

Allergy and anaesthesia: managing the risk

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Learning objectives

By reading this article you should be able to:

- Identify which patients require preoperative assessment by an allergy specialist and the key features in their history that indicate increased risk of allergy.
- Describe measures that can be taken during anaesthesia and surgery to minimise the risk of allergic reactions.
- Outline the key postoperative actions needed to ensure patients' safety during future anaesthetics.

Key points

- It is possible to reduce the risk of allergic reactions in the perioperative period.
- Preoperative assessment is an opportune moment to identify prior allergic reactions.
- The relative risk of allergy should be taken into account for individual drugs.
- When suspected allergic reactions occur, a comprehensive referral to a specialist clinic should be sent; including a clear timeline of the event, all drugs given, and appropriately timed mast cell tryptase samples.
- Collaboration between anaesthetists and allergists is key to planning future anaesthesia.

Perioperative hypersensitivity reactions are unpredictable adverse events that can range in severity from minor to life-threatening. The underlying mechanism may be allergic or non-allergic, although reactions are indistinguishable in clinical practice regardless of the underlying cause. The purpose of this article is to identify key points in the perioperative

period where an increased risk of allergy might be identified and to provide clinicians with pragmatic strategies with which to mitigate this risk.

The Ring and Mesmer classification system is the most widely known and may be used to grade hypersensitivity reactions. Anaphylaxis is the most severe grade of reaction and by definition may be life-threatening. Less severe reactions, of Grades 1 and 2, are nonetheless important and require investigation because future exposure to the triggering drug may result in a serious and avoidable reaction.

The quoted incidence of life-threatening anaphylaxis varies around the world, partly because of the different reporting mechanisms used and variable inclusion of prospective and retrospective work.¹ The UK National Audit Project study (NAP6) estimated an incidence of 1:11,752 in the UK, or one event every 7.25 anaesthetist years, although this was thought to be an underestimate of up to 70%.² Despite optimum clinical care, perioperative anaphylaxis is still associated with significant morbidity and mortality. In the NAP6 report more than 50% of patients required admission to critical care, 70% of whom required Level 3 care. Mortality

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Clinical scenario

A 62-year-old female with a body mass index 43 kg m⁻² presented for elective mitral valve replacement surgery. She had a history of ischaemic heart disease and hypertension for which she was taking ramipril 2.5mg daily. At preoperative assessment she described a previous episode of anaphylaxis to penicillin during surgery she had undergone 15 years ago. She had been given this diagnosis on the day by the anaesthetist but had not undergone formal testing subsequently. She had avoided penicillin ever since and not had further surgery. The anaesthetic chart was unavailable at the time of pre-assessment.

An epidural was sited uneventfully at the T9/10 interspace, but no test dose given. Anaesthesia was induced using fentanyl 100 mcg, propofol 160 mg and rocuronium 50 mg. Around 10 min after induction it was noted that her arterial pressure was 85/50 mmHg and heart rate 124 bpm. Following several boluses of metaraminol, her blood pressure improved to 95/55 but her heart rate was unchanged. Her skin was cleaned using a chlorhexidine-based product and shortly afterwards a urinary catheter was sited using a chlorhexidine and lidocaine-based lubricant gel (Instillagel). Around 5 minutes later she became profoundly bradycardic followed by pulseless electrical activity (PEA) cardiac arrest. Adult life support guidelines were followed, with spontaneous circulation restored after two litres of crystalloid fluid, adrenaline (epinephrine) 50 mcg and 2 minutes of CPR. Surgery was abandoned, and a referral made to allergy clinic. The mast cell tryptase taken at the time of the event was increased at 58 ng ml⁻¹, with a baseline level of 4.8 ng ml⁻¹.

The anaesthetic chart from 15 years earlier was obtained by the allergy clinic. This revealed that the previous adverse event had occurred shortly after a chlorhexidine-coated central line had been inserted, and 15 minutes after co-amoxiclav had been given. The patient described being unable to use mouthwashes because of irritation and swelling around her mouth and lips, and had noticed widespread urticaria when using chlorhexidine-based body wash preoperatively. Skin testing and serum specific IgE for chlorhexidine were positive. Testing for all other agents was negative. Penicillin allergy was excluded with a drug provocation test.

The patient returned for valve replacement surgery four months later and this was completed with no adverse events during anaesthesia or surgery. The chlorhexidine allergy was discussed at the team briefing and again at handover to the recovery staff. However, in the postoperative recovery area, a peripheral cannula hub was swabbed in error with an antiseptic wipe containing chlorhexidine 2%, immediately before an infusion of crystalloid fluids. The patient suffered a repeat episode of cardiac arrest, regaining spontaneous circulation after receiving adrenaline 200 mcg and 10 minutes of CPR. This episode was later confirmed at allergy clinic to be caused by chlorhexidine after negative testing for all other agents. Recovery on this occasion was complicated by a degree of persistent cognitive impairment.

estimates are broadly similar in France, Japan, the US, and the UK at around 4%; one-third of patients experience significant physical or psychological harm.^{1–3} The incidence of less severe grades of reaction is not well defined and is likely to be subject to significant under-reporting. Defined predominantly by skin signs such as urticaria and flushing, less severe reactions can easily be missed during surgery. The patient's skin may be obscured by surgical drapes; symptoms such as itch and abdominal pain cannot be reported; and relatively minor changes in heart rate and blood pressure may be interpreted as physiological responses to anaesthesia and surgery.

The preoperative patient

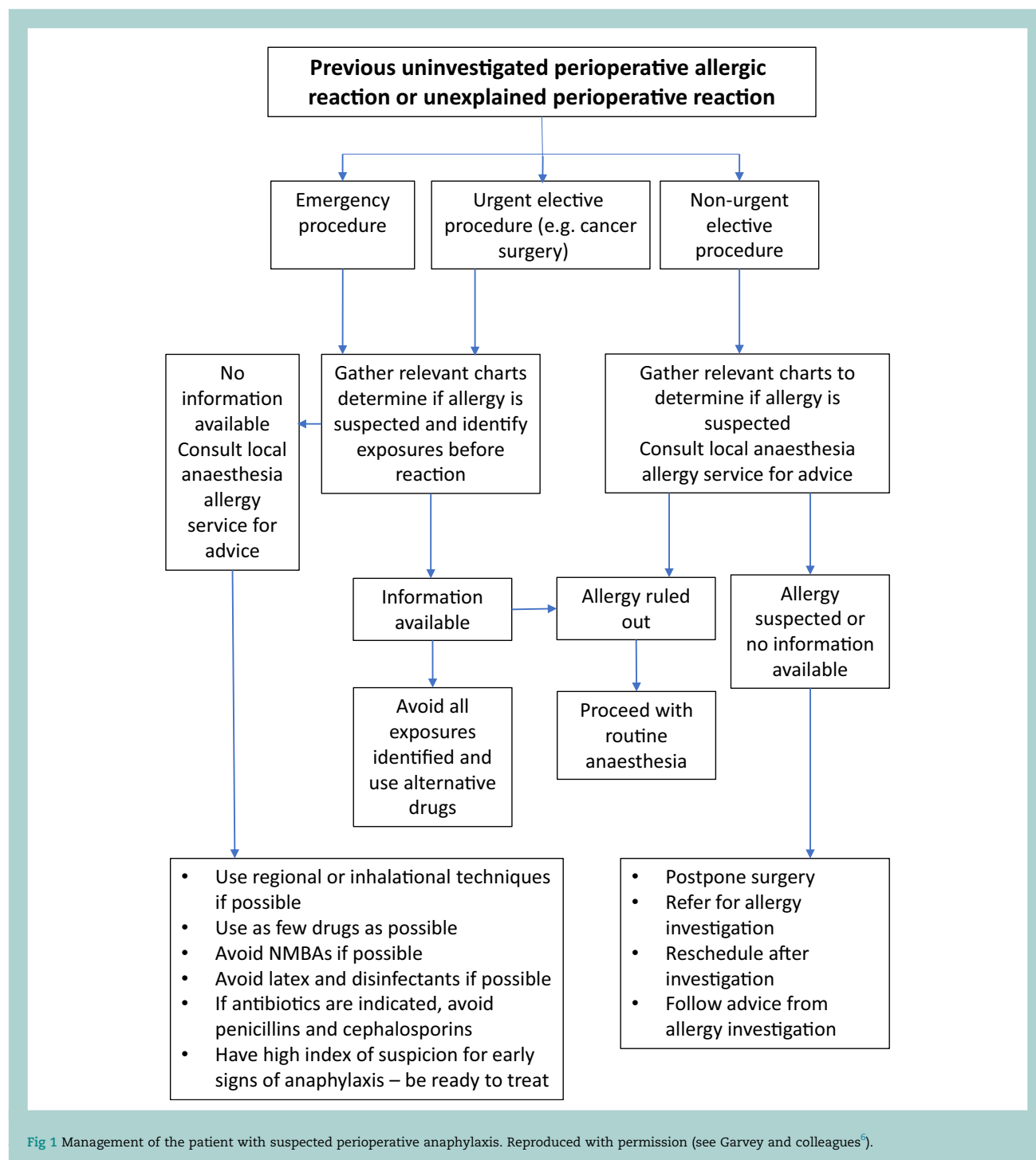
Investigation of previous unexplained or uninvestigated adverse perioperative events

Any patient with a history of unexplained serious perioperative adverse events that meet the criteria for referral to anaesthetic allergy clinic should be investigated before further surgery.^{4,5} This includes those with single or multi-system life-threatening features such as severe unexplained hypotension, bradycardia or cardiac arrest, and severe unexplained bronchospasm. It also includes patients with less severe events such as widespread urticaria or angioedema. Even if the event occurred many years ago there is value in referring the patient to the clinic as the old notes often yield useful clues, and evaluation of the patient and any subsequent anaesthetics they have had can be very informative.

Patients should also be referred when they give a history of perioperative anaphylaxis that has not been formally investigated. Without testing in an allergy clinic, the adverse event may have been attributed to anaphylaxis incorrectly. In addition, anaesthetists in 25% of cases incorrectly identify the causal agent for the allergic reaction.⁵ Attributing anaphylaxis to the wrong causal drug leaves the patient at risk not just of further exposure to the real culprit, but also unnecessary avoidance of non-causal (potentially important) drugs.

What to do when surgery is urgent

If surgery cannot wait, pragmatic advice is needed on how to proceed safely. Occasionally, the only safe course of action is to avoid all drugs used in the previous anaesthetic. If the previous anaesthetic chart is unavailable (a typical scenario) then anaesthesia should proceed using drugs associated with the lowest risk of allergy and using as few drugs as possible. In practical terms, this means avoiding neuromuscular blocking agents (NMBAs) if at all possible, and avoiding chlorhexidine and latex unless the patient can confirm subsequent uneventful exposure to these at least 6–8 weeks after the index reaction. Consideration should be given to avoiding antibiotics if the index reaction was potentially antibiotic-related. The primary care physician may be able to provide useful information about antibiotic exposure subsequent to the index reaction, which may help guide this decision. Most allergy clinics will be able to offer advice and should be asked for their input even if this is on the day of surgery. A useful flowchart detailing the approach to patients with previous suspected perioperative anaphylaxis is shown in Figure 1.⁶



Taking a chlorhexidine history

Chlorhexidine has antibacterial properties and its use has increased dramatically over time with a parallel increase in the number of allergic reactions to it. Many chlorhexidine-based products are used during the perioperative period, for example lubricating gel for urethral catheterisation; skin cleaning solutions; and anti-bacterial wipes used for cleaning cannula hubs and the tops of drug ampoules. Chlorhexidine-containing products are also used widely in the community,

for example in mouthwashes and a variety of other cleansing products. Given the widespread and increasing use of chlorhexidine, the incidence of anaphylaxis to it has probably not yet peaked.⁷ Up to 80% of patients diagnosed with chlorhexidine allergy report a prior history consistent with allergy, which could have been detected before their perioperative reaction.^{8,9} In addition, anaesthetists often misattribute reactions caused by chlorhexidine to other drugs. This is partly because of the delayed onset of reaction seen in chlorhexidine reactions compared with drugs given i.v.⁵ Minor reactions

seen with chlorhexidine, such as urticaria at the site of cannulation, or generalised urticaria after use of chlorhexidine body wash, are an indicator of IgE-mediated hypersensitivity. Subsequent intraoperative chlorhexidine exposure can result in systemic and life-threatening reactions.¹⁰ Anaesthetists are well placed to identify a history of possible chlorhexidine sensitivity during preoperative assessment, but patients rarely volunteer problems with chlorhexidine and will need to be specifically asked. Useful screening questions are shown in [Box 1](#). Where a history of possible chlorhexidine allergy is elicited, this requires further investigation; where surgery is urgent and cannot be delayed for allergy testing, chlorhexidine should be avoided during the perioperative period.

Untested penicillin allergy labels

At least 10% of surgical patients carry a label which has not been formally evaluated and around 95% of these labels are incorrect.¹¹ There is increasing recognition that penicillin allergy labels are associated with harm which includes a 50% increase in surgical site infections, increased length of stay and increased mortality.^{12–17} For surgical patients in the UK, the label results in the use of teicoplanin as an alternative. This antibiotic has the single greatest risk of anaphylaxis of any drug used in the perioperative period.^{3,18} Guidelines from the International Suspected Perioperative Allergic Reactions group (ISPAR) published in 2019 detail a consensus-based approach to the management of patients with a label of penicillin allergy where a penicillin is the first-line antimicrobial choice; other strategies found in the worldwide literature are generally tailored to settings where cephalosporins are the first-line choice.^{19,20} The key determinant of cross-reactivity between penicillins and cephalosporins is side chain similarity. Incidence of clinically significant cross-reactivity appears to be very low, but these figures may be falsely reassuring as most patients' penicillin allergy labels are incorrect in the first instance.²¹ Cephazolin, a first-generation cephalosporin used widely throughout the world as first line prophylaxis, has no shared side chains with penicillin and appears to have very low risk of cross-reactivity in penicillin allergic patients.²²

Reducing the burden of incorrect penicillin allergy labels is key to good antimicrobial stewardship. However, current guidelines in the UK and many other countries do not support the widespread testing of patients, in large part because of the scarcity of allergy specialists to perform this. Novel pathways to test and 'delabel' patients are under development and offer the potential to improve outcomes in perioperative patients and other groups.

Box 1

Screening questions for potential chlorhexidine allergy.

“Do you ever have problems such as itchy rashes or hives, with skin cleaning products in hospital? For example, when you have blood taken, or a drip put in, or have to wash in pink antiseptic bodywash (e.g. Hibiscrub)?”

"Have you ever had problems with rashes or irritation when a urinary catheter was put in?"

“Do you use mouthwashes? And do these cause your mouth to become sore and irritated?”

Strategies to minimise risk during anaesthesia and surgery

Preventing accidental re-exposure

Accidental administration of drugs to which the patient is known to be allergic to is a recognised problem.²³ Chlorhexidine is a particular problem in this respect, with inadvertent exposure made more likely by the ubiquitous inclusion of chlorhexidine in cleaning products (see Fig. 2). This can be compounded by unclear labelling, with use of the terms CHG or CHX rather than chlorhexidine. In patients with confirmed or suspected sensitisation to chlorhexidine, the use of 'chlorhexidine-free boxes' containing alternatives to all the commonly used chlorhexidine products may be useful. Beyond their practical advantages, these boxes may also serve as a physical reminder to all healthcare professionals in contact with the patient that chlorhexidine needs to be avoided. A bedside notice warning of the allergy together with details of which alternative product can be used is an alternative method to try and avoid inadvertent exposure.

Use of prophylactic antihistamines and steroids

These drugs may be used to reduce allergic symptoms such as itch in the hours after an anaphylaxis. However, there is no role for them in the prevention of allergic reactions and their use is not recommended in this situation.⁶

Antibiotic test doses

The rationale supporting the use of an antibiotic test dose is that anaphylaxis is not an all-or-nothing response to an allergen, but instead a dose-related phenomenon that can be triggered at very low doses. In a sensitised individual, a test dose may provoke a degree of mast cell degranulation that is not yet life-threatening, for example urticaria and a mild tachycardia. By treating the patient and withholding further allergen, a worse reaction might be prevented. In principle, this applies to all drugs used in the perioperative setting, although incremental dosing is most practicable with the antibiotics.



Fig 2 Chlorhexidine-containing products commonly found in the operating theatre setting. NMBA, neuromuscular blocking agent.

The counterargument is that an arbitrary dose of 5–10% will be insufficient to cause any degree of reaction in some patients, but a sufficiently large dose in others to cause a life-threatening reaction. The thresholds for reaction vary both between and within patients depending on the degree of sensitisation and the presence of cofactors, and can be highly unpredictable. In addition, there are potential unintended harms from test dosing including delays in the anaesthetic room, delayed antibiotic administration, and accidental omission of the remaining dose.

NAP6 demonstrated that when anaesthetists gave test doses these were generally at high doses with very little time before the remaining dose was given; unsurprisingly this practice did not appear to mitigate the risk of anaphylaxis. At present, no robust evidence exists to support or refute the practice of test dosing. It may be useful to administer the antibiotic 5–10 min before induction so that in the event of an allergic reaction the causal agent is almost certain.

Consideration of the allergy risk for specific drugs

A general consideration for anaesthetists is whether all drugs administered are strictly indicated. However, there are specific considerations which may guide the use of one drug over another, as detailed below.

Neuromuscular blocking agents

These drugs are responsible for a large proportion of all perioperative anaphylaxis, in almost all countries.¹ Debate about which is the most allergenic in the UK was answered by NAP6, which demonstrated an increased risk with suxamethonium but equal risk between the most commonly used non-depolarising agents atracurium and rocuronium.² It is more important to consider whether the use of a NMBA can be avoided altogether, rather than which specific NMBA to use.

Sugammadex

There is current debate in the literature about the relative risk of allergy to reversal agents, with sugammadex recently demonstrated to have a risk of allergy of 1:500 administrations in Japan.²⁴ This trend has not been observed outside of Japan and the implications of this for other countries remain unclear; they may not be obvious until the cost of this drug comes down, facilitating widespread use. Allergic reactions to neostigmine and glycopyrrolate are extremely rare, and these comparative risks should be one of several factors considered when deciding on a suitable NMBA/reversal combination.

Colloids

The incidence of anaphylaxis to colloids is around 6:100,000.²⁵ These solutions are used in 1.7% of UK anaesthetics and more than 50,000 bags of succinylated gelatin-based solutions are given in the UK every year. Whilst a minority of reactions will occur within 5 min of administration, there is typically a delayed onset of anaphylaxis (of up to 70 min) and reactions are often severe.²⁵ There is evidence that the advantages of giving gelatin-based colloids may be outweighed by their risk of anaphylaxis and departments may benefit from having a formal policy on their use.²⁶

Antibiotics

Antibiotics are given in around half of all anaesthetics in the UK and are a leading cause of perioperative anaphylaxis around the world.² As the number of surgeries worldwide

continues to increase, the total number of antibiotic doses given and incidence of allergic reactions will continue to increase. Ultimately, the issue of global antimicrobial resistance linked to overuse of antibiotics may prove a greater problem than that of allergy. Nevertheless, attempts to reduce and rationalise the use of antibiotics around the time of surgery are likely to reduce the burden of allergic reactions; more judicious use of antimicrobial drugs is a valuable part of reducing overall risk.

Management after a suspected anaphylaxis

The immediate management of a patient who has suffered a suspected perioperative anaphylaxis is comprehensively detailed elsewhere, including in the recent consensus guidelines from the ISPAR group in 2019.^{6,27} For the purposes of this article, the key issue is whether to continue or abandon surgery and if surgery is to continue, considerations around drug choices. There is little evidence on the outcomes for patients after perioperative anaphylaxis to guide this decision-making process. In a recent analysis from Australia, the outcomes were similar whether surgery had been abandoned or had proceeded when the reaction was Grade 1–3 cases.²⁸ Most cases of Grade 4 anaphylaxis were abandoned and there were high rates of complications. The decision as to whether to proceed or not should be guided by the degree of surgical urgency and the degree to which the patient has been stabilised; this is inevitably a clinical decision best made by the anaesthetist in discussion with the surgeon. It is important to remember that allergy testing is unreliable for 6–8 weeks after an allergic reaction, so if surgery must proceed before then, only pragmatic advice can be offered from the allergy clinic about which agents to use.

When surgery is to proceed, there are important considerations around the drugs to be used. All potential culprits must be discontinued where possible; this includes any drug given i.v. within 1 h of the reaction occurring, and any gels, bone cements, medical dyes, or cleaning solutions. Surgery should be chlorhexidine- and latex-free, and if an NMBA was used before the reaction and further doses are mandated by the clinical scenario, an NMBA from a different class should be used. It is worth noting that once mast cells have been depleted of mediators there is likely to be a refractory period where further anaphylaxis will not occur even on re-exposure, but this cannot be relied upon when making drug choices after the event. There is a risk of significant fibrinolysis after anaphylaxis. This should be suspected and treated if unexpected bleeding occurs during surgery.

Postoperative steps to improve patients' safety

Referring the patient to allergy clinic

Any patient who has suffered a suspected allergic reaction during surgery should be referred for investigation at a specialist allergy clinic. This includes not just cases of life-threatening anaphylaxis, but also cases where lower grades of reaction are suspected to have occurred. Skin signs such as widespread urticaria or angioedema, alone or in combination with even minor decreases in BP or increases in HR, should trigger referral. The transient skin signs often seen with NMBAs or opioids such as flushing or urticaria seen in the arm in which the drug was injected, or a generalised flushing of the

neck and upper torso which resolves spontaneously, are generally insignificant and do not warrant referral.

Referral to the clinic is the responsibility of the anaesthetist. The referral must include a copy of the anaesthetic chart with details of all drug/compound exposures and not just the i.v. agents administered by the anaesthetist. Chlorhexidine, latex, medical dyes, bone cement, gels and sprays can all cause hypersensitivity and may not be tested for if not documented. Mast cell tryptase (MCT) sampling is key to the referral. An increase in MCT indicates that widespread mast cell degranulation has occurred; this is generally as a result of anaphylaxis, but may also result from clonal mast cell disorders such as mastocytosis. An increase is considered significant when the peak sample is at least $(1.2 \times \text{baseline}) + 2 \text{ ng ml}^{-1}$. This may occur without peak MCT being greater than 11.4 ng ml^{-1} , and anaphylaxis therefore cannot be excluded on the basis of a 'normal' peak MCT. Anaphylaxis also cannot be excluded when there is no MCT increase, as the negative predictive power of this test is not 100%. Samples should be taken as soon as possible once the patient is stable, and again within the first 4 h of the event. A baseline sample should be taken at least 24 h post event; the allergy clinic can generally take this sample if necessary. From a pragmatic perspective, allergists or immunologists would prefer one sample taken at any time in the first 4 h, to no sample at all.

The process of referral can be made considerably easier by the use of 'Suspected Anaphylaxis Follow-Up Packs'. These contain all the information and paperwork required to make a referral to the clinic and inform the patient and primary care physician about the event; a template for these packs is available on the NAP6 resources page of the Association of Anaesthetists website.^{5,29} It is vital that patients understand they may have suffered an allergic reaction and what the potential causes of this are, so that they self-advocate should further surgery be necessary before investigation. The written record from the follow-up packs is a useful way to communicate this information. It is also possible for smartphones to store this information and make it accessible even when the phone is locked, should the patient become incapacitated. However, it is not recommended that patients obtain MedicAlert bracelets detailing all the possible causal agents, as subsequent 'delabelling' is notoriously difficult. The prescribing of adrenaline auto-injectors is not recommended for patients with suspected perioperative drug allergies.

Conclusions

Perioperative hypersensitivity reactions are rare and largely unpredictable events. However, the risk can be mitigated to some extent by thorough pre-assessment and judicious intraoperative use of drugs. In order for the allergy clinic to make a reliable diagnosis and determine which drugs may safely be used in the future, it is vital that all substance exposures are documented, together with a clear timeline of events and appropriately timed tryptase sampling. Collaboration between anaesthetists and allergists is essential in both the investigation of reactions and planning for future anaesthetics.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) are accessible at www.bjaed.org/cme/home by subscribers to BJA Education.

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