

SPECIAL ARTICLE

Management of suspected immediate perioperative allergic reactions: an international overview and consensus recommendations

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Summary

Suspected perioperative allergic reactions are rare but can be life-threatening. The diagnosis is difficult to make in the perioperative setting, but prompt recognition and correct treatment is necessary to ensure a good outcome. A group of 26 international experts in perioperative allergy (anaesthesiologists, allergists, and immunologists) contributed to a modified Delphi consensus process, which covered areas such as differential diagnosis, management during and after anaphylaxis, allergy investigations, and plans for a subsequent anaesthetic. They were asked to rank the appropriateness of statements related to the immediate management of suspected perioperative allergic reactions. Statements were selected to represent areas where there is a lack of consensus in existing guidelines, such as dosing of epinephrine and fluids, the management of impending cardiac arrest, and reactions refractory to standard treatment. The results of the modified Delphi consensus process have been included in the recommendations on the management of suspected perioperative allergic reactions. This paper provides anaesthetists with an overview of relevant knowledge on the immediate and postoperative management of suspected perioperative allergic reactions based on current literature and expert opinion. In addition, it provides practical advice and recommendations in areas where consensus has been lacking in existing guidelines.

Keywords: allergy; anaesthesia; Delphi process; epinephrine; guideline; hypersensitivity reaction; perioperative anaphylaxis; testing

Background and definitions

Few countries have an organised approach to the diagnosis, treatment, and investigation of suspected perioperative allergic reactions and have published guidelines on this subject. In France, patients are referred to many centres with central reporting, and collaboration between anaesthesiologists and allergists exists in most centres. French guidelines have been published and updated.¹ Guidelines have been published in Scandinavia,² a Norwegian network has been formed,³ and a single national reference centre exists in Denmark.⁴ In the UK, an informal network was formed providing guidelines,⁵ and the recent 6th National Audit Project (NAP6)⁶ has increased the focus on perioperative allergy among anaesthesiologists and allergists/immunologists. Spanish practical guidelines for perioperative hypersensitivity reactions have been published in collaboration with the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology and the Spanish Anaesthesia Society.⁷ In the rest of Europe and the USA, investigations are mainly carried out by allergists, not always with regular involvement of anaesthesiologists. A task force of the drug allergy interest group of the European Academy of Allergy and Clinical Immunology has published a position paper with recommendations for investigation of perioperative allergic reactions.⁸ Lastly, the Australian and New Zealand Anaesthetic Allergy Group has published testing and management guidelines.^{9,10} In both countries, investigation is primarily undertaken by anaesthesiologists with varying degrees of allergist involvement.

Ideally, the approach to the immediate and post-event management of this very complex patient group should be harmonised and based on collaboration between anaesthesiologists and allergists/immunologists/dermatologists. The International Suspected Perioperative Allergic Reaction (ISPAR) working group was formed in spring 2018 and consists of 26 experts from these specialties from across the world. The group was convened at the initiative of the *British Journal of Anaesthesia* with the goal to provide an international perspective on current research and opinion in perioperative anaphylaxis. More details on the formation of the group is provided in [Appendix 1](#) and in an editorial in this issue of the *British Journal of Anaesthesia*.¹¹

This paper provides theoretical and practical background knowledge about perioperative allergic reactions relevant to anaesthesiologists based on current literature, and when this is lacking by recommendations based on expert opinion and combined experiences from the ISPAR working group. In addition, a modified Delphi consensus process was performed to develop consensus on recommendations in selected areas in the immediate management of suspected perioperative allergic reactions for which consensus is currently lacking in the literature.

A search in PubMed, without restrictions on dates or language, for combinations of 'perioperative', 'anaphylaxis', 'management', 'treatment', 'guideline', 'anaesthesia', 'allergy', and 'hypersensitivity' was performed, and relevant articles were selected by the authors. Although the term 'perioperative hypersensitivity' may be more precise in terms of encompassing possible underlying mechanisms, there was agreement in the group about using the term 'suspected perioperative allergic reactions' as an overall term, which will be abbreviated as 'perioperative allergy'. The term 'perioperative anaphylaxis' will be used when discussing life-threatening reactions.

Incidence, causal agents, and mortality

The epidemiology of perioperative allergy from studies from several countries^{4,12–21} clearly shows that differences exist between countries. The incidence reported in studies of suspected perioperative hypersensitivity reactions varies from one in 353 to one in 18 600 with substantial geographical variability.^{16,22–34} This variation is multifactorial and includes factors such as differences in local practices and drug preferences, variability in ascertainment, referral practices, comprehensiveness of allergy evaluation, and genetic or environmental factors.

Several series from France have been published over the past 25 yrs and data have been collected in large databases.^{35,36} The incidence of immunoglobulin E (IgE)-mediated reactions of all grades of severity has been estimated to be one in 10 000, but significant underreporting is suspected.³⁷ In the recent NAP6 project from the UK, where only anaphylaxis and fatal cases were included (reactions were graded III–V; where Grade

V included fatal reactions only), the incidence was estimated to be one in 10 000. However, according to the authors, this is likely to be an underestimate. It was suggested that if cases excluded because of incomplete data had been included, the incidence could have been as high as one in 7000.¹⁷

Recent publications have highlighted the risk of allergy to antibiotics,^{17,30} neuromuscular blocking agents (NMBAs) and sugammadex,^{13,16,17,30,31} latex,³⁰ dyes,^{17,30,37} and chlorhexidine.^{17,38} Antibiotics and NMBAs are the leading causes of allergy during the perioperative period.^{17,30,33} While reactions to antibiotics are increasing in many countries, NMBAs still represent a major cause in France, Belgium, Australia, and the UK. Reactions to latex are decreasing with the implementation of primary and secondary prevention measures. The increased use of blue dyes in cancer surgery and of chlorhexidine as a disinfectant is likely to account for the increase in reactions to these agents.³³

Recent studies have shown that recognition of perioperative anaphylaxis is generally prompt, as it occurs in a monitored setting.^{39,40} Most patients with severe reactions were adequately managed with rapid administration of epinephrine in the UK and France.^{39,40} However, fluid administration was not always sufficient.⁴⁰ One study demonstrated that significant delays in treatment with epinephrine occurred in about one-third of cases in Denmark.⁴¹ Per case mortality was estimated to be one in 26.6 cases in the UK for all causative drugs,⁴⁰ an outcome very similar to that observed in France for mortality related to NMBA anaphylaxis,³⁹ and that reported for all causative drugs in the US⁴² and Japan.²⁷ A perioperative anaphylaxis mortality rate of 0–1.4% was recently reported for Western Australia (2000–2009).²⁴

Mechanisms

The perioperative setting is complex with multiple drugs administered simultaneously combined with the effects of anaesthetic and surgical management. The clinical picture can mimic allergic reactions and be interpreted as such, and this may only be disproved when subsequent allergy

investigation is negative.^{8,43} Fig 1 summarises possible mechanisms underlying a clinical picture suggestive of an immediate perioperative allergic reaction, including symptoms unrelated to allergy, but related to effects of drugs or surgical/anaesthetic management.

The most important mechanism to identify is the *specific* activation of the immune system or allergic reactions mediated by specific IgE antibodies towards the culprit agents. IgE-mediated reactions account for 50–60% of cases and carry the risk of more severe reactions on re-exposure than non-IgE-mediated reactions.³³ Rarely, specific IgG is involved, such as with dextrans.

A similar clinical picture can be triggered by non-allergic mechanisms such as *nonspecific* activation of complement, or activation and mediator release from mast cells and basophils.⁴⁴ Among these, activation of a recently identified receptor, mas-related G protein-coupled receptor member X2,⁴⁵ or other unknown receptors, can occur with drugs such as opioids and NMBAs.

Other non-allergic *inflammatory* mechanisms follow different pathways: cyclooxygenase-1 inhibition in the case of NSAIDs and the kinin-kallikrein system in bradykinin-induced angioedema (hereditary, acquired, or caused by angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers).

The different mechanisms and mediators are likely to contribute to variation in the clinical presentation, which is expressed as the severity grade of the allergic reaction and may be correlated with an increase in serum tryptase.⁴⁶ Clinical presentation is also influenced by comorbidity, surgical pathology and technique, and anaesthetic method. Subjects with a clonal mast cell disorder might be at higher risk of severe reactions with either specific or non-specific triggers.⁴⁷

Clinical presentation

The clinical suspicion of a perioperative immediate allergic reaction is based on a pattern of symptoms suggestive of allergy and their onset in relation to the administration of

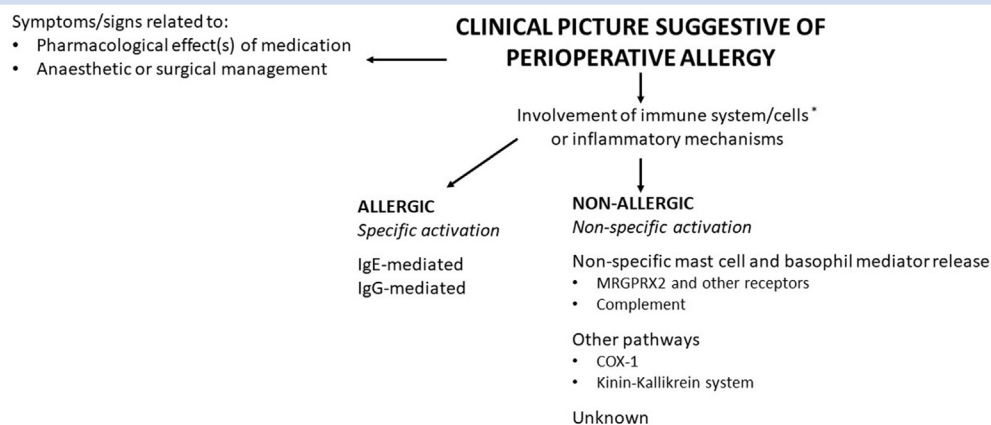


Fig. 1. Possible mechanisms for clinical presentation suggestive of immediate-type perioperative allergy.⁸ *An underlying clonal mast cell disorder can be a risk factor for severe perioperative reactions and may present with or without a specific triggering allergen. COX-1, cyclooxygenase-1; Ig, immunoglobulin; MRGPRX2, mas-related G protein-coupled receptor member X2. © 2019 EAACI and John Wiley and Sons A/S.

potential triggers. Most perioperative immediate allergic reactions occur around the time of induction of anaesthesia.^{1,2,5,48} The Ring and Messmer scale,⁴⁹ modified for the perioperative setting, is used in several guidelines for characterising the clinical phenotypes of perioperative immediate allergic reactions and grading severity (Table 1).^{1,2,48} Grades I and II reactions are not life-threatening and more likely to be non-allergic (i.e. non-specific activation of mast cells and basophils). Grades III and IV reactions are life-threatening, fulfil the criteria for anaphylaxis, and are more likely to be IgE-mediated.^{30,50} The main presentation of a Grade III reaction is sudden onset life-threatening hypotension, often associated with tachycardia, but bradycardia can occur. The onset of bradycardia may be related to rapid capillary leakage with subsequent massive hypovolaemia (Bezold-Jarisch reflex).^{51–53} Bronchospasm is more common in patients with underlying airway hyperreactivity such as asthma, chronic obstructive pulmonary disease, or obesity.^{2,40,54,55} Skin symptoms, such as generalised erythema or urticaria, are usually, but not invariably present and may be hidden by surgical drapes.^{1,2,10,17,50}

A Grade IV reaction is cardiac arrest, with the most common features being pulseless electrical activity and the absence of cutaneous signs.^{10,17,50} Isolated hypotension/cardiovascular collapse or cardiac arrest may be the first presentation of perioperative anaphylaxis.^{1,2,5,10,36} and skin symptoms may be absent until adequate perfusion is restored.^{17,50,56} In the clinical setting, it is important to consider anaphylaxis as a differential diagnosis when perioperative hypotension or bronchospasm does not respond to usual therapy or when cardiac arrest occurs unexpectedly during anaesthesia.^{2,10,17,57}

Differential diagnoses

Non-allergic differential diagnoses of perioperative allergic reactions may be related to anaesthetic or surgical management (Fig 1). If symptoms arise from a single organ system and serum tryptase measured at the time of the reaction is not elevated when compared with the patient's own baseline sample obtained after the reaction, an allergic reaction is less likely, and further investigation may not always be necessary (Table 2).^{8,43} Hypotension, as a single symptom, can have multiple causes (e.g. result from the pharmacological effects of drugs, major bleeding or other types of shock). It may also be seen on induction in patients who take tricyclic antidepressants⁵⁸ or antihypertensive drugs.

Symptoms from the upper airways may be caused by airway swelling after traumatic intubation or angioedema in

patients on ACE-I treatment,⁵⁹ or more rarely hereditary angioedema. Symptoms from the lower airways may be induced by unrecognised aspiration of gastric contents or by airway management in patients with underlying airway hyperreactivity, including those with undiagnosed or poorly controlled asthma.^{54,55}

Isolated skin symptoms can result from non-specific histamine release in response to some drugs, most commonly opioids.^{2,44} These reactions are less severe and may be reduced or prevented by antihistamine pre-treatment before future anaesthetics. However, distinguishing between non-specific histamine release and more specific mechanisms is often not possible clinically. The diagnosis of non-specific histamine release is mostly concluded after further investigations when all substances test negative, and this is corroborated by the history and a normal tryptase result. Exacerbation of urticaria, angioedema, or both can occur in patients previously diagnosed with chronic urticaria/angioedema, which can be difficult to differentiate from an allergic reaction. Patients with cold urticaria have been reported to develop urticaria, or rarely anaphylaxis, with administration of cooled medications.⁶⁰ Finally, patients with systemic mastocytosis or other clonal mast cell disorders can develop reactions that are clinically indistinguishable from IgE-mediated perioperative allergy/anaphylaxis, but are triggered by non-specific triggers such as temperature, stress, mechanical pressure, or some histamine-releasing drugs.^{47,61} These patients may have a concurrent IgE-mediated allergy.^{47,62}

Management of suspected perioperative allergic reactions

Management of suspected perioperative allergic reactions involves the following three key steps: timely diagnosis, appropriate dosing of epinephrine, and appropriate intravascular volume replacement. Under- or overtreatment is more likely to influence outcome in patients with significant cardiorespiratory disease, higher ASA physical status classification, obesity, old age, clonal mast cell disorders, or who are taking beta-adrenergic receptor blockers or ACE-I.^{17,39,47,63}

Perioperative allergy guidelines are consistent concerning the following recommendations: Grade I reactions do not require treatment with epinephrine^{1,2,10}; use of the systematic Airway, Breathing, Circulation, Disability (ABCD) approach^{5,7,10}; call for help^{1,2,5,7,10}; administer oxygen 100%^{1,2,5,7,10}; remove potential triggers^{1,2,5,7,10}; and elevate the legs in the setting of hypotension.^{1,2,5,10} However, recommendations differ on several other points and the evidence base is low. To address this situation, the ISPAR group¹¹

Table 1 Grading of suspected perioperative allergic reactions according to the modified^{1,2,48} Ring and Messmer⁴⁹ scale. Skin or mucosal signs may be absent, especially in Grades III and IV, where they may only appear once adequate perfusion has been restored.

Grade	Clinical signs
I	Skin, mucosal signs, or both: generalised erythema, extensive urticaria, or both with or without angioedema
II	Moderate multi-organ involvement: skin, mucosal signs, or both with or without moderate hypotension, tachycardia, moderate bronchospasm or gastrointestinal symptoms
III	Life-threatening mono- or multi-organ involvement: life-threatening hypotension, tachycardia, or bradycardia with or without cardiac arrhythmia, severe bronchospasm, skin, mucosal signs, or both, or gastrointestinal symptoms
IV	Cardiac or respiratory arrest

Table 2 Non-allergic differential diagnoses to suspected perioperative allergic reactions.^{8,43,55} ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease. © 2019 EAACI and John Wiley and Sons A/S.

Isolated hypotension without tryptase increase
• relative overdose of anaesthetic agents • vasodilatory effect of neuraxial blockade • bone cement implantation syndrome • amniotic fluid embolism • pulmonary embolism • treatments with tricyclic antidepressants • uncontrolled bleeding • other types of shock
Isolated bronchospasm without tryptase increase
• undiagnosed or uncontrolled asthma/chronic obstructive pulmonary disease • airway hyperreactivity (predisposing factors such as asthma, smoking, or viral infection) • inadequate depth of anaesthesia • tracheal tube malposition • aspiration
Isolated angioedema or pharyngeal/laryngeal angioedema without tryptase increase
• soft tissue swelling/oedema as a result of manipulation of the airway during insertion of a supraglottic airway device or handling of difficult intubation • angiotensin-converting enzyme inhibitor elicited angioedema (onset 1–8 h after surgery) • inherited or acquired angioedema
Isolated skin symptoms or combined skin symptoms, hypotension and tachycardia without tryptase increase
• non-specific histamine release • exacerbation of existing chronic urticaria/angioedema • relative overdose of oxytocin • mesenteric traction syndrome
Others
• Clonal or non-clonal mast cell disorders

conducted a consensus development exercise for the management of suspected allergic reactions in adults that covered: dosing of epinephrine and i.v. fluid according to the severity of the reaction; indications for initiating cardiac compressions; management of refractory anaphylaxis; use of corticosteroids and antihistamines; clinical observation of the patient after the event; contents of perioperative anaphylaxis treatment packs; and number and timing of mast cell tryptase samples. Before describing the context for each of these topics, our consensus recommendations and their implications, it is necessary to provide an overview of our consensus-development methodology. Full details are presented in [Appendix 1](#).

Consensus development methods and results

An online modified Delphi process involving a panel of 26 international experts in perioperative allergy was used to score the appropriateness of, and agreement with, a series of statements describing aspects of treatment of perioperative allergy. We used the RAND/UCLA approach⁶⁴ in which the appropriateness of each statement is scored on a scale of 1 (completely inappropriate) to 9 (completely appropriate). A statement was defined as appropriate when the median appropriateness score at the end of the iterative process was >6.9. The level of agreement was based on the disagreement index (DI), which is dependent upon the dispersion of the appropriateness scores. The lower the DI below one, the greater is the consensus; we applied a strict consensus criterion of DI<0.5. We used the appropriateness score and DI values to distinguish between clear and conditional

recommendations: when describing the former we will use ‘we recommend’ and for the latter, ‘we suggest’.

All statements that met our criteria for appropriateness and consensus are presented in detail in [Table 3](#). [Table 4](#) presents a summary of recommendations for use in clinical practice. Details of the statements that did not meet the criteria can be found in [Appendix 1](#), which also contains further details of the selection of the expert panel, conduct of the Delphi process and its stopping criteria, derivation of the DI, use of the median appropriateness score and DI to determine the strength of recommendation and limitations of our consensus development process.

Epinephrine dosing

We *recommend* that the dose of i.v. epinephrine (and i.v. fluid) to treat suspected perioperative allergic reactions should be based on the grade of clinical presentation. This approach is required to avoid under- or overdosing epinephrine and fluid resuscitation.^{40,41,63} We *recommend* that timely administration of epinephrine is required for Grade II–IV reactions. However, we can only *suggest* initial doses for Grades II (20 µg) and III (50 µg) reactions. For Grade II reactions, some of the group maintained that 10 µg was more appropriate than 20 µg. For Grade III reactions, when no other treatment had been administered, some preferred 100 µg to 50 µg, as an appropriate initial dose. However, we were able to *recommend* an initial dose of epinephrine 100 µg in cases of insufficient response to other vasopressors, bronchodilators, or both. When response to the initial dose is insufficient at 2 min, we *recommend* escalation to epinephrine 50 µg for Grade II reactions and *suggest* escalation to epinephrine 200 µg for Grade III reactions (agreement for a

Table 3 Delphi process statements where consensus was reached. Median score = the median appropriateness score from the Delphi process, where appropriateness is rated on a scale from 1 (completely inappropriate) to 9 (completely appropriate). DI, disagreement index where the lower the value below 1, the greater is the consensus. * Median appropriateness score indicates a conditional recommendation (Grade 2C—see [Appendix 1](#)) based on either a median score of seven, or DI>0.4, but <0.5; or both. All other recommendations are strong recommendations (Grade 1C—see [Appendix 1](#)).

Immediate management in adults	Delphi Consensus	
	Median score	DI
Grade II reaction (moderate hypotension or bronchospasm)		
1. When a vasopressor, bronchodilator, or both is clinically indicated: administer i.v. epinephrine 20 µg	8	0.4
2. Administer epinephrine 50 µg at 2 min when unresponsive to initial epinephrine dose	8	0.19
3. If i.v. access is not present or lost, administer i.m. epinephrine 300 µg	7*	0.15
4. Administer crystalloid 500 ml (e.g. balanced salt solutions or NaCl 0.9%) as rapid bolus and repeat if inadequate response	9	0.13
Grade III reaction (life-threatening hypotension or bronchospasm)		
1. Administer i.v. epinephrine 50 µg if no other vasopressors/bronchodilators have been given	7*	0.3
2. Administer i.v. epinephrine 100 µg where unresponsive to other vasopressors/bronchodilators	8	0.25
3. Administer epinephrine 200 µg at 2 min where unresponsive to initial epinephrine dose	8*	0.48
4. Administer crystalloid 1 L as rapid bolus and repeat if inadequate response	8	0.13
Grade IV reaction (cardiac or respiratory arrest)		
1. Follow local advanced life support guidelines including i.v. epinephrine 1 mg	9	0.008
2. Initiate cardiac compressions where there is evidence of inadequate cardiac output	9	0
3. Initiate cardiac compressions where for systolic arterial pressure <50 mm Hg	8	0.19
4. Consider initiating cardiac compressions where end-tidal CO ₂ <3 kPa (20 mm Hg)	7*	0.22
Refractory management		
Where inadequate sustained response after 10 min		
1. Escalate epinephrine dose (doubling the bolus dose)	8	0.16
2. Commence epinephrine infusion (0.05–0.1 µg kg ⁻¹ min ⁻¹) peripherally	8	0.13
3. Commence epinephrine infusion where more than three epinephrine boluses administered	8	0.06
4. Consider bolus of i.m. epinephrine 500 µg while infusion being prepared	8*	0.44
5. Escalate fluid administration up to 20–30 ml kg ⁻¹	8.5	0.13
Where persistent hypotension after 10 min		
1. Add an infusion of norepinephrine (0.05–0.5 µg kg ⁻¹ min ⁻¹), phenylephrine, or metaraminol	7*	0.22
2. Add vasopressin as a bolus 1–2 IU with or without infusion (2 units h ⁻¹)	7*	0.16
3. Add i.v. glucagon (1–2 mg) where patient using beta-blockers	8	0.16
4. Consider use of extracorporeal life support where available	8	0.28
5. Sugammadex has no immediate role in resuscitation of suspected anaphylaxis	9	0.13
Where persistent bronchospasm/high airway pressures after 10 min		
1. Administer inhaled bronchodilators (e.g. salbutamol), volatile anaesthetics	8	0.13
2. Consider i.v. bronchodilators (e.g. ketamine, salbutamol)	8	0.16
Corticosteroids		
1. After adequate epinephrine and fluid resuscitation, i.v. steroids may be administered	9	0.13
Antihistamines		
1. After adequate epinephrine and fluid resuscitation, i.v. chlorphenamine, clemastine or locally available i.v. formulation may be administered (but not a priority)	8*	0.49
2. I.V. promethazine is not an appropriate antihistamine for managing anaphylaxis	8	0.29
Observation		
1. Observe patient in a monitored area for a minimum of 6 h or until stable and symptoms are regressing	8	0.12
2. The risk of biphasic reactions is likely to be low	8	0.17
Perioperative anaphylaxis treatment pack should include		
1. Laminated perioperative management algorithms (focus on epinephrine and fluid)	9	0
2. Details of access to alternative vasopressors (e.g. noradrenaline, phenylephrine, vasopressin)	8	0.29
3. Infusion protocols for alternative vasopressors	8.5	0.13
4. Epinephrine in 2×1 mg in 10 ml (prefilled syringes where available)	7*	0.49
Tryptase testing		
1. Take a minimum of one with ideal of two early samples if possible	9	0.05
2. First sample at 1 h	8	0.29
3. Second sample 2–4 h	8.5	0.13
4. Baseline sample 24 h or later for comparison	9	0

stronger Grade III recommendation was not achieved because some considered repeat dosing with 100 µg more appropriate). For Grade IV reactions we *recommend* initial and subsequent doses of i.v. epinephrine 1 mg as part of standard advanced life support (ALS) guidelines.

Intravenous fluid administration

Sufficient fluid resuscitation is imperative in combating the reduction in preload caused by vasodilatation and capillary leakage. This part of management was assessed as often being

insufficient in the NAP6 study.⁴⁰ We *recommend* an initial crystalloid fluid bolus (rapid administration) of 0.5 L for Grade II and 1 L for Grade III reactions, and for this to be repeated where the clinical response is inadequate.^{1,2,7,10,40} Further fluid resuscitation needs to be tailored to the underlying medical condition and the severity of anaphylaxis. Acute haemoconcentration may be used to evaluate the adequacy of volume resuscitation.⁶⁵ Where available, fluid responsiveness indices or methods used to evaluate stroke volume or cardiac output (e.g. transthoracic or transoesophageal echocardiography) can assist management decisions by assessing ventricular function, filling, and vasodilation.^{65,66} In Grade IV reactions we *recommend* following ALS guidelines. Hypovolaemia is a cause of pulseless electrical activity, and relative hypovolaemia, requiring aggressive fluid therapy, and can be assumed in anaphylaxis.

Indications for initiating cardiac compressions

Cardiac arrest is a clinical diagnosis and we achieved the highest level of agreement to *recommend* guidelines include a statement that cardiac compressions should be initiated when there is evidence of inadequate cardiac output. NAP6 demonstrated a poorer quality of care in patients who had a systolic BP <50 mm Hg⁴⁰ and we *recommend* initiation of cardiac compression when the systolic arterial BP is <50 mm Hg. End-tidal CO₂ has been used as a measure of cardiac output during cardiac arrest.^{67–69} Low end-tidal CO₂ has also been shown to be an early marker of the severity of perioperative anaphylaxis.⁷⁰ We *suggest* cardiac compressions should be considered when end-tidal CO₂ <3 kPa (20 mm Hg) provided other causes of a low end-tidal CO₂ (e.g. airway, ventilation, or monitoring problems) have been ruled out or addressed. This recommendation may be controversial because of a lack of evidence and because it does not appear in any other current anaphylaxis management guidelines. However, we emphasise the need, as with any guideline, that recommendations be implemented taking into context the clinical scenario.

Management of refractory anaphylaxis

Refractory anaphylaxis is not clearly defined but indicates insufficient response to standard treatment. Refractory anaphylaxis can result solely from the pathological process, or be compounded by the underlying medical condition, surgical condition, or both, and anaesthesia. We *recommend* re-evaluation and consideration of additional management strategies after 10 min where there is a sustained insufficient response despite adequate dosing of epinephrine and fluids.^{41,65} Our *recommendations* include doubling the initial bolus dose of epinephrine and starting an epinephrine infusion after a total of three bolus doses. With persistent life-threatening hypotension we *recommend* ensuring that an adequate volume of i.v. fluid has been administered, giving i.v. glucagon 1–2 mg to patients taking beta-adrenergic receptor blockers and considering using extracorporeal life support if skills and equipment are available.^{71,72} We further *suggest* administration of alternative vasopressors such as vasopressin, norepinephrine, metaraminol, or phenylephrine. For persistent life-threatening bronchospasm, we *recommend* adding inhaled bronchodilators and consider adding i.v. bronchodilators. We *recommend* that sugammadex has no immediate role in resuscitation of suspected anaphylaxis.

Corticosteroids and antihistamines

We *recommend* that i.v. corticosteroids may be given after adequate resuscitation. NAP6 results showed no evidence of harm from the use of the antihistamine chlorphenamine in perioperative anaphylaxis,⁴⁰ but no studies have proven a benefit. The use of antihistamines is unlikely to change patient outcome,⁴⁰ and we *suggest* that a locally recommended i.v. antihistamine may be given after adequate resuscitation, but not as a priority.

Mast cell tryptase sampling

International recommendations for the timing of early tryptase sampling vary. In some guidelines, it is suggested to take the first sample at 1 h after reaction onset.^{1,2,10} In others, including NAP6 recommendations, it is suggested to take the first sample as soon as the patient is stable.^{5,7,40,73} In our Delphi process, the strongest consensus supported the first sample being obtained at 1 h after reaction onset and we *recommend* samples at 1 h and 2–4 h with a baseline sample for comparison obtained at least 24 h post reaction.

Post-event observation

NAP6 found no patients had a recrudescence of anaphylaxis, and the ISPAR group agreed that the risk of recrudescence is likely to be low. We *recommend* that all patients be observed in a monitored area for a minimum of 6 h from onset of the reaction.⁴⁰ Most patients with Grades III and IV reactions will require admission to an ICU, particularly where they have required prolonged resuscitation or have ongoing vasopressor requirements.

Perioperative anaphylaxis treatment packs

The use of anaphylaxis treatment kits, including treatment algorithms and instructions for tryptase sampling, has been advocated.^{2,10,40} Our consensus development focused on the contents of such a treatment kit that would be of value in the immediate management of suspected perioperative allergy. We *recommend* that these should include a laminated treatment algorithm with an emphasis on i.v. epinephrine and fluids along with details of access to, and infusion protocols for, alternative vasopressors. In some countries, such as the UK, France, and the USA, prefilled syringes of dilute epinephrine (100 µg ml⁻¹) are available for use in emergencies, but this is not the case in many other countries. We *suggest* inclusion of such prefilled syringes in the anaphylaxis treatment pack when they are available (Table 3). We cannot make a stronger recommendation primarily because of concerns regarding the practicalities of maintaining in-date stocks of rarely used preparations. In either case, familiarity with a method of preparation and correct dilution of epinephrine for i.v. administration is vital, particularly when treating Grade II reactions where our suggested initial bolus dose is 20 µg in adults. There are several methods of safely diluting epinephrine. This should be part of perioperative anaphylaxis training and should be included in supportive cognitive aids.

Management of specific patient groups

Obstetrics

The incidence of drug-induced IgE-mediated allergy in the parturient is low.^{40,74,75} Beta-lactam antibiotics are the agents

most commonly involved; cases attributable to NMBAs have been reported, and the incidence of cases attributed to latex allergy is decreasing.^{40,74–77} The management of anaphylaxis follows the same treatment principles as in the non-pregnant patient and is guided by the clinical presentation (Table 4). The parturient should be positioned with left uterine displacement so that aortocaval compression is avoided.

Prompt resuscitation of the parturient is essential for a good outcome for both mother and neonate, and early treatment with i.v. epinephrine is recommended in maternal anaphylaxis (Grades III and IV).^{1,40,74,77,78} Crystalloid fluid should be given immediately, and large volumes may be necessary. Emergent Caesarean section should be considered early if there is persistent hypotension despite resuscitation.^{1,74} Perimortem Caesarean delivery needs to be considered 4 min after cardiac arrest. Delivery of the foetus should be performed 1 min later if usual resuscitation measures have not achieved return of spontaneous circulation.^{79,80}

Paediatrics

Perioperative anaphylaxis is uncommon in children.^{40,81–83} Only two large series have been published from France,^{36,84} where latex and NMBAs were predominant causes during the period 1989–2004. Only one case of latex allergy was reported in a recent European study evaluating critical events in paediatric anaesthesia,⁸² and none in the NAP6 survey.⁴⁰ Only a few case reports have been published.^{85,86} The diagnosis remained unproven^{87,88} or speculative^{89,90} in the majority of cases, as younger children can rarely cooperate with all

aspects of allergy testing. As in adults, management of perioperative anaphylaxis in children is guided by the clinical presentation (Tables 4 and 5). Fluid therapy with crystalloids (20 ml kg⁻¹, repeated as needed)^{2,5,10} is recommended. Epinephrine remains the drug of choice, but there is no consensus on dosage. Current recommendations in different guidelines are shown in Table 5.^{1,2,5,10}

Mastocytosis

Systemic mastocytosis is characterised by an abnormal increase in tissue mast cells in the skin, infiltrating the bone marrow and other organs, or both. Patients have an increased risk of perioperative immediate hypersensitivity through various non-specific triggers, including histamine-releasing agents and other mechanical and physical factors.^{61,91,92} The use of preoperative H₁-, H₂-, receptor antagonists and corticosteroids is usually recommended, but has not been evaluated in placebo-controlled trials. The best way to avoid mast cell degranulation is to avoid known triggers. The association between drug-induced anaphylaxis and mastocytosis is not as strong as for IgE-mediated venom allergy and mastocytosis.^{61,62} There is no evidence for avoiding specific medications or drug groups in individual patients with no previous history of reactions to drugs.⁴⁷ However, caution has been recommended with atracurium, mivacurium, and other drugs with marked histamine-releasing effect, and these drugs should only be used if clinically indicated.⁶¹ The perioperative course of patients with mastocytosis, including parturients⁹³ and children,⁹⁴ is usually uncomplicated.⁶¹ The management

Table 4 Suggested management of suspected perioperative allergy and anaphylaxis in adults. ALS, advanced life support; ECLS, extracorporeal life support; ECM, external cardiac massage.

	I.V. epinephrine	I.V. fluid (crystalloids)
Grade II	20 µg Bolus Inadequate response at 2 min Escalate to 50 µg Repeat every 2 min If no i.v. access 300 µg i.m.	500 ml rapid bolus Review response Repeat as needed
Grade III	50 µg Bolus OR 100 µg bolus if inadequate response to other vasopressors or bronchodilators Inadequate response at 2 min Escalate to 200 µg Repeat every 2 min	1 L rapid bolus Review response Repeat as needed up to 30 ml kg ⁻¹
Grade IV	1 mg Repeat as per ALS guidelines Suggest ECM if: systolic <50 mm Hg or end-tidal CO ₂ <3 kPa (20 mm Hg)	
Refractory anaphylaxis	Where inadequate response >10 min after symptom onset: Epinephrine: double epinephrine dose If inadequate response after more than three boluses epinephrine: add epinephrine infusion 0.05–0.1 µg kg ⁻¹ min ⁻¹ Hypotension — consider adding: vasopressin 1–2 IU with or without infusion 2 IU h ⁻¹ glucagon 1–2 mg (if on beta-adrenergic receptor blockers) norepinephrine infusion 0.05–0.5 µg kg ⁻¹ min ⁻¹ Suggest ECLS: where available Bronchospasm — consider adding: inhaled or i.v. bronchodilators	
Tryptase	First sample: 1 h post reaction onset Second sample: 2–4 h post reaction onset Baseline sample: at least 24 h post reaction onset	

Table 5 Doses of i.v. epinephrine recommended in children.^{1,2,5,10} ND, no details mentioned.

	I	II	III	IV	Comments
Scandinavia ² (2007)	No	Bolus 1–5 $\mu\text{g kg}^{-1}$	Bolus: 10 $\mu\text{g kg}^{-1}$	ND	• Titrate to response • If large doses are needed: use i.v. infusion (0.05–0.1 $\mu\text{g kg}^{-1}\text{min}^{-1}$)
UK ⁵ (2009)	No	ND	Bolus: 1 $\mu\text{g kg}^{-1}$	ND	• Epinephrine dilution: 1 ml of 1:10 000 for each 10 kg body weight • Titrate to response, starting with a dose of 1/10=1 $\mu\text{g kg}^{-1}$ • Titrate to response
France ¹ (2011)	No	Bolus 1 $\mu\text{g kg}^{-1}$	• Bolus: 1 $\mu\text{g kg}^{-1}$ (up to 5–10 $\mu\text{g kg}^{-1}$) • Infusion: ND	• Bolus: 10 $\mu\text{g kg}^{-1}$ (repeat 1–2 min) • Infusion starting at: 0.1 $\mu\text{g kg}^{-1}\text{min}^{-1}$	
Australia ¹⁰ (2017)	No	Bolus 2 $\mu\text{g kg}^{-1}$	• Bolus: 4–10 $\mu\text{g kg}^{-1}$ (repeat 1–2 min) • Infusion - starting at 0.1 $\mu\text{g kg}^{-1}\text{min}^{-1}$ - up to 2 $\mu\text{g kg}^{-1}\text{min}^{-1}$	• Bolus: 10 $\mu\text{g kg}^{-1}$ (repeat 1–4 min) • Infusion: starting at: 0.1 $\mu\text{g kg}^{-1}\text{min}^{-1}$ up to 2 $\mu\text{g kg}^{-1}\text{min}^{-1}$	

of perioperative anaphylaxis in mastocytosis must be adapted to the severity of the clinical features. First line therapy is with epinephrine and fluids as for other patients (Table 4).⁶¹

Management and decision-making post-event

Once the patient has been treated and stabilised after a suspected perioperative allergic reaction, a decision must be made on whether to continue or abort surgery. This decision will depend on the type of surgery (e.g. elective vs emergency) and the indication (e.g. cancer surgery vs cosmetic surgery).⁵⁶ Very little literature has been published on the outcome of patients after perioperative anaphylaxis. The decision to proceed with or abandon surgery was the recent topic of an analysis from an Australian group.⁹⁵ Outcomes were similar in cases where surgery had been abandoned or proceeded with (once initial stabilisation had been achieved) for all Grade I–III cases of suspected perioperative allergy. Surgery was commonly abandoned in Grade IV events, which generally had a high rate of complications.⁹⁵

Referral for allergy investigation

All Grade II–IV reactions and Grade I reactions with generalised urticaria, erythema, or both should be referred for allergy investigation.⁸ Ideally, investigations should take place in specialised clinics with collaboration between anaesthesiologists and allergists with experience in perioperative allergy investigation.^{8,10} However, this is not available in many countries. The patient should be informed of the perioperative events and about referral for allergy investigation. Written information with details of drug and other exposures to be avoided until investigations have been performed should be provided. To ensure the best possibility of identifying the culprit agent, detailed information should be made available for the specialists who will investigate the patient.^{43,96} This should include a chronological narrative of events, carried out by the anaesthesiologist with contributions from the rest of the anaesthetic and surgical teams, if relevant. Accurate timings of all substances administered in relation to symptom onset, and treatment given and response, should be noted.

Copies of anaesthetic charts, drug charts including premedication, surgical notes, and operating room documentation including all compounds used such as gels, sprays, and haemostatic agents,^{7,8,96} should be included in the referral. ‘Hidden exposures’ (i.e. those compounds not necessarily recorded on the anaesthetic chart, such as chlorhexidine, excipients, and blue dyes) can cause anaphylaxis and will not be investigated if not documented.⁹⁶ Any compound that the patient was exposed to within a 1–2 h timeframe (depending on route of administration) before symptom onset could be the potential culprit.⁸ Guessing the culprit based on timing alone has been shown to be inaccurate and may put the patient at risk of re-exposure to the real culprit agent.^{97–99}

Investigations

From the detailed documentation of events, an investigation programme can be planned for the suspected culprit agents, ideally by collaboration between allergists/immunologists and anaesthesiologists. Investigations comprise a combination of *in vivo* and *in vitro* tests as briefly described below. The aim of allergy investigation is to confirm or disprove an allergic mechanism behind the reaction, and to identify culprit agent(s) and safe drugs, including suitable alternatives.

Serum tryptase

The main purpose of quantification of serum tryptase at the time of the reaction and at baseline is to confirm mast cell degranulation. It can also help rule out or confirm mast cell disorders and mast cell activation syndromes. An increase in serum tryptase at the time of reaction above $1.2 \times \text{baseline} + 2 \mu\text{g L}^{-1}$ is considered clinically relevant.⁸ Elevated baseline values can be seen in mast cell disorders and in other situations such as chronic renal failure.¹⁰⁰ Post-mortem sampling of tryptase can be useful when anaphylaxis is suspected as the cause of death.¹⁰¹

Skin testing

Skin testing is the most widely used method to identify the culprit agent of an immediate allergic reaction. It comprises

skin prick tests and intradermal tests, which should always be interpreted in the light of a relevant negative and positive control.¹⁰² All drugs/agents administered before the reaction should be tested. 'Hidden exposures' commonly used in the perioperative setting, such as latex and disinfectants (e.g. chlorhexidine), should be tested routinely in all patients.^{8,40} For some drugs/agents, an IgE-mediated mechanism is less clearly shown, and a validation of skin testing is lacking. Testing and subsequent interpretation should be performed by experienced personnel using standardised concentrations^{1,8,9} as several drug groups, especially NMBAs and opioids, can cause irritant skin reactions.^{103–107}

In vitro specific testing

Quantification of specific IgE (sIgE) antibodies can be used for a limited number of drugs in the perioperative setting. The reported sensitivity and specificity are very good for sIgE for latex and chlorhexidine, but show great variation for the remaining assays available (some beta-lactam antibiotics and few NMBAs). The basophil activation test can be used in cases of IgE-mediated and non-IgE-mediated hypersensitivity reactions (e.g. opiates). It can be used for identifying the culprit drug or safe alternative drugs, but must be performed by experienced laboratories.¹⁰⁰

Drug provocation testing

When other tests have not provided a culprit agent, investigations may be supplemented by a graded drug provocation test (DPT). This includes the gradual administration of a suspected drug, or in some cases, an alternative drug. Particularly for drug groups where the mechanism is unlikely to be IgE-mediated (e.g. opioids or NSAIDs), DPT may be the only reliable test.^{108,109} DPT has only recently been recommended in perioperative allergy investigation, and very limited literature is available.^{7,8,43,110} When involving drugs specific to anaesthesia, it should only be undertaken in specialised centres after ensuring informed consent.^{7,8,43,110} In most centres where DPT is not routinely used, conclusions must be based on other tests. Results of single tests should always be interpreted in the context of relevant clinical information and serum tryptase results from the time of reaction and a later baseline sample.

The time interval between the acute reaction and testing, patient reactivity, individual characteristics, and total IgE concentration are factors potentially affecting the results of these tests. Some groups suggest that two or more positive test modalities should be obtained before a drug can be considered the culprit to reduce the risk of false positive tests. This approach has proven useful for NMBAs and chlorhexidine, but may potentially be used for other drugs where drug provocation is not possible.^{100,111,112}

Prevention of future perioperative allergic reactions

There is no evidence that prophylaxis with H₁-, H₂- receptor antagonists or corticosteroids prevents or reduces the severity of anaphylaxis.^{113,114} However, there may be a benefit of premedication with antihistamines in patients with recurring Grade I reactions caused by non-specific histamine release. Premedication is recommended in some guidelines to reduce or prevent this type of reaction.^{2,7,8}

For patients with previous perioperative allergic reactions that have been investigated, the identified culprit must be avoided. In cases of allergy to latex or disinfectants, this avoidance requires thorough information of all healthcare personnel involved in managing the patient to avoid accidental re-exposure. One study showed that one-third of patients diagnosed with chlorhexidine allergy were accidentally re-exposed in the healthcare setting.¹¹⁵ A history of a previous uninvestigated perioperative immediate reaction is a known risk factor for a recurrence during subsequent anaesthetics.¹

An approach to the patient with a suspected perioperative allergic reaction who needs surgery is shown in Fig 2. The approach will depend on the urgency of the procedure. If the reaction was severe and the upcoming procedure is elective, the patient should be referred for specialised perioperative allergy investigation before surgery.

A suspicion of allergy should never delay emergency surgery, but the anaesthesiologist should try to get as much information about the reaction and anaesthetic procedure as possible. If information from the reaction is available, all exposures before the reaction should be avoided, and alternatives should be used whenever possible. In the case of emergency surgery where no information is available, use of regional, inhalational, or both anaesthetic techniques should be favoured to minimise i.v. drug exposures. Use of latex, chlorhexidine, NMBAs, and antibiotics from the penicillin or cephalosporin group should be avoided if possible. Decisions on which drugs/techniques to use and which to avoid should always be made after a careful risk–benefit assessment of the specific clinical situation.

If surgery is urgent (e.g. because of cancer) and allergy investigation cannot be arranged within a reasonable timeframe, all available information from the reaction should be gathered. If possible, advice should be sought from local specialists with experience in perioperative allergy investigation on a safe strategy for anaesthesia and surgery.

Unmet needs and future perspectives

There are still many issues to be resolved regarding the treatment of perioperative anaphylaxis and the standardisation of subsequent investigations. Research dedicated to the treatment of anaphylaxis should be supported, as current recommendations are mainly based on expert opinion and animal studies with a low evidence base. The management of refractory anaphylaxis needs new therapeutic strategies, as this still carries a relatively high mortality. Investigations into combinations of epinephrine with other drugs, including the ones already mentioned in guidelines, and others such as methylene blue, are needed.

Training anaesthesiologists in early recognition and correct treatment of perioperative anaphylaxis should also be a priority, to ensure the best outcome for patients. Such training could ideally be undertaken as simulation training utilising cognitive aids, with a focus on correct dosing of epinephrine and fluids in the immediate treatment of perioperative anaphylaxis.

Research into improved diagnostic tests for both IgE-mediated and other types to identify allergy and cross-allergy should also be a priority, as existing tests have limitations.

Serum tryptase is the only marker of anaphylaxis used clinically. Skin testing is a cornerstone of perioperative

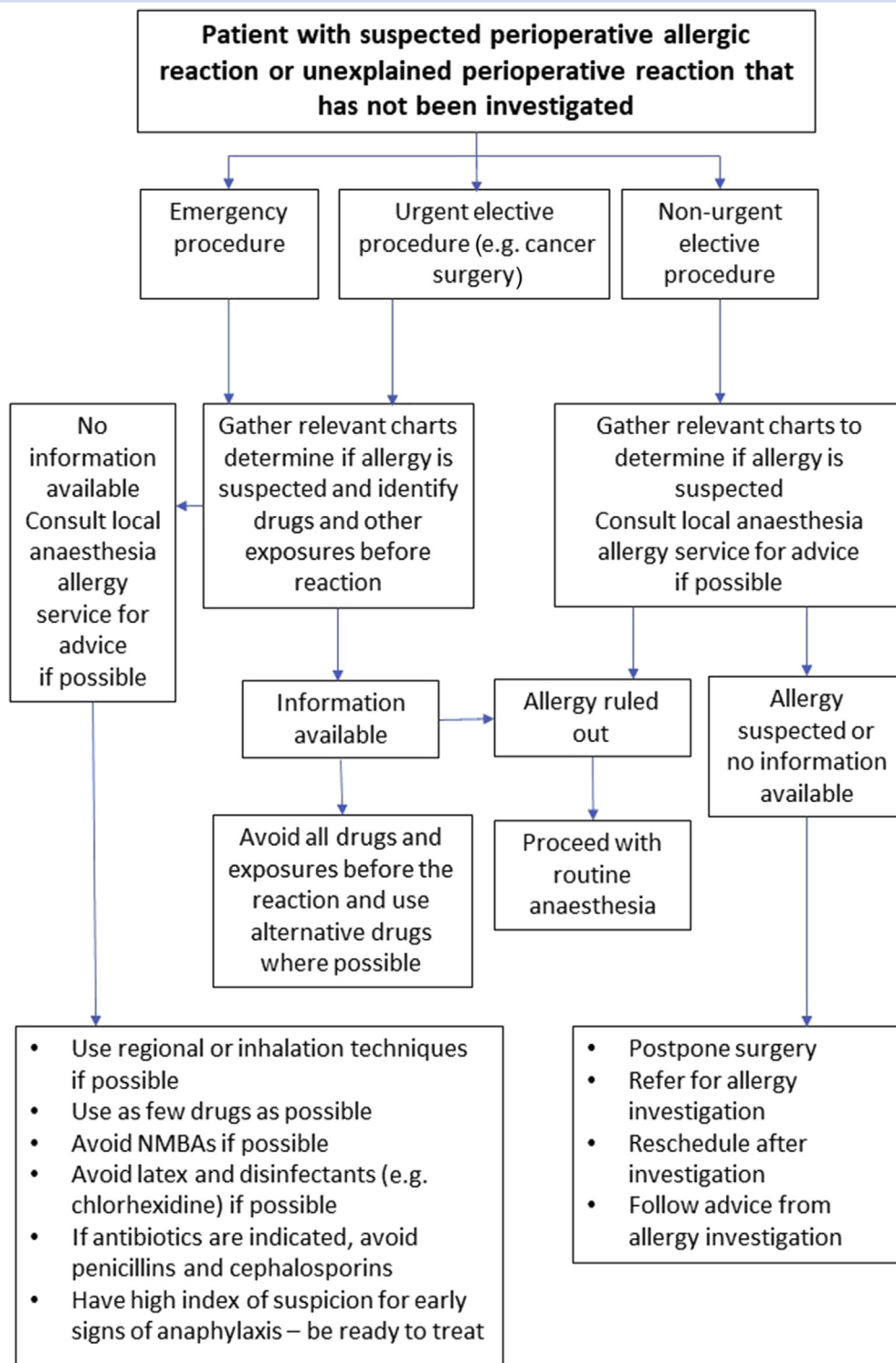


Fig. 2. Management of the patient with a suspected perioperative allergic reaction or unexplained perioperative reaction that has not been investigated. NMBA, neuromuscular blocking agent.

anaphylaxis investigation and standardised diagnostic procedures have been published. However, validation of skin tests varies between drug groups, and for some drugs, skin testing may be impossible because of the irritant effect of the drug.

DPTs, regarded as the gold standard in drug allergy investigation, can be useful in cases of negative allergy testing. However, provocation with anaesthetic drugs requires multidisciplinary expertise, carries a certain amount of risk, and is thus limited to specialised centres.

Conclusions

This paper provides theoretical and practical background knowledge about suspected perioperative allergic reactions based on current literature, expert opinion, and a modified Delphi consensus process. The recommendations are based on the collective experiences of a large international and multidisciplinary group with longstanding perioperative allergy experience. Currently, this is the highest level of evidence possible. Establishing more local, national, and international networks of centres investigating perioperative allergic reactions would increase the capacity to conduct larger studies and share knowledge. This would improve the evidence base, and ultimately the management of these complex patients.

Authors' contributions

Conception of the study: all authors.

Design of the study: LHG, HK, PD, DLH, PMM, SV.

Data collection, analysis, and interpretation: all authors.

Drafting of manuscript: LHG, HK, PD, DLH, PMM, SV.

All authors reviewed drafts of the manuscript and approved the final version.

Declaration of interest

PD: i) has received lecture and travel fees from MSD France (Courbevoie, France); ii) has received lecture and travel fees from Bracco Imaging France (Courcouronnes, France); iii) Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint-Denis, France), Expert for a task force group dedicated to "neuromuscular blocking agents and anaphylactic reactions" (until 2016); iv) belongs until October 2019 to a MSD Expert Board on "neuromuscular blocking agents and fast-tracking anesthesia".

LHG: Consultant & adjudication committee member for Merck, New Jersey USA & Consultant & adjudication committee member for Novo Nordisk Denmark.

PMM is an Editorial Board Member of BJA.

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All other authors confirm that they have no interests to declare.

Disclaimer statement

The guidelines and recommendations included in this article represent the views of the authors. They are based on expert opinion and careful consideration and interpretation of the available evidence in the literature, at the time that they were agreed, along with a formal consensus-development process. They are intended principally for clinicians involved in the management of patients suspected of having a perioperative allergic reaction. Clinicians are encouraged to take the guidelines and recommendations fully into account when exercising their clinical judgement. The guidelines and recommendations do not supersede the individual responsibility for clinicians to make appropriate decisions and give the best care according to the circumstances of individual patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2019.04.044>.

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Appendix 1

Method, additional results and limitations of Modified Delphi Process

Modified Delphi Process

Panel selection

The formation of the working group was initiated by the *BJA* in the Spring of 2018 in anticipation of publication of the NAP6 findings, with a view to publishing a special Issue on perioperative anaphylaxis. The goal was to provide an international perspective on current research and opinion in perioperative anaphylaxis. The group was convened by PMH (anaesthetist and *BJA* Editorial Board Member) and LHG (anaesthetist and allergist and Chair of the EAACI Task Force on Perioperative Hypersensitivity) who approached by email 31 international experts in suspected perioperative allergic reactions. Of these, 14 anaesthetists and 10 allergists/immunologists agreed to participate in the working group and in the modified Delphi Process panel. The details of the panel members and writing group are provided in the list of authors of this paper.

The modified Delphi process was conducted using online questionnaires (Google Forms) where panel members were asked to rate a series of statements on a scale of 1 (completely inappropriate) to 9 (completely appropriate). There was an option to respond N/A (not applicable) to statements that panel members felt to be outside their expertise and three allergists opted out of responding to some statements. Freehand comments on the suitability of the statements were also invited. Analysis of the responses used the RAND approach.¹ The median appropriateness score was used to rate each statement as inappropriate (median score 1 – 3.4), uncertain (median score 3.5-6.9) or appropriate (median score 7-9). Consensus was assessed by the disagreement index (DI), where the lower the value below 1, the greater is the consensus. A value above 1 is considered to represent lack of consensus.² The rationale and derivation of the DI is explained in detail by Fitch et al¹. In brief, when the RAND researchers first developed the 9 point scale of appropriateness they defined agreement and disagreement based on results from panels made up of 9 participants. For agreement, 2 or fewer panelists were required to rate a statement outside the 3-point region (1-3, 4-6, 7-9) that contained the median.

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Formattato: Tipo di carattere:
Corsivo

Disagreement was defined when at least 3 panelists rated the statement in the 1-3 region and at least 3 in the 7-9 region. The DI is a continuous variable derived from a formula that can be applied to a panel of any size and it enables the criterion for agreement/disagreement to be made stricter or more relaxed. It is based on the interpercentile range (IPR, difference between the 33rd and 66th centiles) but is adjusted to reflect the fact that the further the median value is from the central point of the scale (5), the greater is the IPR required to generate disagreement. Computer simulations have demonstrated that the DI indicates agreement/disagreement defined by the “classical” algorithm with a high degree of sensitivity and specificity. We planned at least two rounds to generate a series of statements rated as appropriate with a clear consensus (DI < 0.5). The process was to continue until a clear consensus was reached for each statement (DI < 0.5) or the DI failed to improve by more than 15% in successive rounds.³

Round 1.

Round 1 was conducted in September 2018. Statements concerning the management of suspected allergic reactions were developed by two members of the writing group (LHG, HK) based a review of: current international perioperative⁴⁻⁸ and general anaphylaxis^{9, 10} management guidelines; Cochrane reviews of anaphylaxis treatment with epinephrine,¹¹ antihistamines¹² and steroids;¹³ the NAP6¹⁴ report; and references identified in these papers.¹⁵⁻²⁷

The following recommendations were not put to consensus as they are universally accepted in the management of perioperative anaphylaxis: grade I reactions (generalized erythema and/or extensive urticaria) do not require treatment with epinephrine;^{5, 6, 8} use of the systematic approach ABCD;^{4, 6, 7} call for help;⁴⁻⁸ administer 100% oxygen;⁴⁻⁸ remove potential triggers;⁴⁻⁸ and elevate the legs in the setting of hypotension.^{4-6, 8} In addition to rating the appropriateness of the statements and to comment on them, panel members were also invited to propose additional statements.

Round 2 and subsequent rounds:

Round 2 was conducted in December 2018 after the paper was submitted and reviewed in order to address some queries from the reviewers. Prior to Round 2, panel members received their scores from Round 1 alongside de-identified scores of the other panel

members (as raw data and as summary bar charts), and the calculated median appropriateness and DI values. Information on interpretation of median appropriateness and DI values was provided.

The Round 2 statements did not include recommendations that were rated as appropriate with clear consensus in Round 1. Where Round 1 included statements for different options e.g. the dose of epinephrine, for the same scenario, and one option was rated appropriate with consensus, the alternative option statements were not included in Round 2. LHG and HK reviewed the responses to the statements in Round 1, including the freehand comments, and agreed whether each statement should be included in Round 2 unchanged, in amended form or not included. If the stopping criteria were not met after Round 2, the process for subsequent rounds would follow that of Round 2.

Results

The Round 1 questionnaire was comprised of 43 statements and 24 members of the panel responded. Thirty-seven of the statements were rated as appropriate, 6 had uncertain appropriateness and none was rated inappropriate. The DI was < 0.5 for 38 statements, between 0.5 and 1 for 8 statements and > 1 for one statement. There were 42 freehand comments on the statements in Round 1, but no new statements were suggested.

In Round 2 there were 8 statements of which 5 were unchanged from Round 1, one was amended and two were new statements that addressed potential ambiguity of two statements from Round 1. Twenty-five panel members responded. All but one of the statements met a stopping criterion for the modified Delphi process. It was decided not to pursue a third Delphi round for the statement that did not meet a stopping criterion (If corticosteroid equivalent to 200 mg hydrocortisone has already been given, e.g., 7.5 mg dexamethasone as antiemetic prophylaxis, there is no need for further corticosteroid) because the comments on this statement indicated that we were unlikely to achieve consensus that was an appropriate recommendation.

GRADE Recommendations

The 37 statements that were rated as appropriate, i.e. median score 7-9 and with a DI < 0.5 , comprised the recommendations from this group and are shown in Table 3 of the main

manuscript. Using the GRADE Working Group definition (www.gradeworkinggroup.org), the statements with a median score of 8 or 9 were classified as strong recommendations or GRADE 1 (General agreement that the treatment is beneficial, useful or effective), and those with either a median score of 7 or a DI of > 0.4 , [but \$< 0.5\$](#) were classified as conditional recommendations or GRADE 2 (Conflicting evidence or less well established evidence on the usefulness or efficacy of the treatment) see table A1.²⁸ The quality of the evidence is low for all statements and described as C (Consensus opinion of experts and/or small studies, retrospective studies and case reports).

The modified Delphi process achieved strong recommendations with low disagreement for the majority of the statements mentioned in table 3 of the main manuscript. Statements resulting in recommendations are discussed in the main manuscript. The statements included in the modified Delphi process that did not meet the criteria for inclusion in the recommendations are listed in Table A2.

Limitations

Due to the lack of evidence in the literature, the management statements have a low evidence base. Some centres contributed more than one member to the expert group, which may introduce bias. In order to assess the likelihood of bias from including more than one person from a centre we repeated the calculations of appropriateness scores and DI after including only one score (the average of individual scores) for each centre that had more than one representative. This did not impact on the final rating of appropriateness for any of the recommendations and actually improved the DI scores of more recommendations than it reduced, providing strong evidence that the degree of variability was at least as great among participants from the same centre as the variability among all participants. We therefore present the appropriateness scores and DI calculated using scores of all participants.

		Median	DI	Round after
GRADE of Evidence				which
High Quality, A	Consistent evidence from well performed randomised, controlled trials. Further research is very unlikely to change confidence in the estimate of effect.			excluded
Grade II Reaction (Moderate hypotension or bronchospasm)				
Moderate Quality, B	When a vasopressor and/or bronchodilator is clinically indicated, administer 50 mcg epinephrine IV. If IV access is not present administer 500 mcg IM epinephrine. Further research is very likely to have an important impact on confidence in the estimate of effect & may change the estimate.	5	0.97	1
Refractory management				
Low Quality, C	When persistent hypotension after 10 minutes, consider Methylene blue (1.5mg/kg) as an alternative. Further research is very likely to have an important impact on confidence in the estimate of effect & is likely to change the estimate.	6	1.25	2
Grade of Recommendation				
Grade 1	General agreement that the treatment is beneficial, useful or effective			
Grade 2	Conflicting evidence or less well-established evidence on the usefulness or efficacy of the treatment			

Table A1. Level of Evidence and Recommendation

vasopressor			
Steroids			
If corticosteroid equivalent to 200 mg hydrocortisone has already been given, e.g., 7.5 mg dexamethasone as antiemetic prophylaxis, there is no need for further corticosteroid	6	0.65	2
Tryptase Testing			
First sample immediately after the patient is stable	8	0.5	1
Second sample 4-6 hours	5	0.52	1

Table A2. Delphi process statements not reaching criteria for inclusion in recommendations

References Appendix 1

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