

Short title: Perioperative hypersensitivity reactions

1. Purpose

Anaphylaxis remains a major cause of category one anaesthesia deaths in Australia and New Zealand.^[1] The purpose of this document is to improve patient outcomes by providing guidance to anaesthetists regarding the prevention, investigation and follow up of perioperative anaphylaxis.

2. Scope

This document is intended to apply to:

- specialist anaesthetists, trainees and rural generalist anaesthetists involved in the prevention, management and/or investigation of perioperative anaphylaxis.
- All healthcare facilities and all areas within those facilities in which general anaesthesia, major regional anaesthesia or sedation are provided by anaesthetists.

It is not intended to apply to non-anaesthetist sedationists although it is recognised that the principles may be applicable.

It is not a guideline for the emergency management of anaphylaxis.

Clinical management of perioperative anaphylaxis is covered by the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) and Australian and New Zealand College of Anaesthetists (ANZCA) [Perioperative Anaphylaxis Management Guideline](#).

3. Prevention

Perioperative anaphylaxis is a rare event with few modifiable risk factors. The strongest predictor of perioperative anaphylaxis is the presence of previous perioperative anaphylaxis. The most effectual anaphylaxis intervention is to prevent avoidable re-exposure to a proven allergen.^[2]

Historically, the most likely causes of perioperative anaphylaxis are neuromuscular blocking agents, antibiotics, blue dyes, latex, sugammadex and chlorhexidine. The potential for anaphylaxis should be carefully considered when evaluating the risk and benefits of all medications given during anaesthesia.^[3]

3.1 Preoperative

Anaesthetists should ensure that a comprehensive allergy history is obtained before commencing anaesthetic care and modify the anaesthetic plan accordingly. If an unconfirmed history of a significant drug allergy is reported or suspected then relevant medical records, previous anaesthetic records and past allergy investigations should be carefully scrutinised and discussed with the patient, colleagues and allergy experts as necessary. This is to ensure that an anaesthesia plan is developed that avoids known or suspected allergens as well as drugs and substances with known cross sensitivities.

If there is no previous allergy record or correspondence, consider referral to a perioperative drug allergy service prior to the procedure.

In time-sensitive situations an anaesthetic plan that minimises exposure to potential triggers should be implemented (see appendix 2).

To prevent medication errors, all drugs and equipment containing allergens must be clearly labeled. This is especially important to avoid inadvertent re-exposure to hidden allergens such as chlorhexidine. Chlorhexidine free products should be readily available (see appendix 1).

Patient allergies should specifically be addressed as part of operating room Sign In and Time Out processes and clearly documented on the anaesthetic record.

On occasions the allergy history reveals an allergy label that on close scrutiny does not appear to be an immune-mediated reaction (see appendix 3).

3.2 Intraoperative

If an episode of unexplained perioperative instability occurs clear documentation should include all drugs administered, including those used to treat the episode, along with precise details of the timing and dosage (see *PG06(A) Anaesthesia record* and associated background paper). It is critical that clinicians reviewing the documentation have a clear understanding of the event's progression.

A comprehensive description of the event is invaluable to future anesthetists and the investigating perioperative allergy services. It is important to remember that some patients may not attend their appointment or may be lost to follow-up.

3.3 Postoperative

There should be open disclosure of a suspected episode of perioperative anaphylaxis to the patient and their family. Appropriate documentation should be provided including a list of all potential allergens that the patient was exposed to during the procedure and general information regarding perioperative anaphylaxis.^[4, 5]

The patient should be referred to a perioperative drug allergy service for testing. It is the responsibility of the treating anaesthetist to make this referral and to explain to the patient the importance of attending the appointment.^[6] In addition, a letter should be sent to the patient's general practitioner (GP) informing them of the suspected episode of perioperative anaphylaxis.^[6] The content of this letter should include a description of the events, the agents to which the patient was exposed and the details of the perioperative drug allergy service to which the patient was referred.

The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) website: <https://anzaag.com/> provides information for clinicians and patients in the event of an episode of Perioperative Anaphylaxis. The website has a downloadable generic referral form which details information about the patient and the event which will allow perioperative allergy services to assess a case of suspected perioperative anaphylaxis. There is also information about the geographical location of these services and how to best refer cases.

Until the patient has attended a perioperative drug allergy service, all potential triggers of the reaction need to be carefully considered before subsequent administration. A drug alert needs to be placed in the patient medical record and should only be removed after consulting with a perioperative drug allergy service.

Hospitals must ensure that known patient allergies are able to be clearly documented in the medical record and the medication chart and that clinical staff have the appropriate training to access those records.

Incident reporting to WebAIRS (web-based anaesthetic incident reporting system) and national/state-based reporting systems is recommended.

4. Management of Perioperative Anaphylaxis

Perioperative anaphylaxis is a life-threatening emergency that requires prompt recognition and management. If an episode of anaphylaxis is suspected, anaesthetists are encouraged to declare

an emergency, seek assistance and utilise an appropriate cognitive aid. The use of the [ANZCA/ANZAAG Perioperative Anaphylaxis Management Guidelines](#) is strongly recommended. These guidelines provide information regarding the clinical management of perioperative anaphylaxis for both adults and children. They detail the immediate treatment, treatment in refractory cases, differential diagnosis, post crisis management and investigation.

The decision to defer the surgery or not will depend on several factors including the urgency of the surgery, the severity of the anaphylaxis and the response to initial treatment.^[7] If the decision is to proceed, please refer to appendix 2. Transfer to an intensive care facility should be considered.

5. Paediatric considerations

The preparation of drugs for the management of paediatric perioperative anaphylaxis may be prone to error in the emergency setting.

6. Obstetric considerations

An allergy history should be taken even when there is extreme urgency to deliver the baby.

Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear. Hypotension due to anaphylaxis is exacerbated by neuraxial blockade and or aortocaval compression.

7. Investigation

7.1 Indication for Referral

It is recommended that all cases with a clinical history supporting the diagnosis of perioperative anaphylaxis should be investigated.^[8, 9] This includes paediatric patients of any age. The treating anaesthetist is responsible for referring these patients to an appropriate perioperative drug allergy service. It is also recommended that patients be referred for investigation, prior to surgery, where there is suspicion of a previously un-investigated perioperative anaphylactic reaction.^[10] This may only be practical when surgery is elective.

The indications for referral include but are not limited to one or more of the following:

- Unexplained cardiac or respiratory arrest during anaesthesia
- Unexplained hypotension with or without tachycardia particularly if the hypotension is unresponsive to vasopressors
- Unexplained tachycardia
- Unexplained, bronchospasm, particularly if the bronchospasm is severe and causes a significant decrease in oxygen saturation and or is relatively resistant to treatment
- Widespread urticarial or erythematous rash
- Angioedema
- Tongue or glottic swelling
- An increase in the peak serum mast cell tryptase level above baseline

Skin testing is not validated as a screening tool and referral for skin testing is not appropriate in the absence of a personal history of possible perioperative anaphylaxis.^[11]

7.2 Referral Information

The referral form on the [ANZAAG website](#) can be used for referral to a perioperative drug allergy service. If this form is not used the following information should be included in the referral:

- All agents given intravenously within 60 minutes of the onset of symptoms and agents given within 2 hours if the exposure was mucosal, subcutaneous or oral including any hidden allergens
- Onset time of symptoms and/or signs
- The treatment given and the response seen

- Copies of the anaesthetic chart, medication charts including premedication, the surgical notes, the nursing operating room documentation, Post Anaesthesia Care Unit (PACU) notes and appropriate documentation from the intensive care unit (ICU)
- Tryptase values and timing

Where possible the trade and generic name of medications should be included as excipients may differ between different brands of the same medication.

Hidden allergens are allergenic substances that patients are exposed to during the perioperative period that are not immediately obvious. They include chlorhexidine, povidone iodine, latex, dyes including patent blue and methylene blue, iodinated contrast media, surgically applied haemostatic agents, gelatins and polyethylene glycols.

7.3 Tryptase

The treating anaesthetist should obtain serum for serial serum tryptase measurements. The timing of which is; as soon as practical, 1 hour, 4 hours and greater than 24 hours after the event. The serum tryptase level after 24 hours establishes the baseline level.

An increase in the peak serum mast cell tryptase level above baseline provides useful confirmatory evidence of anaphylaxis. If the clinical picture supports a diagnosis of perioperative anaphylaxis, referral for investigation is recommended even in the absence of an increase in the serum mast cell tryptase level.^[12]

8. Anaesthetic Allergists

Investigation of suspected perioperative anaphylaxis should ideally be conducted by a multidisciplinary team that includes anaesthetists, allergists, immunologists and immuno-pathologists with anaesthetic allergy investigation experience.

Anaesthetists in Australia and New Zealand have been investigating cases of suspected perioperative anaphylaxis since the 1980s and many health services in Australia and New Zealand have anaesthetic allergists who investigate perioperative anaphylaxis. Numerous anaesthetic departments offer fellowships in this area.

9. Investigation Process

The purpose of the investigation of perioperative anaphylaxis is to confirm that the diagnosis is consistent with anaphylaxis, to identify the causative agent/s and to recommend alternatives for subsequent anaesthesia.

Australian and New Zealand guidelines^[5] and international guidelines^[9, 13] outline the process of investigation of perioperative anaphylaxis.

Patients must be informed verbally and in writing of their results and encouraged to be their own advocates to minimise the risk of future exposure to the suspected allergen/s.

A detailed medical report should be entered into the medical record, at both the investigating hospital and the hospital at which the event took place. The report should be sent to the patient, the treating anaesthetist, surgeon and the patient's GP. The patient should be advised to keep a copy of the medical report to inform clinicians of their allergy.

When the patient requires urgent surgery the results of the investigation should be communicated with the referring anaesthetist as soon as possible.

All confirmed anaphylaxis cases should be reported to the Therapeutic Goods Administration in Australia or the Centre for Adverse Reactions Monitoring (CARM) in New Zealand and appropriate state-based reporting systems.

In most cases a personal, wearable, medical alert should be advised.

10. Perioperative Drug Allergy Service Medical Report

The medical report should indicate whether the investigation determined that the perioperative event was secondary to anaphylaxis or was due to aspects of anaesthesia (mechanical or pharmaceutical), surgery, or comorbid diseases factors such as severe asthma, smoking, or other causes. If the event was secondary to anaphylaxis the culprit agent should be listed if identifiable.

Recommendations should be given for safe anaesthesia. In general, these recommendations should advise which drugs and substances are to be avoided, and which drugs and substances may be given.

On occasions the perioperative drug allergy service may believe that a drug provocation test is required to complete the investigation of the perioperative event. The anaesthetic allergist may request that the drug provocation test is performed by the attending anaesthetist at a subsequent anaesthetic. Under these circumstances the anaesthetic allergist should communicate the plan for a drug provocation test with the attending anaesthetist and provide a written set of recommendations. Proceeding with a drug provocation test is at the discretion of the attending anaesthetist.

The medical report may also include a mechanism for the anaesthetic allergist to be updated on subsequent anaesthesia.

11. Perioperative Anaphylaxis Lead

Anaesthetic Departments in larger hospitals should have an anaesthetist designated as the Perioperative Anaphylaxis Lead. This role is separate to that of an anaesthetic allergist.

The activities of the perioperative anaphylaxis lead are aimed at ensuring that:

- With the support of the director of the anaesthetic department, anaesthetists are trained in the recognition and management of perioperative anaphylaxis
- Medications required for the treatment of perioperative anaphylaxis are easily accessible
- An “Anaphylaxis Box” which contains the ANZCA/ANZAAG Anaphylaxis Management Guidelines, investigation packs and patient information is readily available in all treatment areas
- Advice is provided to colleagues on appropriateness of referrals
- Referral pathways for perioperative anaphylaxis investigation are clear
- Liaison with local perioperative drug allergy service occurs
- Anaesthetists are aware of the requirements for notification of local, state and national drug pharmacovigilance systems
- There is a coordinator for local, regional and national audits of perioperative anaphylaxis cases
- Anaesthetists are aware of the information that must be provided to the patient and the GP following an episode of perioperative anaphylaxis.
- Pathways are in place to identify adverse sequelae that occur during subsequent procedures
- There is regular educational activity concerning perioperative anaphylaxis
- Cases of perioperative anaphylaxis are presented at departmental meetings and that learning points are acted on
- Appropriate dissemination of college documents regarding perioperative anaphylaxis occurs

Definitions

Anaphylaxis, allergic hypersensitivity and non-allergic hypersensitivity are defined in the [PG69 Background Paper](#).

The following definitions are specific to this document:

- **Immune sensitisation:** The production of antibodies by B cells when the immune system registers a substance as a threat.
- **Hidden allergens** are allergenic substances that patients are exposed to that are not immediately obvious.
- **Excipient:** An inactive substance that serves as the vehicle or medium for a drug or other active substance

See further below for appendices. This document is accompanied by a background paper (PG69BP) which provides more detailed information regarding the rationale and interpretation of the Guideline.

References

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Related ANZCA documents

College documents considered in developing this document:

CP23 Policy for professional document framework

CP24 Policy for the development and review of professional documents

PG06(A) Guideline on the anaesthesia record

PG28 Guideline on infection prevention and control in anaesthesia

PG51(A) Guideline for the safe management and use of medications in anaesthesia

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Appendix 1 - Chlorhexidine hypersensitivity

1. Purpose

The purpose of this appendix is to guide the perioperative management of patients with suspected or proven hypersensitivity to chlorhexidine to prevent inadvertent exposure and subsequent hypersensitivity reactions in these patients.

2. Scope

This appendix is intended to apply to all anaesthesia providers. It should also serve as guidance to non-anaesthetists who manage sedation.

3. Background

Chlorhexidine (1:6-Di-4'-Chlorophenyldiguanidohexane) is a broad-spectrum antimicrobial agent. Recognition of the efficacy of chlorhexidine as an antimicrobial agent has seen its use increase within hospital environments and the community.

The true incidence of perioperative chlorhexidine anaphylaxis is difficult to estimate due to the difficulty in accurately ascertaining the total number of exposures to chlorhexidine, the absence of mandatory reporting and the certainty of a diagnosis of chlorhexidine hypersensitivity. Chlorhexidine accounted for almost 10% of cases of perioperative anaphylaxis in NAP 6 ^[1] and was the third most prevalent cause of anaphylaxis after antibiotics and neuromuscular blocking agents (NMBAs) with an estimated incidence of 0.78 per 100,000 exposures.

4. General Principles:

4.1 Increasing recognition of chlorhexidine as an allergen

Chlorhexidine was first developed for use in 1954 by Imperial Chemical Industries, Manchester, United Kingdom. The first report of cutaneous hypersensitivity was from Calnan in London in 1962 ^[2]. Further reports of anaphylaxis to chlorhexidine were reported by Okano ^[3] in 1983 and Nishioka ^[4] in 1984.

A governmental warning was issued in Japan in 1984 ^[5] prohibiting the use of chlorhexidine on mucosal membranes. Warnings specific to hypersensitivity reactions from chlorhexidine impregnated central devices, such as central venous access devices (CVADs), have also been issued by the Food and Drug Administration in the United States of America ^[6] and by the Therapeutic Goods Administration in Australia in 2012.^[7]

Chlorhexidine anaphylaxis is typically delayed when absorption occurs across skin or mucosa, compared to the intravenous administration of allergens where anaphylaxis manifests within a few minutes of administration.

Individual patients have suffered multiple episodes of anaphylaxis caused by chlorhexidine as a result of failure to identify chlorhexidine as an antigen, or failure to recognise the presence of chlorhexidine in products found in the hospital environment.⁽⁸⁾ This finding highlights the need for chlorhexidine-free management guidelines to protect patients from iatrogenic injury.

4.2 Difficulty in identifying products containing chlorhexidine

Chlorhexidine is present in antiseptic solutions for the disinfection of skin. It is present in a large number of other products that may not be as well recognised including lubricants used for indwelling urinary catheter insertion, impregnated into central venous catheters, dressings, surgical drapes and other medical devices. Its presence may be hidden due to the difficulty of identification of its presence in some products and the frequent changes to product availability.

The inconsistent labelling of products that contain chlorhexidine presents a barrier to successful avoidance of these products in the chlorhexidine hypersensitive patient. There is no universal

symbol to ensure easy identification of chlorhexidine, such as there is for latex. The print outlining product composition is often small and not placed in a prominent or uniform position.

Hospital products change in accordance with purchasing contracts and evolution of clinical guidelines, particularly infection control recommendations.

Chlorhexidine is widely used in products available to the general community such as antiseptic handrubs, mouthwashes, toothpastes and throat lozenges.

A register of all chlorhexidine products is an important resource in ensuring the safe management of chlorhexidine hypersensitive patients. As there is a need for frequent updates to maintain currency of the register it is particularly important to recognise that the absence of a product on the register is not a guarantee that the product is chlorhexidine-free. All health workers must endeavour to prevent exposure to chlorhexidine in the chlorhexidine hypersensitive patients by checking every product that the patient is exposed to on each occasion of care. This is a time consuming and laborious task but it is necessary to prevent inadvertent chlorhexidine exposure in the chlorhexidine hypersensitive patient.

4.3 Difficulty avoiding contact with chlorhexidine products once allergy has been identified

During a hospital stay, an individual patient may transition through many departments of a hospital, including the emergency department, operating theatres, intensive care units, general wards, and radiology.

A system for clear identification of the chlorhexidine hypersensitive patient is necessary to achieve continuity of the knowledge of their allergy status as they progress through the system.

It is often worthwhile to develop a plan, ideally in the pre-admission setting, for anticipated medical procedures that may occur during the patient's hospital stay. This plan can include alternative antiseptics and approaches to procedures.

It is essential that non-chlorhexidine alternatives are maintained as standard stock in all clinical environments within hospitals to ensure safe care for these patients.

The use of alcohol only containing swabs is recommended for the cleaning of intravenous bungs^[9] yet chlorhexidine containing products are often substituted for alcohol only swabs due to their lack of availability in a clinical environment. This leads to increased exposure and may lead to sensitisation to chlorhexidine.

Patients require education about their chlorhexidine hypersensitivity and advised to notify each new staff member involved in their care, wherever possible, of their chlorhexidine hypersensitivity.

Simple measures should be taken to isolate the patient from common forms of chlorhexidine exposure. For example, they should be housed in single rooms wherever possible, with all chlorhexidine products removed from the immediate environment and replaced with chlorhexidine-free alternatives.

5. Summary

Chlorhexidine is an excellent antimicrobial agent and a common cause of anaphylaxis in the perioperative environment.

Exposure to chlorhexidine in the clinical environment is routine. Avoidance of recurrent anaphylactic reactions should begin with the identification of the chlorhexidine hypersensitive patient and substitution of all chlorhexidine containing products that the patient is exposed to.

Careful planning and implementation is required to prevent inadvertent exposure to chlorhexidine in chlorhexidine hypersensitive patient as they move throughout the hospital system.

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Related ANZCA documents

PG28 Guideline on infection prevention and control in anaesthesia

Note: The content of ANZCA professional document **PG60(POM) Guideline on the perioperative management of patients with suspected or proven hypersensitivity to chlorhexidine 2016** has been incorporated into **PG69 Appendix 1 Chlorhexidine hypersensitivity 2025**.

Appendix 2 - A suggested management plan for urgent surgery after suspected perioperative anaphylaxis.

When time sensitive surgery is required for a patient who has had suspected perioperative anaphylaxis that has not been investigated the case should be discussed with an anaesthetic allergist or a clinical immunologist prior to surgery as it is generally possible to provide safe anaesthesia and avoid postponement of surgery.

1. Management Plan

All agents administered intravenously within 60 minutes of the onset of symptoms should be avoided.

All agents administered via mucosal, subcutaneous or oral route, including any hidden allergens, within 2 hours of the onset of symptoms should be avoided.

Inhalational agents may be used.

When proceeding with anaesthesia under these circumstances the team must be prepared to manage perioperative anaphylaxis. The ANZCA [Perioperative Anaphylaxis Management Guidelines](#) should be consulted, and the management cards should be at hand.

The use of regional or neuraxial anaesthesia may allow avoidance of some of the agents used during the previous general anaesthetic and vice versa.

2. Advice Regarding Specific Drug Classes

Neuromuscular blocking agents (NMBAs), antibiotics and blue dyes have the highest incidence of perioperative anaphylaxis with a rate of between 1:1500 and 1:100 000. Opioids, induction agents and local anaesthetic agents rarely cause anaphylaxis.

2.1 Neuromuscular Blocking Agents (NMBAs)

There is variable cross reactivity between NMBAs, therefore all NMBAs should be avoided, if possible, if a NMBA was used during the previous anaesthetic.

Various techniques can be used to avoid the use of NMBAs including:

- The use of a remifentanyl infusion, magnesium sulphate and topical anaesthesia as adjuncts to deep anaesthesia in facilitating laryngoscopy and intubation. If remifentanyl was used in the previous anaesthetic, consider the use of alfentanil.
- Awake intubation under topical anaesthesia.
- Sufficient surgical muscle relaxation can usually be provided with an adequate depth of anaesthesia and adjunct neuraxial or regional anaesthesia.

2.2 Antibiotics

An alternative antibiotic with a low risk of cross reactivity and appropriate antimicrobial spectrum should be used. Advice should be sought if there is uncertainty regarding the antibiotic to be administered.

2.3 Blue Dyes

Avoid both patent blue and methylene blue if either were used in the previous anaesthetic.

2.4 Chlorhexidine

Avoid the use of chlorhexidine as it is ubiquitous in the perioperative environment and it should be assumed that the patient was exposed to it unless its use can definitely be ruled out (see appendix 1).

2.5 Iodinated Contrast Media (ICM)

Avoid if possible if ICM was used during the previous anaesthetic. If this is not possible, discussion is required with an anaesthetic allergist, clinical immunologist or a radiologist to determine the lowest risk alternative.

2.6 Latex

Avoid its use.

2.7 Opioids

Use an opioid from an alternative class.

2.8 Induction Agents

Induction agents include propofol, thiopentone, and ketamine. Use an alternative agent.

2.9 Local Anaesthetic Agents

Use an agent from an alternative class if possible. There is little cross reactivity between amide local anaesthetic agents. The use of an alternative amide agent is likely to be low risk.

2.10 Blood Products

Blood products may have been the cause of the previous anaphylactic reaction.

2.11 Colloids

Avoid their use if they were used during the previous anaesthetic.

2.12 Hidden Allergens

Scrutinise the operative surgical and nursing notes for the presence of any agents not listed in the anaesthetic record.

Appendix 3 - Allergy Labels

Many patients attend hospital with an allergy label. If an allergy is documented, an accurate allergy history should be taken. Some allergy labels such as “family history of allergy” or of side effects such as nausea or headache with no other allergy features may, after discussion with the patient, be removed.

Unverified antibiotic allergy labels are a growing health burden which has a significant impact on clinical outcomes through the inappropriate avoidance of first line antibiotics. This leads to increased surgical site infections, antimicrobial resistance, mortality and drug reactions to second line agents.^[1] If, after an accurate history has been taken, there is uncertainty regarding an antibiotic allergy label the patient should be referred to an allergist.^[1,2, 3]

An antibiotic with a low risk of cross reactivity and appropriate antimicrobial spectrum should be used if there is known or uncertain hypersensitivity to the labelled antibiotic. Advice should be sought if there is uncertainty regarding the antibiotic to be administered.

Cross reactivity amongst beta lactam antibiotics is much less common than previously thought and is mainly the result of the similarity of side chains. As an example, ampicillin, amoxicillin, cefaclor and cefalexin share a similar R1 sidechain and demonstrate cross reactivity. Alternatively, cefazolin has a unique side chain amongst the beta lactam antibiotics and there is growing evidence that cefazolin is not cross reactive with other beta lactam antibiotics. The evidence suggests that it is safe to administer cefazolin when patients have had a previous immediate hypersensitivity reaction, including anaphylaxis, to other beta lactam antibiotics.^[4,5] If a previous severe cutaneous adverse reaction (SCAR), such as Steven Johnson’s Syndrome, has occurred as a result of exposure to a beta lactam antibiotic, all beta lactam antibiotics, including cefazolin, should be avoided until immunological advice has been obtained.

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