PG69BP Guideline on the prevention, investigation and follow up of perioperative hypersensitivity reactions and anaphylaxis Background Paper 2025

Short title: Perioperative hypersensitivity reactions BP

1. Purpose of guideline

Anaphylaxis remains a major cause of category one anaesthesia deaths in Australia and New Zealand.[1]

The PG69 Perioperative hypersensitivity reactions professional document and background paper amalgamates hypersensitivity and anaphylaxis related issues including prevention, referral, investigation, appropriate documentation of investigation, patient education, the anaesthetic allergist and the role of a departmental anaphylaxis lead.

EMERGENCY Management of perioperative anaphylaxis (POA) is outlined in the ANZCA/ANZAAG Perioperative Anaphylaxis Management Guidelines.

2. Background

The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) was formed in 2010. Members of this group include anaesthetists, immunologist/allergists, infectious disease physicians, nurses and technical laboratory specialists. ANZAAG is a not-for-profit organisation with a focus on assisting and educating colleagues to deliver quality care for patients in the field of perioperative anaphylaxis.

ANZAAG developed the first edition of the Perioperative Anaphylaxis Management Guideline (PAMG) in 2013 which were endorsed by ANZCA. ANZCA and ANZAAG collaborated on the 2016 and 2022 PAMG and the online Perioperative Anaphylaxis Management Emergency Response module.

The ANZAAG website (https://anzaag.com) provides information for clinicians and patients in the event of an episode of perioperative anaphylaxis. There is information for clinicians, primarily regarding management and referral of patients as well as documentation to assist patient understanding of perioperative anaphylaxis and to assist in the avoidance of allergens in the future. The downloadable generic referral form, requests detailed information about the patient and the event which will aid the perioperative drug allergy service in determining a causative agent. There is also information about the geographical location of these services and how to best refer cases.

3. Hypersensitivity, Allergy and Anaphylaxis

3.1 **Hypersensitivity** is an umbrella term to cover reproducible symptoms or signs, initiated by exposure to a substance at a dose tolerated by normal subjects and that is outside the primary pharmacological actions. **Allergic hypersensitivity** is mediated by IgE. Non-allergic hypersensitivity does not involve IgE, rather it is mediated through non IgE pathways, e.g. MRGPRX2.[2]

3.2 **Anaphylaxis** is a severe, life-threatening, generalised or systemic hypersensitivity reaction.[3] It may be allergic or non-allergic.

4. Pathophysiology and Clinical Presentation of Perioperative Anaphylaxis

The key effector cells of anaphylaxis are mast cells and basophils. Degranulation of mast cells can be triggered by allergic (IgE) and non-allergic pathways (complement, COX-1, Kinin-Kallikrein system, MRGPRX2 and other receptors) mechanisms, resulting in the release of mediators including histamine, proteases, prostaglandin, leukotrienes and platelet activating factor. The clinical features seen are the result of mediator actions.

The diagnosis of anaphylaxis is a clinical one and the treatment is the same regardless of the mechanism. A high index of suspicion by anaesthetists is essential for early recognition and prompt treatment.

Clinical presentation is influenced by patient comorbidities and pharmaceutical treatments, surgical pathology, and surgical and anaesthetic techniques. The evolution of the clinical scenario depends on the physiological reserve of the patient and the effectiveness of the treatment administered.

Perioperative anaphylaxis generally presents with cardiovascular, respiratory and mucocutaneous features.

4.1 Cardiovascular

Hypotension is the most common presenting feature (46%) and was present at some point in 98.5% of cases in the Royal College of Anaesthetists 6th National Audit Project.[4] Hypotension is usually accompanied by tachycardia (effect of histamine on cardiac H2 receptors, endogenous catecholamine effects on cardiac beta receptors and reflex sympathetic activation) although bradycardia may be more common in severe anaphylaxis.

Hypotension is generally the result of decreased cardiac preload and afterload. Reduction in preload is secondary to fluid loss and redistribution of blood between vascular compartments.[5] Reduction in afterload is secondary to vasodilation.

Cardiac output may be initially maintained or increased if cardiac preload is adequate.[5] Inadequate preload or developing myocardial dysfunction will result in a reduction in cardiac output.

Myocardial dysfunction may occur secondarily to hypoperfusion of the myocardium and/or an increased myocardial oxygen demand due to tachycardia.[5] Myocardial dysfunction is more common in patients with pre-existing cardiac disease.

4.2 Respiratory

1.5% had bronchospasm as the only feature.[4] Many patients presenting for surgery have a predisposition to bronchospasm due to asthma, which may be poorly controlled or even undiagnosed, chronic obstructive pulmonary disease, smoking and intercurrent viral respiratory tract infections. Anxiety, irritant volatile anaesthetics, airway instrumentation and histamine releasing drugs may trigger bronchospasm. Anaphylaxis is not the most common cause of perioperative bronchospasm. When anaphylaxis does occur bronchospasm is triggered by the actions of degranulation products including histamine, leukotriene and PAF which are all potent bronchoconstrictors. Histamine is also a potent vasodilator of the tracheobronchial circulation causing submucosal swelling.

Pulmonary oedema is a rare complication of anaphylaxis.

4.3 Mucocutaneous

Urticaria occurs due to vasodilatation, increased blood flow and increased capillary leakage in the superficial dermis.

Angioedema (non-pitting, non-gravity-dependent, transient swelling of the skin or mucous membranes) is due to the same pathophysiological process but occurs in the deeper tissues. It may occur as part of anaphylaxis (histaminergic) but may also be bradykinin or complement mediated (non-histaminergic).[6]

Airway swelling is an uncommon feature of perioperative anaphylaxis. In NAP6 it was reported in less than 1% of Grade 3 reactions and in none of the Grade 4 reactions.[4] Bradykinin-mediated angioedema often involves the upper airways and does not respond to treatment with antihistamines, corticosteroids, or adrenaline. It may be triggered by airway manipulation during anaesthesia and is often prolonged.

5. Incidence

Estimates of the incidence of perioperative anaphylaxis are influenced by the heterogeneity of studies (multicentre/single centre, prospective/retrospective, etc), differences in terminology and geographical location.

Perioperative anaphylaxis in Western Australia has been estimated to occur at a rate of 1 in 11,000 anaesthetics [7], 1:in 10 000 anaesthetics in the United Kingdom [8], 1:in 7 000 anaesthetics in the USA [9] and 1: in 10 000 in France) [10].

In Australia and New Zealand, neuromuscular blocking agents (NMBAs) [11, 12], antibiotics [13], chlorhexidine, blue dyes and sugammadex are the most common causes of perioperative anaphylaxis. Amongst the NMBAs, suxamethonium and rocuronium have a higher incidence of anaphylaxis than vecuronium, with cisatracurium and atracurium showing a lower incidence.[11, 14] Perioperative anaphylaxis associated with cefazolin has been estimated to be 1:4800 exposures.[15]

The most comment culprit agents identified in NAP6 [4] were antibiotics 47%, NMBAs 33%, chlorhexidine 9%, and Patent Blue dye 4.5%. Of the antibiotics co-amoxiclav and teicoplanin were the most common causes.

In France [9] the most common culprit agents were NMBAs (60%), antibiotics (25%) and patent blue dye (2%). Suxamethonium and rocuronium were the NMBAs most commonly responsible for perioperative anaphylaxis. Cefazolin was the culprit in 52% of antibiotic induced perioperative anaphylaxis.

6. Mortality

Perioperative anaphylaxis is associated with significant morbidity and a reported mortality rate of 2% in the USA [9] and 4% in both France [16] and the United Kingdom [4].

7. Review of issues

7.1 Prevention

Perioperative anaphylaxis is unpredictable. Reduction in its prevalence relies on preventing repeat exposure to known patient allergens, ensuring that episodes of suspected perioperative anaphylaxis are investigated and then avoiding known or suspected allergens.

The presence of excipients can lead to unintentional re-exposure to allergens and complicates the investigation of perioperative anaphylaxis as anaphylaxis may be secondary to the active medication or the excipient. ANZCA supports the clear labelling of all active agents and excipients present in all medical products to prevent unintentional patient re-exposure to known allergens and to facilitate investigation of perioperative anaphylaxis.

Ninety per cent of anaphylaxis due to antibiotics presents within ten minutes of administration.[4] The Therapeutic Guidelines [17] state that surgical antibiotic prophylaxis must be administered before surgical incision and that short acting agents (including cefazolin) should be given no more than 60 minutes before incision. Antibiotics should be given as per manufacturer's instructions regarding dose and speed of injection. The decision to administer antibiotics prior to or following induction of anaesthesia is at the discretion of the attending anaesthetist. Administration of antibiotics several minutes before induction of anaesthesia would likely improve the detection of anaphylaxis, may simplify treatment, and will help investigation when anaphylaxis occur.[4]

Unlike other regions of the world, there is currently no Australian and/or New Zealand Registry which records all episodes of perioperative anaphylaxis. An Australian and New Zealand Registry would provide accurate regional data for scientific research, to inform evidence based perioperative anaphylaxis management guidelines and identify the relative risk posed by the use of individual agents.

Reporting cases via webAIRS is encouraged.

7.2 Management

It is recommended that the clinical management of perioperative anaphylaxis should be guided by the use of the ANZCA/ANZAAG Perioperative Anaphylaxis Management Guidelines.

Mortality and morbidity associated with perioperative anaphylaxis can be reduced by prompt recognition and appropriate treatment.

7.3 Investigation

ANZAAG [18], the European Academy of Allergy and Clinical Immunology (EAACI) [19] and the Association of Anaesthetists of Great Britian and Ireland (AAGBI) [20] have developed guidelines outlining the process of investigation of perioperative anaphylaxis, the full details of which are not appropriate to include in this document. These guidelines should be utilised to ensure consistency of investigation and the provision of the best advice for future care of the patient.

7.3.1 Tryptase

Tryptase is an anaphylaxis biomarker. If anaphylaxis is suspected a series of tryptase measurements should be undertaken with samples taken; as soon as practical, at 1 hour, 4 hours and greater than 24 hours (baseline level). It is generally accepted that a serum mast cell tryptase level greater than 2mcg/L plus the baseline level multiplied by 1.2 is indicative of mast cell degranulation (anaphylaxis).[21] If the clinical picture is suggestive of anaphylaxis referral for investigation is recommended even in the absence of an increase in the serum mast cell tryptase level.[22]

7.3.2 Drug Provocation Testing

Drug provocation testing is the controlled administration of a drug to diagnose a patient's hypersensitivity, or not, to that drug. The decision to perform, or not perform, a drug provocation test should be made on a case-by-case basis as part of a formal allergy investigation with established protocols, after balancing the risk-benefit ratio. Drug provocation testing in the perioperative setting is not routinely advised and should only be carried out under the guidance of a perioperative allergy service.

7.3.3 Suspected Causative Agent

Following the investigation of perioperative anaphylaxis the culprit agent remains unknown in approximately 30 to 60% of cases.[23]

Guessing the causative agent, at the time of anaphylaxis is not reliable. Kriogaard [24] found that in 73% of cases the suspected cause did not match the results of subsequent investigation.

7.3.4 Access to Perioperative Drug Allergy Services

There is currently limited access to perioperative drug allergy services for paediatric patients in Australasia.

Access to perioperative drug allergy services can be limited in remote areas. Health regions need to consider access to these important services in their service development planning.

8. Anaesthetic Roles

8.1 Anaesthetic Allergist

The term anaesthetic allergist is a recognised term for the many anaesthetists in Australia, New Zealand, France, and the United Kingdom whose anaesthetic practice includes the investigation of perioperative anaphylaxis.

Anaesthetists endeavour to provide the safest possible care for their patients and the occurrence of perioperative anaphylaxis can be devastating for both the patient and the anaesthetist concerned. The sense of responsibility to uncover what has happened and whether a cause can be found that may reduce the risk for subsequent anaesthesia has motivated many anaesthetists to enter this area of practice. The anaesthesia community in Australia and New Zealand have had a role in ensuring that allergy events are investigated for the last 50 years, with the establishment of perioperative drug allergy services being substantially anaesthesia led.[25]

In the early years of perioperative anaphylaxis investigation, the establishment of allergy skin testing by anaesthetists was promoted widely as being relatively simple to perform and easy to interpret but over time it has been realised that the decision to investigate or not and how to undertake and communicate the findings is more complex. In recent years anaesthetists have reached out to the immunology/allergology communities with the formation of several collaborative groups that include anaesthetists, immunologists, and others. The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) and the International Suspected Anaesthetic Reactions Group (ISPAR) are two examples.

Many perioperative drug allergy services in Australia and New Zealand involve immunologists in their teams. Ad hoc investigation/skin testing is not recommended with referral to an established perioperative allergy service being promoted.

Ideally the investigation of perioperative anaphylaxis should be a team effort that includes anaesthetists and allergist/immunologists.[19] Multidisciplinary conferences, conjoint services or case by case discussions are suggested. A minimum of 20 cases per year is recommended [20, 26] in order for staff to be able to maintain familiarity with the subject area but it is conceded that geographical isolation may result in smaller volume services.

8.2 Perioperative Anaphylaxis Lead

The role of an anaesthetic departmental Perioperative Anaphylaxis Lead was first proposed in guidelines produced by the British Society of Allergy and Clinical Immunology in 2009. The report stated that: "*A lead anaesthetist should be identified in each major hospital for clinical governance and notified of each case of anaphylaxis. The responsibility would be to provide initial guidance on blood sampling for serum tryptase and to assist in the process of referral to a specialist centre for further investigation*".[26]

As part of NAP6 [4] an organisation pre-survey was sent to departments of anaesthesia that included a question regarding anaesthesia leads. The response rate was 91%. The responses indicated that 43% of the 323 anaesthetic departments surveyed had an anaphylaxis lead.

NAP 6 [4] identified numerous areas for improvement regarding the treatment and follow up of perioperative anaphylaxis cases. One of the recommendations was to reiterate that each department of anaesthesia should have a Perioperative Anaphylaxis Lead and this recommendation was supported by the Royal College of Anaesthetists.[27] It is envisaged that this role would assist with the uptake and implementation of the NAP 6 recommendations and the coordination of a follow up survey in addition to the other responsibilities. Their estimate of time allocated to be allocated to this role was 1 hour per week, on average. By comparison this is the same amount of time they recommend that an educational supervisor should be allocated per trainee.

There is no current data regarding the number of hospitals in Australasia that have an anaphylaxis lead role as part of their department portfolios, but it is probable that many hospitals already have this role in place.

The role of the Perioperative Anaphylaxis lead spans four areas: education, case management and referral, audit, and prevention.

9. Summary

It is the anaesthetist's duty to attempt to reduce the prevalence of perioperative anaphylaxis, recognise and treat anaphylaxis when it occurs and then refer appropriately for further investigation. Patients who experience anaphylaxis require follow up and are likely to need support. Staff who are involved with an anaphylaxis incident are likely to need support particularly when there has been an adverse outcome.

Related ANZCA documents

ANZCA/ANZAAG. Perioperative anaphylaxis management guideline. 2022. Available from: https://www.anzca.edu.au/safety-and-advocacy/standards-of-practice/perioperative-anaphylaxis-management-guidelines Accessed 20 Mar 2025.

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PG69 Appendix 1 - Chlorhexidine hypersensitivity

The ANZCA Safety and Quality Committee acted as the DDG and delegated the task to the Anaesthetic Allergy Subcommittee as the expert panel. Membership of the expert panel for *PG60 Guideline on the perioperative management of patients with suspected or proven hypersensitivity to chlorhexidine* in 2016 (superseded to *PG69 Appendix 1 Chlorhexidine hypersensitivity* 2025):

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