.

Trust reporting

Seventy per cent of cases included in NAP6 were reported to trust reporting systems (Table 1). In the vast majority of cases this was reported by the index anaesthetist (Figure 1). Others who reported included nursing staff, surgeons, anaesthetic assistants and ICU staff. Of the ten deaths, eight were reported to local incident reporting systems.

Table 1. Reporting to trust/board incident systems

Reported to the trust: Part A	Number	%
Yes	187	70.3%
No	71	26.7%
Unknown/blank	8	3.0%
Total	266	100%

Figure 1. Reports of perioperative anaphylaxis to trust/board reporting systems
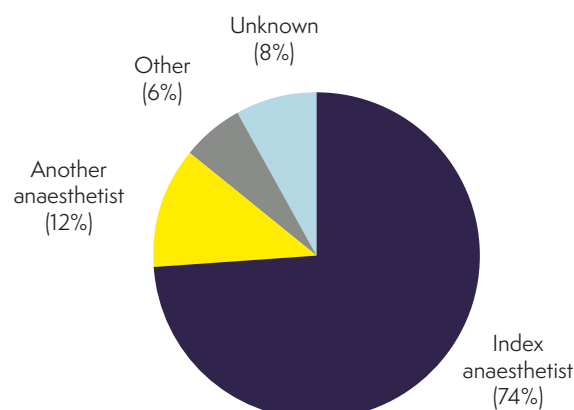
Reporting to MHRA

In all cases, reporting to the MHRA occurred in 15.8% of cases before attending the allergy clinic and in 23.7% after the clinic visit (Tables 2 and 3). In children, reporting to the MHRA occurred in 9.1% of cases before attending the allergy clinic and in 18.2% after the clinic visit.

#### Table 2. Reports to the MHRA before attending the allergy clinic (all cases)

Reported to MHRA before allergy clinic attendance	Number	%
Yes	42	15.8%
No	164	61.7%
Unknown	54	20.3%
Blank	6	2.2%
Total	266	100%

Table 3. Reports to the MHRA after attending the allergy clinic (all cases)

Reported to MHRA after allergy clinic attendance	Number	%
Yes	63	23.7%
No	68	25.6%
Unknown	52	19.6%
Blank	83	31.1%
Total	266	100%

The index anaesthetists were responsible for 44% of reports to the MHRA before allergy clinic assessment and Local Coordinators accounted for another 14% (Figure 2). Others who reported to the MHRA included other anaesthetists (7), pharmacists (2), and ICU doctors (1). Of the ten deaths, three were reported to MHRA.

Figure 2. Individual reporting to MHRA, before allergy clinic attendance
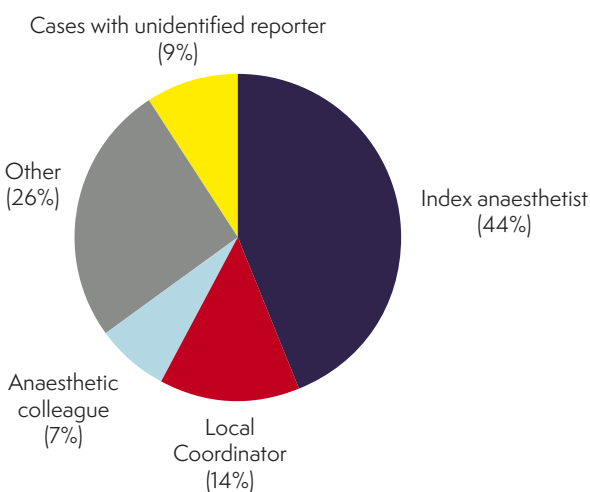
MHRA data

We liaised with the MHRA to determine whether data held by them would be informative. In the year January to December 2016 the MHRA received 901 reports of suspected 'anaphylactic or anaphylactoid reactions' via the Yellow Card system. Of these, 464 (51%) could potentially have occurred during the perioperative period, though for some drug groups it is highly likely that many did not – for instance antibiotics may have been administered at any time – and many other drugs included in miscellany are also used in non-perioperative settings. Reports to the MHRA included some likely anomalous reports such as reactions to sevoflurane, sodium chloride, water, steroids, and adrenaline.

We are not aware of the grades of reactions reported, nor the degree of suspicion of anaphylaxis. It is of course inevitable that many of these reactions were not hypersensitivity reactions. It is overall very difficult to compare these data with NAP6 data, and some anomalies are clearly evident. It is however of note that there were significant numbers of reactions to co-amoxiclav (35), teicoplanin (72), amoxicillin (20), rocuronium (34), atracurium (27), suxamethonium (17), chlorhexidine (22), and Patent Blue (17), all of which ranked in the top 11 most frequently reported drugs and between them accounted for 27% of all reports.

Tables 4 and 5 provide a breakdown of these data.

Table 4. Main drug groups reported to the MHRA as causing anaphylactic or anaphylactoid reactions in 2016

Drug group or drug	Number	% of all reports
All drugs	901	-
Potential perioperative drugs	464	51%
		% of all potential perioperative drugs
Antibiotics	237	51%
NMBA	79	17.%
Sugammadex	8	1.7%
Induction and maintenance agents	14	3.0%
Opioids and analgesics	33	7.1%
Antiemetics, local anaesthetic and miscellany	53	11.4%
Chlorhexidine	22	4.7%
Patent Blue dye	17	3.7%
Iodine	1	0.2%

Table 5. Drugs of prominence in NAP6 and MHRA datasets compared

	MHRA	% of potential perioperative drugs reported to MHRA	NAP6	% of NAP6 reports with identified trigger
Teicoplanin	72	15.5%	36	18%
Co-amoxiclav	35	7.5%	46	24%
Amoxycillin	20	4.3%	0	0.0%
Piperacillin and tazobactam	18	3.9%	1	0.5%
Gentamicin	15	3.2%	3	1.5%
Flucloxacillin	6	1.3%	2	1.0%
Cefuroxime	7	1.5%	4	2.0%
Rocuronium	34	7.3%	27	13.6%
Atracurium	27	5.8%	23	11.6%
Suxamethonium	17	3.7%	14	7.0%
Mivacurium	1	0.2%	1	0.5%
Sugammadex	8	1.7%	1	0.5%
Propofol	10	2.2%	1	0.5%
Midazolam	2	0.4%	0	0.0%
Thiopental	1	0.2%	0	0.0%
Sevoflurane	1	0.2%	0	0.0%

Discussion

Reporting of serious incidents and near-misses are essential to the understanding of untoward events occurring in healthcare. Without data we are destined to miss opportunities to detect and potentially mitigate issues which could be more common than we perceive. Reporting of untoward events and near-misses is a professional responsibility of all healthcare professionals.

This means that everyone involved in healthcare has a part to play in reporting, and strong leadership in this by medical professionals is essential. There also needs to be a permissive environment and a culture of reporting. This can only be fostered by using data generated as a learning opportunity, and not as part of a vehicle to blame individuals where an error by a healthcare professional is seen to be the root cause of an issue. It is important to start the conversation with 'What happened within the system that facilitated this set of circumstances?', and not 'Who's to blame and how were they allowed to do this?'.

The MHRA Yellow Card scheme is for medicines and devices. It can be accessed for reporting online (https://yellowcard.mhra.gov.uk/) and by phone, post or app. NHS Improvement also provides guidance on reporting patient-safety incidents (NHS Improvement 2017b).

In the case of perioperative anaphylaxis, there is a danger of multiple reporting and also of incorrect data being reported and recorded. The index anaesthetist may report a case and identify a suspect culprit agent. After attending the allergy clinic and further investigation, the event may or may not be confirmed as a hypersensitivity reaction and, if confirmed, a causative agent (or agents) may or may not be identified. This may then be reported by the allergy clinic. Ensuring that the MHRA does not have incomplete, duplicate, inaccurate or out-of-date data would require considerably more coordination than currently exists. In NAP6 panel discussions it was noted how little information is received back from the MHRA regarding perioperative (or other) anaphylaxis. This may be a flaw in the current reporting system that makes it inadequate for generating a meaningful and representative picture of perioperative anaphylaxis.

In some respects, the NAP6 reporting of perioperative anaphylaxis could be illustrative of what reporting to the MHRA might ideally be. NAP6 engaged with all NHS hospitals, and received numerous reports of events in which the suspected culprit agent was reported by the anaesthetists, both immediately and then again after allergy clinic investigation, with those reports being systematically linked. NAP6 is providing, through this report, rapid feedback to those reporters, which is potentially of value to the learning process of reporters and departments and may reduce risk to patients. While the MHRA seemingly cannot provide the same level of capture, analysis and feedback as achieved by NAP6 in this project, it may be possible to identify key lessons to be learned, and we make several recommendations below. This topic is also discussed in Chapter 4, The lay perspective.

Overall, reporting at local level for these serious incidents is reasonably good, but it could still be improved. While local information is fed into the National Reporting and Learning System, it is unclear how this is filtered and analysed and what is done with the resultant findings. There appears to be a lack of national reports of such analysis to aid in the learning process.

From data received by NAP6, reporting to the national regulator of drugs and medical devices (MHRA) appears very poor, and it is likely that not only are reporting rates normally lower than during NAP6 (a substantial number of reports made to the MHRA were by NAP6 Local Coordinators), but also that, due to the processes involved, the data collected by MHRA is unlikely to accurately identify causative agents. There is currently very little feedback from the MHRA on this matter.

Recommendations:

National

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

Institutional

- The departmental lead should ensure all cases have been reported to the trust's incident reporting system
- 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

- The departmental 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

- The departmental lead should be informed of the case
- The MHRA case identifier should be included in the referral to the allergy clinic
- 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.

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Notes

Notes

Anaesthesia, Surgery and Life-Threatening Allergic Reactions
RCoA 6th National Audit Project: Perioperative Anaphylaxis

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