Special Article

Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists Perioperative Anaphylaxis Management Guidelines

H. Kolawole*, S. D. Marshall†, H. Crilly‡, R. Kerridge§, P. Roessler**

Summary
Anaphylaxis is an uncommon but important cause of serious morbidity and even mortality in the perioperative period. The Australian and New Zealand College of Anaesthetists (ANZCA) with the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) have developed clinical management guidelines that include six crisis management cards. The content of the guidelines and cards is based on published literature and other international guidelines for the management of anaesthesia-related and non-anaesthesia-related anaphylaxis. The evidence is summarised in the associated background paper (Perioperative Anaphylaxis Management Guidelines [2016] www.anzca.edu.au/resources/endorsed-guidelines and www.anzaag.com/Mgmt%20Resources.aspx). These guidelines are intended to apply to anaphylaxis occurring only during the perioperative period. They are not intended to apply to anaphylaxis outside the setting of dedicated monitoring and management by an anaesthetist. In this paper guidelines will be presented along with a brief background to their development.

Key Words: anaphylaxis, perioperative medicine, adrenaline, resuscitation

Introduction
Anaphylaxis is an uncommon but potentially life-threatening and occasionally lethal event in the perioperative environment. In the last two ‘Safety of Anaesthesia’ reports for Australia and New Zealand, anaphylaxis was the cause of about a third of deaths classified as Category One (where it is “reasonably certain” that the cause of death is directly related to the anaesthesia or other factors under the control of the anaesthetist). The recommendation from the 2014 report was that “anaphylaxis remains one of the less preventable causes of anaesthesia-related deaths, but early diagnosis and appropriate crisis management with escalating doses of adrenaline and aggressive fluid replacement are paramount”. The diagnosis and management of anaphylaxis in the perioperative setting can be confounded by altered conscious state, cardiovascular and respiratory function due to underlying patient pathology and the effects of anaesthesia.

Four key steps to effectively manage perioperative anaphylaxis are: 1) timely diagnosis, 2) early administration of recommended doses of adrenaline (epinephrine), 3) aggressive administration of intravenous fluids, and 4) escalation of therapy where the clinical response to initial therapy is inadequate. Unfortunately, some episodes of anaphylaxis are resistant to conventional treatment, due to the severity of the anaphylaxis and/or the underlying patient comorbidities. In these situations refractory management strategies will be required as well as a systematic approach to ensure alternative diagnoses have not been overlooked.

This paper presents the Australian and New Zealand College of Anaesthetists (ANZCA) with the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) co-badged Perioperative Anaphylaxis Management Guidelines, which were launched at the ANZCA Annual Scientific Meeting in May 2016.

Guideline Development
In 2013, ANZAAG developed and published management guidelines online that were also endorsed by ANZCA. The
The purpose was to facilitate the timely diagnosis and effective management of perioperative anaphylaxis.

Following the introduction of the guidelines, their utility was assessed by ANZAAG through observations made during simulation, feedback from anaesthetists after management of episodes of intraoperative anaphylaxis, and from the many anaphylaxis emergency response workshops conducted throughout Australasia. Research was also conducted on the guidelines in two separate simulation environments in Australia.

In 2015–16 the initial guidelines were revised and redesigned cognitive aids were developed in a further collaboration between ANZAAG and ANZCA.

There are no randomised controlled trials of sufficient quality on which to prepare evidence-based guidelines for the management of perioperative anaphylaxis. The content of the guidelines is consequently based upon a review of the literature focusing on management of anaesthesia-associated anaphylaxis as well as non–anaesthesia-related anaphylaxis (see Tables 1 and 2).

A noteworthy difference between these Perioperative Anaphylaxis Management Guidelines and others is their presentation as six management cards serving as cognitive aids for crisis management. These include a suggested team structure as summarised below.

Scope

These guidelines are intended to apply to anaphylaxis occurring during the perioperative period. They are not intended to apply to anaphylaxis outside the setting of dedicated monitoring and management by an anaesthetist. Alternative guidelines should be utilised outside this setting.

Use of the ANZAAG–ANZCA anaphylaxis management cards

The cards have been designed for use during an anaphylaxis event with one team member assigned to read the cards and ensure all the items have been checked off. The team for anaphylaxis management should have at least three members with specific roles: Team Leader, Card Reader and Adrenaline (epinephrine) Preparation. It may be necessary to enlist the assistance of other trained staff members.

It is recommended that all members of the anaesthesia team are familiar with the cards and their likely roles during an emergency.

For the immediate and refractory management phases, separate adult and paediatric cards are provided. The differential diagnosis card and post crisis cards can be used for either adult or paediatric patients.

Anaphylaxis Box

It is recommended that an Anaphylaxis Box is prepared and available to complement the introduction of the anaphylaxis management guidelines.

The box should include laminated anaphylaxis management cards, local infusion protocols for adrenaline (epinephrine), noradrenaline (norepinephrine), vasopressin and salbutamol, as well as collection tubes for measuring serum tryptase. The box may also contain patient form letters, patient information brochures and ANZAAG referral forms, which can be found on the ANZAAG website at www.anzaag.com. There are six cards for the diagnosis and treatment of anaphylaxis, including two for paediatric use.

Diagnosis of anaphylaxis

1. Early recognition and prompt management of anaphylaxis is essential.
2. Anaphylaxis should be considered if skin signs co-exist with bronchospasm or hypotension.
3. Hypotension or tachycardia alone, especially where this is unresponsive to vasopressors or is unanticipated should

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<tr>
<th>Level of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>Systematic reviews, meta-analyses, randomised controlled trials.</td>
</tr>
<tr>
<td>Level II</td>
<td>A randomised controlled trial.</td>
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<tr>
<td>Level III-1</td>
<td>A pseudorandomised controlled trial.</td>
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<tr>
<td>Level III-2</td>
<td>A comparative study with concurrent controls (case-control study).</td>
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<tr>
<td>Level III-3</td>
<td>A comparative study without concurrent controls.</td>
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<tr>
<td>Level IV</td>
<td>Descriptive studies that include analysis of outcomes (single subject design, case series).</td>
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<tr>
<td>Level V</td>
<td>Case reports and expert opinion that include narrative literature, review, and consensus statements.</td>
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<th>Grade of recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice.</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations.</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation(s) but care should be taken in its application.</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution.</td>
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NHMRC, National Health and Medical Research Council.
raise suspicion. Bradycardia may also be a presenting sign of anaphylaxis.21,22

4. Bronchospasm or difficulty with ventilation may be a feature of anaphylaxis or the sole presenting feature in some cases.23

5. The absence of skin signs does not rule out the diagnosis, as skin signs may not appear until the circulation is restored.23

6. Mild reactions, Grade 1, which include mucocutaneous signs only, such as erythema, urticaria, and peripheral angioedema do not warrant immediate treatment with adrenaline (epinephrine)24, but rather close observation and escalation of therapy if severity worsens (Grade D recommendation).

Severity of anaphylaxis

1. A critical step once the provisional diagnosis of anaphylaxis has been made is the grading of the severity of anaphylaxis in order to administer the recommended initial dose of adrenaline (epinephrine).

2. The Perioperative Anaphylaxis Management Guidelines use a four level anaphylaxis grading scale outlined on card 5, Differential Diagnosis Card.25 (see Figure 5).

3. The Immediate Management Card also has the words ‘Moderate’ and ‘Life Threatening’ as descriptors of ‘Grade 2 and 3’ respectively in the ‘Initial IV Adrenaline Bolus’ section.

4. Since clinically grading anaphylaxis in the perioperative environment is complex, four members of ANZAAG published a new grading scale, the Perioperative Anaphylaxis Grading System (PAGS) with the aim of guiding initial anaphylaxis management and facilitating research.26

This system defines three grades of anaphylaxis: A. Moderate, B. Life Threatening, and C. Cardiac Arrest.

5. The descriptor words on the Immediate Management Card enable PAGS to be applied to the Perioperative Anaphylaxis Management Guidelines. With PAGS ‘Life Threatening Anaphylaxis’ can be distinguished from ‘Moderate Anaphylaxis’ in an adult by the presence of any one of these signs:

- systolic blood pressure of <60 mmHg
- life-threatening tachy- or bradyarrhythmia
- oxygen saturation <90%
- inspiratory pressures of >40 cmH2O
• severe difficulty inflating the lungs
• airway angioedema

As a result, the recommended initial intravenous (IV) adrenaline (epinephrine) bolus dose is readily selected from the Immediate Management Card (Grade D recommendation).

Immediate management

Card 1 adult (see Figure 1) and card 2 paediatric, defined as a patient less than 12 years of age (see Figure 2).

1. Adrenaline (epinephrine) is pivotal in management and, in the recommended doses, causes vasoconstriction, bronchodilation, increased cardiac output, reduced mucosal oedema, and reduced mediator release (Level IV evidence, Grade C recommendation).\(^\text{17,19}\)

2. The mainstay of the management of moderate to life-threatening anaphylaxis during anaesthesia is carefully titrated IV adrenaline with close monitoring of cardiovascular responses (Level IV evidence, Grade D recommendation).\(^\text{11-14}\)

3. As adrenaline has a narrow therapeutic window clinicians need to be aware of the potential for toxicity including accidental overdose, particularly during crisis management.\(^\text{24,27-29}\)

4. Intramuscular (IM) adrenaline into the lateral thigh should be considered in the initial management of perioperative anaphylaxis where IV access is not yet established or is lost, where haemodynamic monitoring is not in situ at the start of the reaction, or while awaiting preparation of an adrenaline infusion (Level I evidence, Grade B recommendation).\(^\text{6,7,19,30-33}\)

5. After three boluses of adrenaline via either the IV or IM route an adrenaline infusion should be prepared and commenced as early as possible in the clinically appropriate dosage (Level III-3 evidence, Grade D recommendation).\(^\text{11,34-36}\)

6. Aggressive management of fluid resuscitation is a critical step in ensuring blood flow to vital organs. Repeated boluses of 20 ml/kg may be required (Level IV evidence, Grade D recommendation).\(^\text{34,37-39}\)

7. Large bore IV access should be secured as soon as possible.

8. Patients should be returned to the supine position as soon as possible where continued resuscitative efforts are required (Level IV evidence, Grade D recommendation).\(^\text{10,11,15,30,40}\)

9. Cessation of the administration of potential triggers should be briefly reviewed at the time of diagnosis to ensure possible allergens such as colloid infusion are discontinued (Level V evidence, Grade D recommendation).\(^\text{6}\). Muscle relaxants are the most common cause of anaphylaxis during anaesthesia in Australia and New Zealand.\(^\text{11-41}\)

Antibiotics are also common triggers. Anaphylaxis to chlorhexidine is an emerging concern and further use of this agent should be avoided if it was administered prior to the development of symptoms (Grade D recommendation).\(^\text{46-48}\).

10. If airway oedema is suspected then early endotracheal intubation should be considered.

11. Anaphylaxis in the setting of anaesthesia may present as cardiac arrest, most commonly pulseless electrical activity (PEA). In this circumstance immediate good quality cardiopulmonary resuscitation should commence. At this time the Australian Resuscitation Council (ARC) and New Zealand Resuscitation Council (NZRC) recommendations\(^\text{49}\) for non-shockable rhythms are 1 mg of adrenaline immediately then repeated every four minutes. Cases of recovery from anaesthesia-related anaphylaxis suggest that higher doses of adrenaline and additional vasopressors may be required before return of adequate cardiac output and blood pressure. As a result, these guidelines recommend administering adrenaline every one to two minutes if required initially with rapid administration of adequate volume resuscitation and the early addition of alternative vasopressors when initial therapy is inadequate (Level IV evidence, Grade D recommendation).\(^\text{35}\).

Figure 3. Adult Refractory Management Card. Reproduced with permission.
Refractory management

Card 3 adult (see Figure 3) and card 4 paediatric (see Figure 4).

1. If physiological variables do not stabilise following immediate management then further treatment options should be added.

2. The diagnosis of anaphylaxis should be reviewed to ensure alternative diagnoses with different treatment paths are considered and the most appropriate therapy is administered. Card 5 (see Figure 5) is the Differential Diagnosis Card that lists alternative diagnoses, and relevant therapy.

3. Standard monitoring as recommended by ANZCA PS18 Guidelines on Monitoring during Anaesthesia should be utilised throughout resuscitative efforts.

4. An arterial line is highly recommended where possible to aid cardiovascular monitoring, blood sampling and continuous monitoring of adrenaline effects (Grade D recommendation).

5. Transthoracic echo (TTE) or transoesophageal echo (TOE), where available, may allow better targeting of therapy by assessing ventricular function, filling and vasodilation (Grade D recommendation).

6. In the setting of resistant hypotension alternative vaspressors have been used. They should be used only after recommended doses of adrenaline and IV fluid volumes have been administered. The adrenaline should be continued even when these agents are added (Level V evidence, Grade D recommendation).

7. Where it is available cardiac bypass/extracorporeal membrane oxygenation (ECMO) may be considered to re-establish adequate perfusion (Grade D recommendation).

8. High airway pressure is less likely to be the predominant feature of anaphylaxis. Alternative treatments for resistant bronchospasm may be used when clinically indicated. Alternative causes of high airway pressure such as airway device or circuit malfunction and tension pneumothorax should be sought and eliminated as the cause (Level V evidence, Grade D recommendation).

to minimise aortocaval compression. Peri-mortem caesarean delivery may be required in order to facilitate resuscitation of the mother (Level V evidence, Grade D recommendation)⁵,⁶,³⁻⁶,⁴.

Post crisis management
Card 6 (see Figure 6):

1. Steroids have been of benefit in the management of other allergic diseases and they are recommended as part of secondary management. They may be useful in cases where there is a protracted reaction (Level V evidence, Grade D recommendation)⁶,¹¹,⁶⁵,⁶⁶.

2. Oral antihistamines are useful for the symptomatic treatment of urticaria, angioedema and pruritus (Level 1 evidence, Grade B recommendation)⁵,¹³,⁶⁷,⁶⁸.

3. The decision to proceed with or abandon surgery will be determined by the urgency of the surgery, the grade of anaphylaxis, the response to treatment and the patient’s underlying comorbidities.

4. An acute elevation of serum tryptase level is supportive of the diagnosis of perioperative anaphylaxis.

5. Serum tryptase levels are recommended to be collected at 1, 4 and 24 hours⁶⁹,⁷⁰.

6. Most patients who have had a moderate to life-threatening reaction will require admission to an intensive care unit/high dependency unit for around 24 hours. Where the reaction has been either minor or moderate and settled quickly with treatment, a minimum of six hours close monitoring is recommended (Level V evidence, Grade D recommendation)⁶.

7. Prior to discharge from hospital, patients who have had a suspected anaphylaxis require a letter that contains a description of the reaction and the agents administered prior to the reaction.

8. Referral to an anaesthetic allergy testing centre is required to investigate the reaction. The anaesthetic allergy testing centres in Australia, New Zealand, Hong Kong and Malaysia are listed on the ANZAAG website—www.anzaag.com.

Conclusion
Anaphylaxis is a life-threatening emergency that requires prompt recognition and institution of life-saving therapy. The Perioperative Anaphylaxis Management Guidelines (including cards) have been developed to assist anaesthetists in managing this potentially life-threatening situation. In view of the difficulty in conducting research into anaphylaxis management the evidence base for all recommendations is weak, but is based on consensus expert opinion from multiple bodies internationally. ANZCA and ANZAAG will continue to update this resource in line with best international practice.

Conflict of interest
No conflict of interest with any of the authors.

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References


