Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists perioperative anaphylaxis management guideline 2022

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Abstract

Perioperative anaphylaxis is a potentially life-threatening emergency that requires prompt recognition and institution of life-saving therapy. The Australian and New Zealand College of Anaesthetists and Australian and New Zealand Anaesthetic Allergy Group have partnered to develop the anaphylaxis management guideline along with crisis management cards that are recommended for use in suspected anaphylaxis in the perioperative setting. This is the third version of these guidelines with the second version having been published in 2016. This article contains the revised Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists perioperative anaphylaxis management guideline, with a brief review of the current evidence for the management of anaphylaxis in the perioperative environment.

Keywords

Anaphylaxis, perioperative anaphylaxis, perioperative medicine, adrenaline, epinephrine, resuscitation

Introduction

Perioperative anaphylaxis remains the most common cause of death directly attributable to anaesthesia in Australia and New Zealand. The Australian and New Zealand College of Anaesthetists (ANZCA) safety of anaesthesia report for the 2015–2017 triennium¹ identified eight deaths in which anaphylaxis directly related to anaesthesia or other factors under the control of the anaesthetist could with reasonable certainty be established as the cause. The report also highlighted the need for training in crisis management to maximise the benefit of resuscitation when anaphylaxis is suspected and that simulation-based training is recommended for such very low frequency events. Anaphylaxis is one of the options included in ANZCA's continuing professional development mandatory emergency response activities.² The pathophysiology of anaphylaxis can escalate quickly, and therefore the management of anaphylaxis should place emphasis on early recognition and treatment in order to avoid serious morbidity and mortality.

Scope

These recommendations are intended for use only in the perioperative setting. They reflect the special circumstances of perioperative anaphylaxis in which

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there is continuous dedicated monitoring by an anaesthetist and a higher frequency of sudden onset severe symptoms compared with non-perioperative anaphylaxis. For anaphylaxis in the non-anaesthesia setting the Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines³ apply.

One of the features of the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) and ANZCA perioperative anaphylaxis management guideline is in its presentation rendering it applicable to crisis management in the perioperative setting. This paper presents the updated ANZCA and ANZAAG cobadged perioperative anaphylaxis management guideline,⁴ which was released in May 2022. It provides the rationale for the update, outlines guideline development, and highlights key changes.

Guideline development

The second version of the ANZCA/ANZAAG perioperative anaphylaxis management guideline⁵ was released in 2016. The most recent 2022 review was performed as part of a routine 5 yearly review of the ANZCA guideline. It is timely as there have been a number of significant publications in the years since the 2016 guideline was published, including:

- NAP6 (6th National Audit Project: Perioperative Anaphylaxis) reported the findings of a year-long UK-wide audit of perioperative anaphylaxis focusing on grade 3, 4 and 5 reactions, published in May 2018.⁶
- *British Journal of Anaesthesia* special perioperative anaphylaxis issue, 2019, included international consensus guidelines and reviews.⁷
- Updated resuscitation guidelines: Resuscitation Council of the UK,⁸ European Resuscitation Council,⁹ American Heart Association,¹⁰ Association of Anaesthetists of Great Britain and Ireland (AAGBI),¹¹ Brazilian Society of Anaesthesiology and Brazilian Association of Allergy and Immunology,^{12,13} Japanese Society of Anesthesiologists,¹⁴ Australian and New Zealand Committee on Resuscitation (ANZCOR)¹⁵ and ASCIA.³

The key changes to the revised guideline are:

- Cardiac compressions should be initiated at a systolic blood pressure of less than 50 mmHg in the anaesthetised patient.
- A graded approach to volume replacement:
 - An initial crystalloid fluid bolus of 500 mL in a moderate (grade 2), and 1000 mL in a life

threatening (grade 3) reaction, repeated as required and titrated to clinical response.

- In a cardiac arrest (grade 4) reaction the recommendation remains for an initial bolus of 2000 mL.
- Graded intravenous (IV) adrenaline (epinephrine) bolus doses, with lower starting doses for each grade of reaction and suggested dose escalation depending on response.
- Pregnancy: Manual left uterine displacement, rather than left lateral tilt, should be applied during the management of hypotension or cardiac arrest due to anaphylaxis in the pregnant patient to minimise aortocaval compression.
- Oesophageal intubation has been added to the differential diagnosis list for refractory bronchospasm and has been included on the immediate management cards for adults and paediatrics.¹⁶

Due to the paucity of randomised controlled trials of sufficient quality on the management of anaphylaxis the recommendations in this guideline are consensus statements developed by ANZAAG and ANZCA after an extensive literature review. In common with other guidelines, most of the recommendations are grade D and are based on level IV or level V evidence. When stronger evidence is available it has been noted alongside the recommendation (Tables 1 and 2).

Use of the ANZAAG/ANZCA anaphylaxis management cards

The cards have been designed for use in real time during a perioperative anaphylaxis event, with one team member assigned to read the cards and ensuring all items have been checked off.

Table I. Levels of evidence (based on National Health and Medical Research Council (NHMRC)).¹⁷

Level of evidence	Description
Level I	Systematic reviews, met-analysis, randomised controlled trials
Level II	A randomised controlled trial.
Level III-I	A pseudorandomised controlled trial.
Level III-2	A comparative study with concurrent controls (Case-control study)
Level III-3	A comparative study without concur- rent controls
Level IV	Descriptive studies that include analysis of outcomes (single subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, review, and consensus statements

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
В	Body of evidence can be trusted to guide practice in most situations
С	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommen- dation must be applied with caution

Table 2. NHMRC grades of recommendation.¹⁷

NHMRC: National Health and Medical Research Council.

As with any clinical emergency it is recommended that all members of the anaesthesia team are familiar with the cards and their likely roles.

Team structure

It is important to send for help early during a suspected perioperative anaphylaxis, due to the potential for multiple simultaneous tasks. A consultant anaesthetist should be present or notified.

The anaesthesia team for anaphylaxis management has at least three team members with specific roles:

- 1. Team leader;
- Card reader—this role requires no specific anaesthesia expertise and requires the cards to be read out verbatim to ensure no omissions;
- 3. Adrenaline preparation and administration.

Additional roles if resources allow:

Fluid management and preparation; cannulation—IV and intra-arterial access; scribe; cardiopulmonary resuscitation (CPR) rotators (in the case of cardiac arrest).

Diagnosis of anaphylaxis

- As anaphylaxis is a clinical diagnosis and symptoms mimic other perioperative events, diagnosis can be challenging. A high index of suspicion by anaesthetists is therefore essential for early diagnosis and treatment.
- 2. In conscious or minimally sedated patients, anaphylaxis may also have additional respiratory, gastrointestinal, or central nervous system symptoms and signs in addition to itching or flushing. These include rhinorrhoea, cough, dyspnoea, circumoral tingling, difficulty swallowing, nausea, abdominal pain, irritability, confusion, or a sense of impending doom.¹⁸
- 3. The diagnosis of anaphylaxis should be considered when hypotension is unexplained and out of

proportion to that which could be expected on the basis of patient factors (age, co-morbidities) and the stage of the operation and/or when there has been a lack of sustained response to usual restorative measures.

- While tachycardia is common it can be masked by concomitant β-blocker use, and bradycardia may be observed in some patients.¹⁹
- 5. The diagnosis of anaphylaxis should be suspected when bronchospasm and difficulty with ventilation are resistant to commonly employed treatment manoeuvres.
- 6. The differential diagnosis card aids the consideration of alternative causes of clinical signs by classifying the common ones with a view to expedite management (e.g. needle decompression to treat tension pneumothorax).
- Oesophageal intubation has been added as a differential diagnosis for refractory bronchospasm. During cardiac arrest and CPR, the end-tidal carbon dioxide (CO₂) trace is attenuated but present. In oesophageal intubation the end-tidal CO₂ trace is a flat line.¹⁶

Severity of anaphylaxis

- 1. The severity of anaphylaxis will guide the recommended doses of IV fluid and adrenaline, therefore it is suggested that the anaesthetist characterises the grade of reaction.
- 2. The four severity classes are described in detail on the differential diagnosis card (Figure 1) and can be referred to during an anaphylaxis event.
- 3. The immediate management card outlines treatment options based on the grade of anaphylaxis, when these grading descriptors are utilised: mild (grade 1); moderate (grade 2); life-threatening (grade 3); and cardiac arrest (grade 4).

Immediate management

The immediate management of anaphylaxis cards include adult (Figure 2) and for children under 12 years old, paediatric (Figure 3) cards.

- 1. The card for immediate management has been designed as a cognitive aid for use during a crisis.
- 2. The main points of managing the crisis are listed on the left-hand side of the card, whereas the right-hand side gives more detailed instructions. Actions are listed in order of priority, with the most important at the top.
- 3. Adrenaline (epinephrine) is the first line treatment for anaphylaxis,^{10,20–23} and is pivotal in the management of anaphylaxis. Adrenaline not only treats the clinical manifestations but also reduces response

Anaphylaxis during Anaesthesia Differential Diagnosis Card					
	Possible Causes & Actions				
Cardiac Arrest	 Hypoxia Hypovolaemia Hypo/hyperkalaemia/metabolic disorders Hypo/hyperthermia Toxins Toxins 				
High Airway Pressure/ Airway Compromise	Dyspnoea, wheeze, stridor, difficulty inflating lungs • Oesophageal intubation -> "No Trace = Wrong Place" • Circuit malfunction -> Check using Self inflating Bag • Misplaced/kinked Airway device -> Check using Self inflating Bag • Tension pneumothorax -> Decompress • Exacerbation of Asthma -> Treat as per Refractory Management • Foreign Body -> Consider bronchoscopy • Acid aspiration -> Consider bronchoscopy				
Hypotension	Hypovolaemia Sepsis Drug overdose Vasodilation by drugs Neuraxial blockade Embolism: Thrombotic, Air or Amniotic Vasovagal				
Skin and Mucosa Hives, flushing, erythema, urticaria, sweiling head and neck or peripheries	Direct Histamine Release C1-esterase deficiency Venous obstruction Head down position Cold induced anaphylaxis				
Absence of tachycardia or cutaneous signs does not exclude anaphylaxis Anaphylaxis is usually rapid in onset but is occasionally delayed					
Mild (Grade 1)	Generalised mucocutaneous signs: Erythema, Urticarla+/- Angloedema				
Moderate (Grade 2)	Moderate – Multi-organ manifestation may include: • Hypotension, tachycardia • Evidence of bronchospasm, cough, difficult ventilation • Mucocutaneous signs				
Life Threatening (Grade 3)	Life Threatening and requiring immediate and specific treatment: Severe hypotension Bradycardia or tachycardia, arrhythmias Severe bronchospasm, and/or airway oedema Cutaneous signs may be absent, or present only after correction of hypotension 				
Arrest (Grade 4)	Cardiopulmonary Arrest				
Appendix 1 ANZAG-ANZCA Percoperative Anaphylixis Management Gudelines version 3 January 2022. The scientific rationale and endence base for the recommendations on this card is explained in more detail at www.arzca.edu.au and www.anzer.com @ Copyright 2022 – Australian and New Zealand College of Anaesthetists, Australian and New Zealand Anaesthetic Alergy Group. All rights reserved.					

Figure 1. Differential diagnosis card and grading of anaphylaxis.

amplification, 20,21 and cannot be substituted by any other medication. 24

- 4. Judicious use is advised in patients with higher risks of overdose: including extremes of age, patients with hypertension, ischaemic heart disease, hypertrophic cardiomyopathy (HOCM) or hyperthyroidism.
- 5. The benefits of intramuscular (IM) adrenaline^{20,21,24,25} for the management of anaphylaxis far exceed the risks (level 1 evidence).
- 6. Due to ease of preparation and administration of IM adrenaline into the lateral thigh, it should be considered in the initial management of many circumstances of perioperative anaphylaxis (grade B

Anaphylaxis during Anaesthesia Immediate Management



			Adults 12+
CARDIAC ARREST Pulseless Electrical Activity (PEA) Or SBP < 50mmHg		 Immediately start CPR 1 mg IV Adrenaline, Repeat 1-2 minutely pm Elevate legs. 2 L Crystalloid ALS GUIDELINES for non-shockable rhythms 	
DR	Danger and Diagnosis Response to stimulus	Unresponsive hypotens Remove triggers e.g. chi Stop procedure. Use mi	orhexidine, synthetic colloid
S	Send for help and organise team	 Call for Help and Anaph Assign a designated Lee Assign a Reader of the or 	ader and Scribe
AB	Check/Secure Airway Breathing - 100% oxygen	 Check capnography – Confirm FiO₂ 100% Consider early intubation 	"No Trace = Wrong Place" n: airway oedema
С	Rapid fluid bolus Plan for large volume resuscitation	 If hypotensive: Elevate legs Moderate - 500mL Crystalloid Life threatening - 1000mL Crystalloid heeded Large bore IV access. Warm IV fluids if possible 	
	Adrenaline Bolus Repeat as needed	Initial IV Adrenaline Bolus (Adult) Dilution 1 mg in 10 mL = 100 microg/mL • Give dose below every 1-2 minutes prn	
	Prepare Infusion		
No IV access OR awaiting 1:1000 = 500 micro	aline (Adult) s or haemodynamic monitoring Adrenaline Infusion		
No IV access OR awaiting 1:1000 = 500 micro Every 5 m Adrenaline >3 boluses	aline (Adult) s or haemodynamic monitoring Adrenaline Infusion 1mg/mL og (0.5mL)	Give dose below every Moderate 10-20 microg (0.1-0.2mL) If no response	1-2 minutes prn Life Threatening 50-100 microg (0.5-1mL) If no response 200 microg (2mL) 50 mL saline 3 microg/min 40 microg/min
No IV access OR awaiting 1:1000 = 500 micro Every 5 m Adrenaline >3 boluses	aline (Adult) s or haemodynamic monitoring Adrenaline Infusion 1mg/mL og (0.5mL) inutes prn lateral thigh e INFUSION (Adult) s of Adrenaline start infusion	Give dose below every Moderate 10-20 microg (0.1-0.2mL) If no response 50 microg (0.5mL) 3 mg Adrenaline in 5 Commence at 3 mL/hr = Titrate to max. 40 mL/hr = (infusion rate 0.05 - 0.5 microg)	1-2 minutes prn Life Threatening 50-100 microg (0.5-1mL) If no response 200 microg (2mL) 50 mL saline 3 microg/min 40 microg/min rog/kg/min)

Figure 2. Immediate management adult card.

recommendation), including when there is a suspicion of evolving moderate (grade 2) anaphylaxis, or in an awake patient.

- 7. The mainstay of the management of moderate to severe perioperative anaphylaxis is carefully titrated IV adrenaline with close monitoring of cardiovascular responses.⁷
- 8. The dose of IV adrenaline should be based on the severity of clinical presentation.⁷
- a. Grade 1 (mild): no adrenaline required.
- b. Grade 2 (moderate): $10-20 \ \mu g$ IV adrenaline. Escalate to $50 \ \mu g$ if insufficient response to initial dose. Consider initial IM adrenaline as a safe and effective alternative.

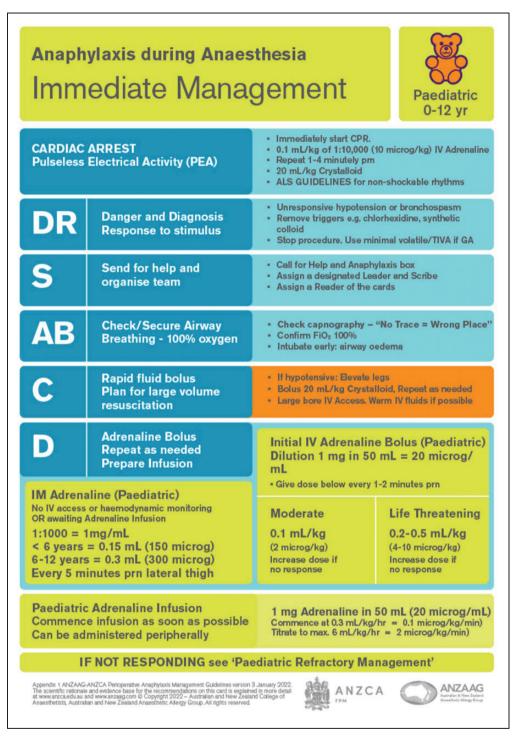


Figure 3. Immediate management paediatric card.

- c. Grade 3 (life threatening): $50-100 \,\mu\text{g}$ IV adrenaline. Escalate to $200 \,\mu\text{g}$ if insufficient response to initial dose.
- d. Grade 4 (cardiorespiratory arrest) 1000 μg IV adrenaline immediately, repeated every 1–2 min.
- Adrenaline infusions without bolus administration²⁶ (level III evidence) can be effective in the management of severe refractory anaphylaxis.
- 10. In a profoundly hypotensive patient, cardiac compressions should be initiated at a systolic blood pressure of less than 50 mmHg in the anaesthetised patient.⁶
- 11. The excessive use of adrenaline in association with inadequate volume replacement can result in a hyperdynamic underfilled heart and dynamic left

Anaphylaxis during Anaesthesia Refractory Management



	Adults 12+	
Request more help	 Consider calling arrest code May require assistance with fluid resuscitation 	
Triggers removed?	 Chlorhexidine including impregnated CVCs Synthetic Colloid disconnect and remove Latex remove from OR 	
Monitoring	Consider Arterial line Consider TOE/TTE	
Resistant Hypotension - Additional IV fluid bolus 50 mL/kg - Continue Adrenaline Infusion - Add second vasopressor - Consider CVC - TOE/TTE - Cardiac bypass/ECMO if available	Adult Recommendations Additional IV fluid bolus 50 mL/kg Noradrenaline Infusion 3 – 40 microg/min (0.05 - 0.5 microg/kg/min) and/or Vasopressin bolus 1– 2 units then 2 units per hour If neither available use either Metaraminol or Phenylephrine Infusion Glucagon 1– 2 mg IV every 5 min until response Draw up and administer IV (Counteract β blockers)	
Resistant Bronchospasm • Consider: • Oesophageal intubation • Circuit malfunction • Airway device malfunction • Tension pneumothorax • Continue Adrenaline Infusion • Add alternative bronchodilators	Adult Recommendations Salbutamol • Metered Dose Inhaler 12 puffs (1200 microg) • IV bolus 100-200microg +/- infusion 5-25microg/min Magnesium 2 g (8 mmol) over 20 minutes Consider Inhalational Anaesthetics and Ketamine	
Pregnancy	 Manual Left Uterine Displacement Caesarean within 5 minutes if arrest or peri-arrest 	
Consider other diagnoses	See 'Differential Diagnosis Card'	
Once stable refer to 'P	ost Crisis Management'	
Appendix 1 ANZAAG-ANZCA Perceptrative Anaphyliatis Management Guidelines version 3 January 2022. The scientific relionale and evidence base for the recommendations on this card is explained in more detail at www.anccencedua.au and www.anzaa.com © Copyright 2022 – Australian and New Zealand College of Anaesthetistis, Australian and New Zealand Anaesthetic Allergy Group. All rights reserved		

Figure 4. Adult refractory management card.

ventricular outflow obstruction even in an anatomically normal heart.²⁷

The new recommendation is for an initial fluid bolus of:

- a) 500 mL in grade 2 (moderate) and 1000 mL in grade 3 (life-threatening) reactions, to be repeated as required, and titrated to clinical response;
- b) grade 4 reactions (cardiac arrest) initial bolus of 2000 mL.
- 13. Crystalloids are recommended for fluid resuscitation in anaphylaxis.^{3,9,11,15}
- Cease administration of potential triggers such as colloids and medications (chlorhexidine, dyes) particularly in cases of refractory anaphylaxis.²⁴

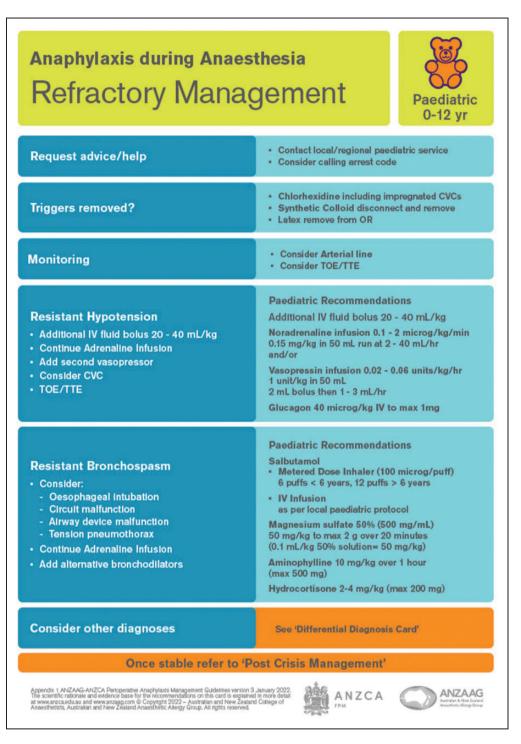


Figure 5. Paediatric refractory management card.

15. In the pregnant patient, manual left uterine displacement should be performed as part of the management of anaphylaxis, in the presence of hypotension or cardiac arrest.²⁸

Refractory management

Adult (Figure 4) and paediatric (Figure 5) cards:

1. For a patient who fails to respond to appropriate therapy for presumed anaphylaxis, echocardiography may

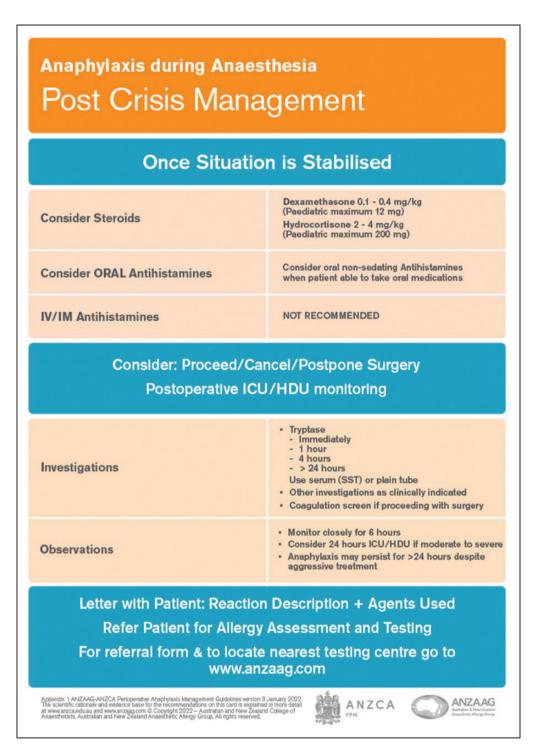


Figure 6. Post crisis management card.

be helpful in confirming the diagnosis of anaphylaxis or suggesting another diagnosis, such as decompensated HOCM or Takotsubo cardiomyopathy.

2. When extracorporeal membrane oxygenation is available, it should be considered in the management of perioperative anaphylaxis refractory to maximal standard treatment.

3. In the presence of adequate cardiac contractility as shown on echocardiography, vasopressors may be added, when adrenaline infusions and fluid boluses have been inadequate in achieving targeted blood pressure.

- 4. Noradrenaline, vasopressin and metaraminol are included for the management of refractory anaphylaxis. Metaraminol and phenylephrine are included to accommodate those environments where alternatives to adrenaline are limited.²⁹
- 5. Adrenaline remains the first line treatment of bronchospasm in cases of anaphylaxis. Bronchodilators are not first line in suspected anaphylaxis, as they do not prevent or relieve other manifestations of anaphylaxis such as hypotension.^{3,8}
- 6. Additional treatments for resistant bronchospasm include inhaled or IV bronchodilator,^{7,8,30} IV magnesium,³¹ which needs to be infused slowly due to its potential to cause hypotension, inhalational anaesthetics, and ketamine.⁷

Post-crisis management

(Figure 6)

- Steroids are recommended to be administered after all acute management has been completed and patients are stable, and may be useful in cases of protracted reactions or biphasic response.^{25,32}
- Oral antihistamines, particularly non-sedating antihistamines, are suitable in the post-acute period.
- Tryptase levels are important in differentiating anaphylaxis from other causes, and should be collected when any suggestion of perioperative anaphylaxis is raised.
- A serum tryptase sample should be taken as soon as possible after the onset of symptoms and then repeated at 1 h, 4 h and after 24 h.

Conclusion

Perioperative anaphylaxis is an uncommon challenging and potentially life-threatening event. The updated perioperative anaphylaxis management guideline and the anaphylaxis cards replace the previous 2016 guideline, and can guide a perioperative team to achieve crucial time-critical management steps. It is recommended that the guideline be widely promoted, be made available in all anaesthetising locations, and used in current anaphylaxis management continuing professional development teaching.

Author Contribution(s)

Robyn Tran: Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing. **Karen Pedersen:** Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Helen Kolawole: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Validation; Writing – original draft; Writing – review & editing.

Peter Roessler: Formal analysis; Project administration; Writing – original draft; Writing – review & editing.

Richard Scolaro: Formal analysis; Project administration; Writing – review & editing.

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